North Carolina Department of Environmental Quality
and
North Carolina Department of Health and Human Services

Secretaries' Science Advisory Board
Review of the North Carolina Drinking Water Provisional Health Goal for GenX

October 30, 2018

FINAL

Section 1 – The Secretaries' Science Advisory Board

The Secretaries for the North Carolina Departments of Environmental Quality (DEQ) and of Health and Human Services (DHHS) established their Science Advisory Board (SAB) in July 2017. It is founded on recognition that clean air, water and land are critical to quality of life, to protect health and to promote a vibrant economy for all North Carolinians. The Board comprises experts in toxicology, epidemiology, environmental science, environmental engineering, medicine and other disciplines and their expertise will help guide the two agencies in carrying out their responsibilities to protect the safety and health of the citizens. The Board provides advice on the adverse effects of environmental contaminants, monitoring and measuring exposure to environmental contaminants, and on their control.

The Board performs or recommends reviews and evaluations of contaminants released to the environment; acts as consultants on DEQ's determinations to regulate releases of contaminants; assists both agencies in identifying contaminants of emerging concern and helps determine whether the contaminants should be studied further; assists the Secretaries in providing expertise to evaluate the human and environmental impacts of exposure to hazardous contaminants; and provides input to DHHS as the agency establishes health goals for emerging contaminants.

Specifically, the charter of the NC DEQ and NC DHHS Secretaries' Science Advisory Board (SAB) describes the duties of the board as:

> *(a) To perform or recommend reviews and/or evaluations of matters concerning the release of contaminants to the environment that are placed on the Board agenda by DEQ or DHHS.*
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> *(b) To advise the EMC* [Environmental Management Commission] *on information concerning the regulation and evaluation of releases of contaminants that come to the attention of the Board.*
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> *(c) To review the effects of chemicals that are proposed to be regulated by DEQ as contaminants and to recommend the necessity and/or urgency for controlling the releases of such chemicals that are found to cause deleterious environmental and human health effects with priority given to the study of contaminants for which control has been deferred pending further study.*
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> *(d) To act as consultants regarding the DEQ's determinations to regulate releases of contaminants and in determining factors for establishing acceptable levels for contaminants and for remediation levels for contaminants in other media.*

(e) To recommend concentrations of contaminants in a "range of risks" to DEQ and EMC for regulation that will minimize adverse health responses in the exposed citizenry and to advise the EMC of the scientific basis for these recommendations.

Section 2 – The Board's Charge for GenX

The Departments asked the Board to review information on GenX[1], including a review of the DHHS provisional drinking water health goal and of available scientific information about health and environmental concerns and their control, and to provide recommendations to DEQ on the starting point for developing regulatory standards.

During the January 29, 2018 SAB meeting DEQ and DHHS were asked for clarification on the type of deliverables the Board was requested to provide to the agencies. DEQ requested the Board provide recommendations on a reference dose which would be used to establish water quality standards for GenX. DHHS requested the Board review and provide recommendations on the derivation and calculation of the health goal for GenX, including the point of departure (POD), the calculation parameters, the uncertainty factors, and the options to use benchmark dose (BMD) modeling in lieu of a NOAEL (No Observed Adverse Effect Level) approach, and to provide feedback on any future modifications to these values and calculations that may be considered as additional GenX-related health studies are published.

Section 3 – GenX in North Carolina

GenX, $C_6HF_{11}O_3$, is a clear, colorless liquid with high water solubility (100,000 – 300,000 mg/L), apparent low organic carbon partitioning capacity (estimated K_{ow} 1.3 – 2.0)[2], that under normal environmental conditions exists as an anionic acid (2.8 *p*Ka acid dissociation constant)[3] (Hoke et al., 2016). Biodegradability test data (Mitsubishi Chemical Medience Corporation, 2009; Kaplan, 2010) indicate GenX is not easily biodegradable and therefore expected to be relatively persistent in the environment. With its high water solubility at environmentally-relevant pH, GenX will move readily in water (i.e., surface water, groundwater, rainwater). The fate of GenX in terms of ultimate sites of deposition in the environment is uncertain. Potential transport

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[1] GenX is correctly the name of the manufacturing process, but is commonly used, and is used here, to refer to a key chemical in the process: 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-propanoic acid (CASN 13252-13-6)

[2] K_{ow} is the octanol-water partitioning coefficient, the ratio of the equilibrium concentration of a dissolved chemical in a two-phase system of n-octanol and water. n-Octanol serves as a surrogate to biota lipids and K_{ow} values are used as an indicator of a chemicals tendency to bioaccumulate, or to be taken-up by organisms from the environment.

[3] The pKa predicts that GenX will be in acid form (as a negative ion, or an anion) at pH levels at or above a pH of 2.8.

mechanisms of GenX and other PFAS released into the environment from industrial sources are illustrated in Figure 1.

GenX is an artificial chemical and does not occur naturally. It is produced commercially for use in manufacturing non-stick coatings and may be an unintended by-product of other processes that produce related compounds. The Chemours (formerly DuPont) facility in Fayetteville NC has manufactured GenX since 2010 (Sun et al., 2016) as a replacement for PFOA and PFOS[4], two chemicals which have been associated with health effects in animals including developmental, reproductive, immunological, and cancer adverse health outcomes (EPA 2016a, EPA 2016b) and are part of the same broad family of chemicals known as per- and polyfluoroalkyl substances (PFAS). GenX has also been produced as a by-product of the facility's vinyl ether manufacturing process for more than three decades. GenX, and previously PFOA, have been released from the DuPont/Chemours plant in Fayetteville to air and to surface water. Public concern about GenX and related compounds escalated in June 2017 following reports that GenX had been detected in the Cape Fear River (Sun et al., 2016), which is the primary source of drinking water to the city of Wilmington and some other communities in North Carolina. GenX and other PFAS were also found in finished municipal drinking waters sourced from the Cape Fear River downstream of the Chemours/DuPont plant. GenX has also been found in the environment close to the Chemours/DuPont plant in Fayetteville. There are presently no federal nor state standards for GenX for water, soil, air or food.

Section 4 – The Board's GenX Review Process

The Board addressed GenX at its meetings on October 23, 2017; December 4, 2017; January 29, 2018; March 19, 2018; April 30, 2018; and June 18, 2018. It invited and received comments from concerned entities during public comment portions of those meetings and between meetings, and thanks the persons and entities that contributed comments. Board members reviewed extensive documentation provided by the Departments and accompanying written submissions and sought insights from related activities in the Netherlands, where GenX has been found in the environment around a Chemours facility (Netherlands 2016). The Board recommended additional analyses by the Departments and received the results. The Board recognizes the participation of staff of the Department of Agriculture and Consumer Services in its discussions. A summary of the meetings, documents and work are provided below and related documents are available on the SAB website at https://deq.nc.gov/news/hot-topics/genx-investigation/secretaries-science-advisory-board.

October 23, 2017 – During this meeting, the Department of Environmental Quality and the Department of Health and Human Services identified priority areas about which they requested

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[4] The chemical name for PFOA is perfluorooctanoic acid (CASN 335-67-1). The chemical name for PFOS is perfluorooctane-sulfonate (CASN 1763-23-1).

input from the Board. Issues relevant to PFAS and GenX were identified as among those priorities.

The family of per- and poly-fluoroalkyl substances (PFAS) contains many compounds, including more than 3000 manufactured chemical structures (Wang Z, et al., 2017). Some older or “legacy” PFAS compounds (those PFAS produced historically and commonly represented by larger PFAS compounds), e.g. PFOA and PFOS, have substantial health data and regulatory standards. However, the PFAS family also contains many emerging compounds about which there are few or no health or ecological effects data, and for which there are no regulatory standards. Many of these emerging PFAS compounds have been found as environmental contaminants in North Carolina. GenX is one of the emerging PFAS compounds for which there are no current environmental regulatory standards for water, soil, air or food. However, there are health data regarding GenX that were judged sufficient by DHHS to calculate a “reference dose” (RfD)[5] and provisional health goal (PHG) for drinking water. The state agencies requested the Board examine and provide input on the current reference dose and provisional drinking water health goal for GenX. The Division of Air Quality (DAQ) also identified researching the inhalation risks and potential acceptable ambient levels for GenX and other emerging compounds as their current priorities.

DHHS stated that health data for other emerging PFAS compounds identified in NC were insufficient to calculate a health goal. The Board was asked to consider how or if the presence of the additional compounds may influence the calculation of a GenX provisional health goal for drinking water. The Board was requested to consider a standardized approach for addressing other emerging PFAS with limited health data and establishing provisional health goals for drinking water among its recommendations.

December 4, 2017 – An interim DEQ report and discussion on the GenX investigation and actions taken by DEQ was given. It included the regulatory programs and framework, history of GenX and PFAS production at Chemours-Fayetteville Works site, surface water monitoring results, additional emerging compounds, enforcement actions, groundwater monitoring results, information on air emissions from the Chemours-Fayetteville Works facility, and DEQ’s planned next steps under emerging compounds

DHHS provided documentation describing their role in drinking water recommendations. DHHS gives guidance on public health by conducting health risk assessments, communicating those

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[5] Reference dose (RfD) is a risk assessment term employed by the U.S. EPA to articulate non-cancer, non-mutagenic health-risk effects associated with systemic toxicity study data. The EPA states “In the case of systemic toxicity, however, organic homeostatic, compensating, and adaptive mechanisms exist that must be overcome before a toxic endpoint is manifested.” The EPA defines a reference dose as: “The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.” Source: https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments

risks and giving guidance on the levels of exposure to certain contaminants. When issuing guidance on drinking water, DHHS follows established methodology and rules and uses established reference standards when available. In the event, such as with GenX, when no existing health goal or standard is available, DHHS calculates a provisional health goal for drinking water based on health data available at that time and following methodology endorsed by the U.S. Environmental Protection Agency (EPA). DHHS monitors and may update a provisional health goal for drinking water based on new information provided by laboratory animal studies, epidemiologic studies, or other sources. The DHHS health goal is not legally enforceable.

DHHS also provided information on available GenX health studies relevant to calculating a provisional health goal for drinking water and provided documentation on how the provisional health goal for drinking water for GenX was calculated including the NOAEL used as the point of departure, uncertainty factors, and a relative source contribution.

The Board noted that the methodology used by DHHS to develop the GenX drinking water provisional health goal followed commonly accepted human health risk assessment practices.

January 29, 2018 - Four representatives from the Netherlands, where there is also a Chemours facility using GenX in their production operations, joined the SAB meeting via video conference and shared their process for, and considerations in, calculating their GenX water quality standard of 150 ng/L.

DHHS shared further information about the studies used as the basis of their provisional health goal for GenX and discussed the process and calculations relevant to it. Information shared included the considerations of the POD, uncertainty factors (UF) and modifying factors (MF), relative source contribution (RSC) and physicochemical properties. Information was also shared on other states' calculations for other PFAS health goals and the Netherland's calculation for a GenX health goal. Further, DHHS reported that there were sufficient dose-response data to support benchmark dose modeling, but insufficient data to determine a cancer slope factor. The SAB recommended pursuing bench mark dose modeling to identify a point of departure for the health goal calculation more precise than the one generated with the NOAEL-based approach.

During the meeting the U.S. EPA's Office of Water provided an update on their development of a GenX toxicity value. The EPA also noted they would not be developing a cancer slope factor at this time because of the single available carcinogenicity study, which used the rat model. Prior studies suggest rats are less sensitive than mice to adverse effects associated with some PFAS.

March 19, 2018 - The DEQ shared an update of the groundwater investigations around the Chemours site. DEQ also provided information on GenX emissions, stack testing, and rain water testing. DEQ staff had been working on the groundwater assessment related to the Chemours facility in Bladen County. A major component of that work included groundwater sampling of private drinking water wells by both Chemours and DEQ. DEQ has evaluated the current groundwater data and has looked for sources of the contamination while also evaluating other media that may need further investigation.

DEQ had worked collaboratively with the Departments of Agriculture & Consumer Services (DA&CS) and DHHS to determine next steps regarding other media that may need to be assessed. One component of the collaborative effort included reviewing the literature associated with the presence of perfluorinated compounds in other media.

DEQ presented to the SAB a vegetable garden crops study conducted in the Netherlands (Netherlands 2018). The study was performed at the request of the Netherlands National Institute for Public Health and the Environment per request from the city of Dordrecht. It looked at the presence of GenX in garden crops and addressed: (1) What are the concentrations of GenX and PFOA in selected crops from vegetable gardens in the vicinity of the DuPont Chemours facility in the Netherlands; and (2) Is the allowable daily intake, referred to as the "Tolerable Daily Intake" (TDI), via food from GenX and PFOA exceeded by consumption of vegetable crops in a typical consumption pattern. DEQ staff awaited an English translation of this study, but preliminary information provided indicates that GenX was detectable in home-grown produce grown within 1-kilometer of the Chemours site in the Netherlands, however levels did not exceed health-based limits when looking at average daily intake for individuals. Based on this investigation, health officials in the Netherlands recommended that vegetables within 1-kilometer radius of the plant not be consumed "too often" but recommended no limitations for produce grown beyond a 1-kilometer radius. The results of the Netherlands' produce study do not provide information directly relevant to the North Carolina concern other than as an indication that common home-grown produce may provide an exposure pathway for PFAS released into the environment.

Another study was presented to the SAB by DEQ that had been conducted by the Minnesota Department of Health (Scher et al., 2018). The study began in 2010 in the Minneapolis-St. Paul area where high levels of PFAS were found in drinking water. Sources of drinking water were ultimately utilized for irrigation for residential gardens. The Minnesota study focused on PFOA, PFOS, PFBA, PFBS, PFPeA, PFHxA, and PFHxS[6]. It found uptake and bioaccumulation of PFAS into the terrestrial food chain, represented by home-grown produce, increased as irrigation with PFAS-contaminated water increased. The results confirmed those of other studies indicating that fate and transport of PFAS is predominantly influenced by chain-length and functional group, resulting in the PFAS profile modification as a mixture moves from the source though various environmental compartments, and that short-chain PFAS are more mobile and water soluble than long-chain PFAS. The Minnesota Department of Health (MDH) reported the preferential uptake and bioaccumulation of short-chain PFAS by plants, and that this uptake was PFAS-specific, plant species-specific and plant tissue-specific, with preferential translocation from roots to more distant plant structures generally increasing with decreasing

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[6] PFBA CASN 375-22-4, PFBS CASN 375-73-5, PFPeA CASN 2706-90-3, PFHxA CASN 307-24-4, and PFHxS CASN 355-46-4

chain-length. MDH reported that the home-grown produce in their study area may constitute a “measurable” contribution to overall PFAS exposure for high-level produce consumers in areas where irrigation is with PFAS-contaminated groundwater. These risk evaluations are specific to the exposure conditions and populations included in the MDH study and do not provide information directly relevant to risks specific to North Carolina populations.

DHHS provided information on the Peroxisome Proliferator-Activated Receptor alpha (PPARα) mode of action (MOA) and PPARα-mediated outcomes associated with PFAS in animal studies and the relevance of this mode of action to human health. DHHS described findings that some cancer outcomes in animal studies of PFAS may be mediated by activation of PPARα and may not be relevant to human outcomes. DHHS also noted that PPARα activation has not been confirmed for the hepatocellular necrosis endpoint selected by DHHS as the critical effect for the RfD and calculation of the drinking water provisional health goal. DHHS shared information from the EPA’s PFOA and PFOS Lifetime Health Advisories (EPA 2016a, EPA 2016b) and the U.S. Centers for Disease Control and Prevention’s (CDC) Agency for Toxic Substances and Disease Registry (ATSDR) draft Toxicology Profile for PFAS (ATSDR 2012) which finds evidence of interspecies difference in levels of PPARα expression and responsiveness, and PPARα-independent mechanisms involved in PFOA and PFOS toxicity in non-cancer endpoints such as liver toxicity, including hepatocellular necrosis.

DHHS reported that the U.S. EPA Office of Water and Office of Pollution Prevention and Toxics is working on a GenX reference dose and that DHHS is in communication with EPA as they continue their work.

DHHS presented their progress on the benchmark dose modeling. DHHS staff received training on use of benchmark dose modeling software from U.S. EPA staff. DHHS presented the first stage of the work, which included data tables with each statistically significant endpoint for GenX from the seven available GenX oral toxicity studies (DHHS 2018). The SAB provided guidance on appropriate and significant endpoints relevant to human health and response levels for each endpoint. Recommendations informed what DHHS would use in the benchmark dose modeling and input into the benchmark dose modeling software to provide options for a point of departure.

April 30, 2018 - DEQ presented an update on the continuing investigation of environmental contamination, bioaccumulation, and potential sources of exposure. Well water, groundwater, and soil testing continue. Rain water testing had expanded to a 7-mile radius from the Chemours plant. The full extent of contamination has still not been determined. As part of a pilot study, granulated activated carbon (GAC) filters were to be installed to evaluate the efficacy of this treatment method for PFAS removal. Fish tissue, water, and sediment samples had been collected from a private lake near the facility and were being tested as part of the continuing investigation into environmental contamination and bioaccumulation of GenX and other PFAS.

DHHS reported that it had consulted with U.S. EPA and a member of the SAB and is continuing to work on benchmark dose modeling.

June 18, 2018 - DHHS presented a summary report on the benchmark dose modeling of the available GenX animal studies (DHHS 2018). DHHS requested that the SAB consider the results as they make recommendations about GenX health and regulatory levels in North Carolina. The DHHS noted that the U.S. EPA continued to work toward releasing a GenX RfD this summer.

DEQ, DHHS and DA&CS have continued to collaborate in gathering information related to the presence of perfluorinated compounds in other media. DEQ presented sediment and fish tissue data to the SAB from a preliminary PFAS study of a privately-owned artificial lake near the Chemours-Fayetteville facility (DEQ 2018)**.** Surface water, sediment and three species of fish had been collected in March and April 2018. Fish filet tissue samples were prepared. All samples were analyzed for 33 PFAS. Twenty PFAS were detected in the study, including GenX in the surface water, sediment and one species of fish, Redear Sunfish. DEQ classifies adult Redear Sunfish classified as an insectivorous species (DEQ 2014) and they are noted as opportunistic feeders, foraging mostly on aquatic clams and snails in native habitats (WRC 2018). The same 16 PFAS, the highest number of PFAS detected in the sampled media, were detected in the lake surface water and water collected from a surface spring that flows into the lake. The 16 PFAS detected in the water samples included PFOA and PFOS, as well as short-chain and long-chain PFAS. GenX was the only PFAS detected in the lake sediment. PFOS was also detected in the Redear Sunfish 7-fish composite and two composite samples of Largemouth Bass, each made-up of fish of a different size range (a 5-fish composite of smaller fish and a 2-fish composite of larger, presumably older, fish). Four additional long-chain "legacy" PFAS (11, 12, 13 and 14-chain PFAS) were detected in the two Largemouth Bass samples and a sample from a single Blue Catfish.

Section 5 – Adoption of a Non-Cancer Approach to GenX Health Effects

As stated above, DHHS noted there were insufficient data from the available toxicology studies to quantitatively assess a cancer endpoint related to GenX exposures. There exists a single 2-year rat carcinogenicity study. Rats have been observed to be less sensitive to some PFAS-associated adverse effects than mice. DHHS used non-cancer endpoints identified in the available animal studies, which are assumed to have a threshold below which there are no observable adverse effects due to homeostatic and adaptive mechanisms. The U.S. EPA Integrated Risk Information System (IRIS)[7] program provides a discussion of the approach for assessing risks for health effects other than cancer and gene mutations from chronic chemical

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[7] IRIS is the U.S. EPA's Integrated Risk Information System. The IRIS Program supports EPA's mission is to protect human health and the environment by identifying and characterizing the health hazards of chemicals found in the environment. Available at: https://www.epa.gov/iris

exposures[8]. EPA states, "*Chemicals that give rise to toxic endpoints other than cancer and gene mutations are often referred to as "systemic toxicants" because of their effects on the function of various organ systems. In addition, chemicals that cause cancer and gene mutations also commonly evoke other toxic effects (i.e., systemic toxicity). Based on our understanding of homeostatic and adaptive mechanisms, systemic toxicity is treated as if there is an identifiable exposure threshold (both for the individual and for populations) below which there are no observable adverse effects. This characteristic distinguishes systemic endpoints from carcinogenic and mutagenic endpoints, which are often treated as nonthreshold processes.*"

The Board identifies that the appropriate approach to determining a safe concentration for a chemical in drinking-water depends on how it causes harm. The Board determined that data were insufficient to establish whether GenX is a human carcinogen. The Board judged that based on the available evidence the most sensitive endpoint for GenX observed in multiple studies is a non-cancer endpoint (hepatocellular single cell necrosis), i.e., that there is some level of exposure below which does not represent a non-cancer risk to human health, and recommends that the U.S. EPA approach for assessing threshold non-cancer risks be applied.

Section 6 – Derivation of the GenX Reference Dose

It is necessary to identify the daily oral exposure amount below which a chemical would not cause adverse health effects if consumed for a lifetime. This is called the reference dose (RfD). The EPA defines a reference dose as "*An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's non-cancer health assessments*."[9]

To calculate a reference dose, DHHS reviewed seven repeat oral dose studies in rodents of 28 days or longer that were provided by Chemours/DuPont during the U.S. EPA Toxic Substances Control Act (TSCA)[10] review process (DHHS 2018). DHHS focused on repeat oral dose studies because this is most applicable to long-term human exposure from drinking water. DHHS consulted with toxicologists and risk assessors at U.S. EPA, the National Institute of Environmental Health Sciences (NIEHS), and ATSDR to identify applicable toxicology information and risk assessment procedures.

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[8] Accessed at https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments

[9] Source: U.S. EPA IRIS Glossary, accessed at: https://iaspub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&vocabName=IRIS%20Glossary#formTop

[10] Under the Toxic Substances Control Act (TSCA) and the Pollution Prevention Act, EPA evaluates potential risks from new and existing chemicals and finds ways to prevent or reduce pollution before it gets into the environment. U.S. EPA TSCA program web-page available at: https://www.epa.gov/chemicals-under-tsca

The first step in calculating a RfD is to identify a point of departure (POD). DHHS released an initial assessment of GenX in drinking water that used a no observed adverse effect level (NOAEL) of 1.0 mg/kg-day from a 2-year chronic study in rats as the POD (DHHS 2017). After further review of the repeat oral dose studies and conversation with experts at U.S. EPA, an updated assessment was provided in July 2017 that identified the NOAEL of 0.1 mg/kg-day for liver toxicity endpoints from two sub-chronic studies in mice (28-day study and a reproductive screen) as a more appropriate POD for calculation of a provisional health goal (PHG) for GenX in drinking water (DHHS 2017). The sub-chronic studies were chosen as the critical studies because they demonstrated adverse effects at the lowest doses tested and the effects were seen across multiple studies at the same or similar doses. DHHS subsequently used the NOAEL of 0.1 mg/kg-day as the POD for calculations of the RfD.

DHHS used the default uncertainty factors (UFs) recommended by U.S. EPA to derive a RfD from the POD. An expanded discussion of default U.S. EPA uncertainty factors is provided in Appendix A. DHHS did not apply a modifying factor (MF) because NOAELs from multiple studies were identical, or within the same order of magnitude, with similar health endpoints (liver toxicity). Additionally, DHHS staff concluded that the uncertainty factors discussed below adequately addressed the uncertainties of the database. The default uncertainty factors used were the following:

- Sub-chronic to chronic uncertainty factor (UF_S): A factor of 10 to account for the uncertainty involved in extrapolating from less than chronic NOAELs to chronic NOAELs
- Interspecies uncertainty factor (UF_A): A factor of 10 to account for the uncertainty involved in extrapolating from animal data to humans
- Intraspecies uncertainty factor (UF_H): A factor of 10 to account for the variation in sensitivity among the members of the human population

The RfD was calculated to be 0.0001 mg/kg-day by dividing the point of departure by the uncertainty factors.

$$\text{RfD, mg/kg-day} = (\text{POD, mg/kg-d}) / (UF_S \times UF_A \times UF_H)$$

$$0.0001 \text{ mg/kg-day} = 0.1 \text{ mg/kg-d} / (10 \times 10 \times 10)$$

DHHS presented the process used to calculate the provisional health goal for GenX in drinking water to the SAB during the October 23, 2017 meeting. In response to a request from the Board, DHHS compiled data from the seven repeat oral dose studies to be used in benchmark dose (BMD) modeling to potentially refine the point of departure (DHHS 2018). The benchmark dose approach conveys more dose-response information than the NOAEL-approach and applies EPA's BMD software for the analysis and modeling of dose-response relationships to identify dose levels corresponding to specific response levels near the low-end of the observable range of the data (EPA 2012). The benchmark dose-response assessment involves defining the POD and extrapolating from the POD to a response level of relevance for human exposures (the Benchmark Response, BMR). Benchmark dose lower bound (BMDL) values may be used rather than NOAELs or lowest observed adverse effect levels (LOAELs) as the point of departure for derivation of toxicity values such as a reference dose. Benchmark dose modeling work was completed by DHHS in May 2018 and presented to the SAB during the June 18, 2018 meeting.

The modeled BMDLs for selected endpoints were presented by DHHS, while they cautioned that some of these values may be inappropriate to consider as a POD since the endpoints had very large BMD-to-BMDL ratios, indicating poor model fit and a large confidence interval on the BMD and perhaps inadequate data for modeling these endpoints (EPA 2012). The Board recommended refining the modeled BMDL ranges to exclude those with BMD-to-BMDL ratios >20. The refined range of BMDLs modeled by DHHS is 0.0492 to 25.3 mg/kg-day for selected hematology endpoints, 0.151 to 5.55 mg/kg-day for selected hepatic endpoints, and 3.06 to 635 mg/kg-day for selected developmental endpoints. A full report of the benchmark dose modeling efforts, results and limitations can be found in a separate document provided to the SAB on May 26, 2018 (DHHS 2018).

Based on available evidence, and calculations undertaken by DHHS staff on the request of the Board, the Board recommends the provisional reference dose (RfD) of 0.0001 mg/kg-day. The Board considers this is a reasonable health-based target action level for the state. The benchmark dose modeling effort generated a range of POD that were consistent with the NOAEL approach. As additional studies on the health effects associated with GenX become available, and the U.S. EPA's development of a GenX toxicity value is completed, review and refinement of the RfD and the drinking water provisional health goal (PHG) should be undertaken by the agencies.

Section 7 – Calculation of the DHHS GenX Provisional Health Goal for Drinking Water

To be protective of sensitive life-stages DHHS used the 95th percentile water intake and average body weight for a bottle-fed infant for calculation of a provisional health goal for GenX in drinking water. Bottle-fed infants drink more water compared to their body weight than other age groups and are therefore considered a sensitive sub-group for drinking water exposures.

In calculating health goals for exposure from drinking water, it is necessary to consider other routes of potential exposure, including air and food for example. GenX has been measured in samples of food (specifically fish) and rainwater in North Carolina, however data on the extent of exposure from these other routes is limited. DHHS used a relative source contribution (RSC) of 20% to account for other possible routes of exposure, consistent with EPA guidance (EPA 2000) when data on the extent of exposure from other routes are few. Use of this relative source contribution allocates 80% of a person's GenX exposure to sources other than drinking water.

Applying these factors, the DHHS provisional health goal for GenX in drinking water was calculated as 140 ng/L (DHHS 2017). This level is not a boundary line between a “safe” and “dangerous” level of a chemical but represents the concentration of GenX in drinking water at which no adverse non-cancer health effects would be anticipated over an entire lifetime of exposure. The provisional health goal for GenX in drinking water is subject to change based on new information but was calculated with the best currently available information and using default factors when specific information is limited. For more details and information on the calculation of the provisional health goal, see https://ncdenr.s3.amazonaws.com/s3fs-public/GenX/NC%20DHHS%20Risk%20Assessment%20FAQ%20Final%20Clean%20071417%20PM.pdf.

140 ng/L PHG = (0.0001 mg/kg-day RfD x 7.8 kg BW_{infant})/1.1 L/day IR_{infant} x 1E06 ng/mg x 0.2 RSC

Where:

PHG = DHHS drinking water Provisional Health Goal, nanograms per liter, protective of bottle-fed infants
RfD = Reference dose in milligrams GenX per kilogram body weight per day
BW_{infant} = Body weight, 7.8 kilograms for a bottle-fed infant (birth to 12 months of age)
IR = Intake rate of drinking water for a bottle-fed infant, 1.1 liters per day
1E06 = 1,000,000 nanograms per milligram conversion factor
RSC = Relative Source Contribution, proportion of total GenX exposure from drinking water, 0.2
RSC = U.S. EPA drinking water default value

The DHHS GenX PHG of 140 ng/L relates to the 150 ng/L water quality standard for GenX developed by the Netherlands Institute for Public Health and the Environment and presented to the Board at the January 29, 2018 meeting. The Netherlands group noted they used a 0.1 mg/kg-day point of departure from a chronic study in rats as it was the longest exposure study available. The study reported effects to the liver, changes in albumin level and the albumin/globulin ratio at the lowest effect level (LOAEL). The Netherlands agency applied an additional safety factor to adjust for possible toxicokinetic differences between humans and the GenX study test species, as to reflect difference reported for PFOA. The toxicokinetics adjustment factor was calculated as the difference in the elimination half-life of PFOA in humans to monkeys. The Netherlands agency staff stated application of the toxicokinetics factor was supported by the chemical similarity of PFOA and GenX, the similarity in toxicological effects for the two chemicals and indications of half-life differences among humans and other species reported for other PFAS compounds. Other factors applied in their calculation included a factor of 10 for human population sensitivity variation (interspecies variability) and a 20% factor for the total allowed daily uptake for water (2 liters per day for a 70 kg adult).

The Board noted the exposure of an adult consuming drinking water contaminated with GenX at the provisional health goal concentration of 140 ng/L and assuming EPA-referenced default exposure parameters (70 kg body weight and 2 liters per day water intake) and 100% of the

GenX exposure from drinking water indicates an adult exposure dose equal to 1/25th of the reference dose (0.0001 mg/kg-day GenX RfD) calculated by DHHS. This calculation indicates an additional margin of safety for an adult consumer ingesting drinking water contaminated with GenX at the PHG level, as the PHG was calculated to be protective of a bottle-fed infant representing the population group with the highest water intake per body weight.

$$(140\text{ ng/L GenX} \times 2\text{ L/day } IR_{adult})/70\text{ kg } BW_{adult} \times 1E06\text{ ng/mg} = 4E\text{-}06\text{ mg/kg-day adult dose}$$

$$(1E\text{-}04\text{ mg/kg-day RfD})/(4E\text{-}06\text{ mg/kg-day adult dose}) = 25$$

Where:

IR_{adult} = Intake rate of drinking water for an adult, 2 liters per day
BW_{adult} = Body weight, 70 kilograms for an adult

The Board judges that the U.S. EPA default assumption that 20% of exposure be attributed to drinking-water is appropriate and common U.S. EPA default values for consumption and body weight were also used for the calculation of the GenX point of departure, reference dose and the drinking water provisional health goal. The Board judges that protection of the most susceptible segment of the population, that is the group with the greatest water intake to body weight, bottle-fed infants, is appropriate.

Section 8 – Ecological, Produce and Air Concerns

Ecological implications of GenX exposure are poorly understood in the natural environment because there is very little environmental monitoring data on invertebrate, fish and wildlife receptors. Laboratory studies on GenX accumulation in common carp (28-day bioconcentration factor[11], BCF <30 L/kg-tissue) and toxicity to green algae (72-hour no observed effect concentration (NOEC) >107 mg/L), daphnids (21-day NOEC for reproduction 4.17 mg/L), and fishes including Japanese medaka (96-hour EC50 >100 mg/L)[12], rare gudgeon (96-hour EC50 >150 mg/L) and rainbow trout (90-day reproduction NOEC of 8.9 mg/L) (Hoke et al., 2016) indicate adverse effects at exposures much higher than reported environmental concentrations. There was no effect on bobwhite quail at dietary concentrations up to 100 mg/kg (Newsted et al., 2008). The extent to which these commonly tested species are

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[11] A Bioconcentration Factor (BCF) is a proportionality constant relating the chemical concentration in fish to the concentration in water under steady-state conditions. It measures the tendency of a chemical to accumulate in fish. Measurements of BCFs are generally undertaken in a controlled laboratory environment.

[12] EC50 is the "effect concentration" of a test substance that results in specified effect to 50% of the test population. Common measured effects include mortality, reduced growth or reduced reproduction. Source: https://iaspub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&vocabName=IRIS%20Glossary#formTop

adequate surrogates for the diversity of free-living invertebrates, fish, and wildlife in the Cape Fear basin is unknown.

The Board heard in March and April 2018 DEQ collected surface water, sediment and fish from a privately-owned lake less than 1-mile from the Chemours facility for a limited PFAS study (DEQ 2018). The study identified 20 different PFAS in the study samples of the 33 PFAS included in the target analyte list. GenX was detected in the lake surface water (968 ng/L), a surface spring feeding the lake (1160 ng/L) and in the lake surface sediment (1,800 ng/kg dry weight sediment). GenX was also detected in one of three species of fish collected from the lake, the 7-fish Redear Sunfish filet composite (270 ng/kg wet weight tissue). Five other PFAS were also detected in the three-fish species, including the legacy 8-carbon PFOS, as well as the legacy 11, 12, 13 and 14-carbon PFAS compounds PFUdA, PFDoA, PFTrDA and PFTeDA[13] (361 to 2840 ng/kg-wet weight). These data indicate the current-use and historical PFAS are present in environmental compartments in the area near the Chemours facility and may be attributed to releases from the Fayetteville facility.

There is little information on ecological toxicity benchmarks for these and most other PFAS, limiting our ability to assess potential ecological harm related to individual PFAS exposures, or to mixtures of PFAS compounds which may occur in areas where these compounds are manufactured or used in production. There is also inadequate information on the potential for ecological effects associated with additive, long-term exposures to sensitive receptors.

Measured air emissions of the GenX compounds from some of the processes at the Chemours/DuPont plant are significantly higher than previously understood or reported. GenX has also been measured in rainwater as far as 20 miles downwind of the facility, indicating atmospheric transport and deposition of this compound. Testing of private drinking water wells near but upgradient of the Chemours/DuPont plant has shown concentrations of GenX. The combination of environmental measurements and analysis by DEQ strongly indicate a causal link between GenX air emissions and widespread groundwater degradation near the Chemours/DuPont plant.

Section 9 – The Significance of the Circumstances

Board members heard compelling testimony from citizens, some clearly distressed, expressing profound concern for their health and that of their family members and others. The degree of public concern calls for action by the state to promote safe environmental conditions and to give practical guidance to those who are concerned to protect their own health and that of their family and community, especially more vulnerable persons. Large centers of population that are, or have been, exposed (such as those of the Lower Cape Fear Basin), and people with

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[13] PFUdA CASN 2058-94-8, PFDoA CASN 307-55-1, PFTrDA CASN 72629-94-8, PFTeDA CASN 376-06-7

high levels and multi-media exposure (such as those living close to the Chemours plant in Fayetteville), are of special concern.

Comprehensive characterization of PFAS present in the environment and identification of all routes of exposure, and the implications of additive exposures are desirable, but the evidence needed to undertake these tasks is not currently available. Agencies and organizations with the capacity to persuade and facilitate the acquisition of this knowledge are urged to do so to enhance protection of human health and the environment. Studies are needed to characterize current and changes to PFAS burdens in nearby environmental matrices that may serve as long-term sources of PFAS to the local and regional environment, even as local emission sources to the environment may be controlled. In circumstances where concentrations observed in environmental matrices may not have implications to the health of non-human ecosystem components, these concentrations may provide long-term sources of exposure to sensitive human receptors through uptake by plants, animals or fishes consumed by humans.

Section 10 - Recommendations in Response to the Board's Charge for GenX

The Board recommends the reference dose developed by DHHS to DEQ as the foundation for establishing health-protective environmental standards including for groundwater and surface water.

The Board recommends the use of the current reference dose and provisional health goal developed by DHHS as the foundation for protecting affected and sensitive populations and providing corresponding risk assessments and advice.

NC DHHS developed a health-protective provisional health goal for drinking water for the most vulnerable population exposed to GenX using the best available science as federal and state standards were not available. DHHS followed the Board's recommendation to further evaluate the provisional health goal developmental process by using benchmark dose modeling to possibly refine the point of departure.

Section 11 – Other Recommendations

GenX is an 'emerging hazard', meaning one about which current scientific studies are few and new information is being produced. The Board judges that the available evidence is adequate to inform the adoption of the reference dose and the provisional health goal described here. Because there is ongoing research in North Carolina, nationally and internationally, and there are likely to be other studies:

- The DEQ and DHHS encourage and support efforts to more fully understand the impacts of Gen X and long-term additive exposures to mixtures of PFAS, including their persistence, environmental fate, and effects on human health and ecological receptors.
- The Board recommends re-opening and updating this document as health values for GenX or other PFAS become available from the U.S. EPA, with consideration of utilizing benchmark dose modeling data to identify a range of risk values applicable.
- The Board counsels that the recommendations made here be reviewed within three years by the Board and Departments with a view to ensuring the adequacy of health protection and the efficacy of control measures. This will require ongoing monitoring and evaluation of environment and health conditions by the Departments.
- That DEQ and DHHS collaborate with the NC Department of Agriculture and Consumer Services and others to improve understanding of the relevance to local populations of exposure to GenX through foodstuffs, in particular with a view to determining whether standards for foodstuffs and/or guidance to local populations on food-related exposures are necessary and can be scientifically justified.
- That GenX and other PFAS releases to the air be characterized to evaluate inhalation exposures for humans, as well as the implications for contamination of soil, surface water, groundwater and the food web.
- That the Departments recognize the concern of population members that exposure to GenX has occurred concurrent with exposure to other related emissions from the Chemours/DuPont plant and support efforts to understand possible interaction among the toxicity of and exposure to the associated chemicals and potential approaches to their combined regulation.
- That the Departments further recognize the concern of population members about the accumulation of these chemicals in the environment (for example in soils, river sediments and through bioaccumulation in animals) causing continuing human exposure.
- A possible alternative to limit exposure to Gen X to the greatest extent possible would be to use the Practical Quantitation Limit (PQL), which is defined purely as the lowest concentration of a contaminant that can be reliably detected within specified limits of precision and accuracy during routine laboratory operating conditions. This report would not preclude the policy decision to adopt a PQL as the regulatory standard, however the charge of this Advisory Board was to recommend a science and risk based level that would be health protective for Gen X.

Figure

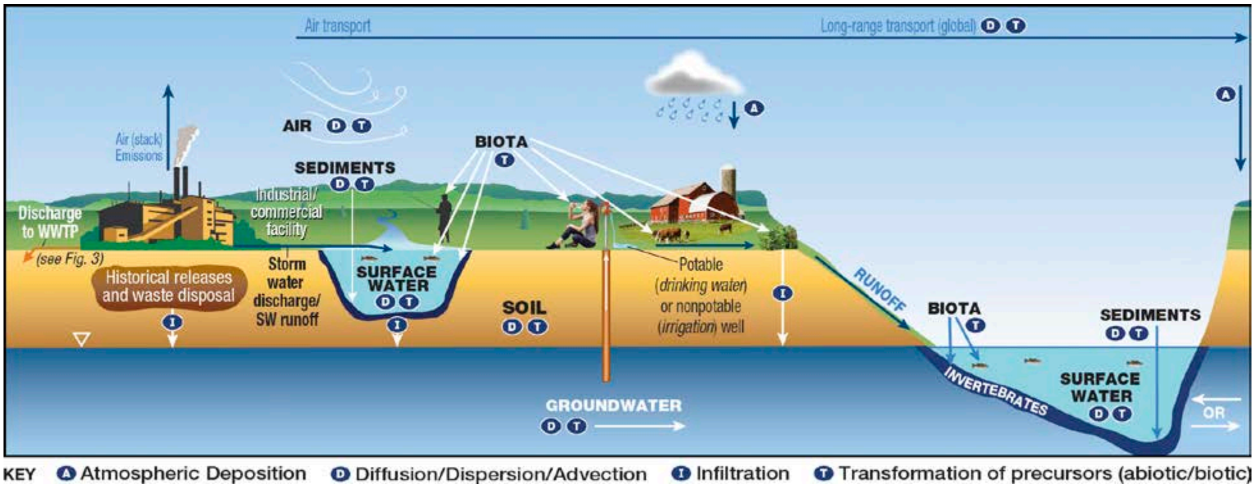

Figure 1. PFAS industrial source conceptual site model. Source: *Environmental Fate and Transport for Per- and Polyfluorinated Substances*. Interstate Technology and Regulatory Council (ITRC), Washington, DC. March 2018. https://pfas-1.itrcweb.org/

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Appendix A

Review of Uncertainty Factors Used in Calculation of the NC DHHS Provisional Drinking Water Health Goal for GenX

Review of Uncertainty Factors (UFs) Used in Calculation of the NC DHHS Provisional Drinking Water Health Goal for GenX

Standard uncertainty factors and modifying factors (Section 1.2.2.2.4: https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments)

i. Intraspecies UF: Factor of 10 to account for the variation in sensitivity among the members of the human population. In general, intraspecies variability in sensitivity to toxic effects can be due to a variety of factors, including age, sex, disease status, nutrition, genetics, etc.

   Used in GenX Provisional Health Goal calculation to account for potential sensitivity differences within the human population. There is no information available to justify use of any number besides the default factor of 10.

ii. Interspecies UF: Factor of 10 to account for the uncertainty involved in extrapolating from animal data to humans. Interspecies differences in sensitivity to toxic effects can be due to a variety of factors such as difference in metabolism and kinetics.

   Used in GenX Provisional Health Goal calculation (only rat and mice studies available). There is a large interspecies difference in half-life of legacy PFAS such as PFOS and PFOA, but there is not enough information to determine if this large interspecies variability would also occur with GenX. In the absence of data on the human half-life for GenX, DHHS used the default interspecies uncertainty factor of 10.

   DHHS was recently made aware that in the absence of PBPK modeling or chemical-specific data, EPA accounts for interspecies differences in calculating oral reference doses using allometric scaling, as outlined in a guidance document titled "Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose". This approach uses a dosimetric adjustment factor and a reduced interspecies uncertainty factor to replace the former default interspecies uncertainty factor of 10. DHHS is including this information in the interest of providing the SAB with all information needed to make fully informed recommendations.

iii. Sub chronic-chronic UF: Factor of 10 to account for the uncertainty involved in extrapolating from less than chronic NOAELs to chronic NOAELs. It is generally assumed that longer exposure times would result in adverse effects at lower concentrations due to accumulation of the toxicant or inability of an organism to repair injury from the substance.

   Used in GenX Provisional Health Goal calculation because the NOAEL from 28-day mice study and a reproductive screen in mice with a sub-chronic exposure duration was used as opposed to a NOAEL from a chronic (ex: 2 year) study. Sub-chronic *studies were used because adverse effects were observed at lower doses, and these effects were consistently seen across multiple studies at the same or similar doses (ex: the 90-day study in mice and the 90-day study in rats). To be health protective, studies with adverse effects at the lowest doses tested were used as the critical studies for determining the point of departure.*

iv. LOAEL-NOAEL UF: Factor of 10 to account for the uncertainty involved in extrapolating from LOAELs to NOAELs.

Not used in GenX Provisional Health Goal calculation because NOAELs were available so an additional uncertainty factor was deemed unnecessary.

v. Modifying factor: additional uncertainty factor that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and data base not explicitly treated above; e.g., the completeness of the overall data base and the number of species tested. The default value for the MF is 1.

Not used in GenX Provisional Health Goal calculation. Professional judgement from DHHS staff determined that a modifying factor was not necessary based on the following justification: Seven repeated dose oral studies ≥ 28 days in duration in two rodent species were reviewed, including a 2-year chronic study in rats and a reproductive/developmental toxicity screen in mice. NOAELs from several studies were identical or within the same order of magnitude with identical or similar health endpoints (liver toxicity). Additionally, DHHS staff concluded that the uncertainty factors discussed above adequately addressed the uncertainties of the database.

Appendix B

Benchmark Dose Modeling Report for GenX

NC DHHS

May 26, 2018

BENCHMARK DOSE MODELING REPORT FOR GENX

Prepared by:
Occupational and Environmental Epidemiology Branch
Epidemiology Section
Division of Public Health
Department of Health and Human Services

Prepared for:
North Carolina Secretaries' Science Advisory Board

May 26, 2018

Contents

Purpose

This report was prepared by staff in the Occupational and Environmental Epidemiology Branch (OEEB) of the North Carolina Division of Public Health (DPH), Department of Health and Human Services (DHHS). The purpose of this report is to provide the Secretaries' Science Advisory Board (SAB) with the results of benchmark dose modeling of certain priority endpoints for GenX in a timely and succinct manner. This report was created in response to a request from the North Carolina SAB during their review of the DHHS provisional health goal for GenX in drinking water. Benchmark dose modeling was requested to help refine the point of departure for calculating reference doses. This report is not intended to provide a comprehensive review of all scientific information available for GenX, but rather to provide the SAB with a matrix of BMDL values to consider when making recommendations regarding health or regulatory levels for GenX in the state of North Carolina.

Background

In June 2017, the N.C. DHHS was notified of a chemical called GenX found in drinking water sourced from the lower Cape Fear River. GenX refers to the hexafluoropropylene oxide dimer acid (CASRN 13252-13-6) and its ammonium salt (CASRN 62037-80-3) (Figure 1). In solution, both dissociate into the same anion.

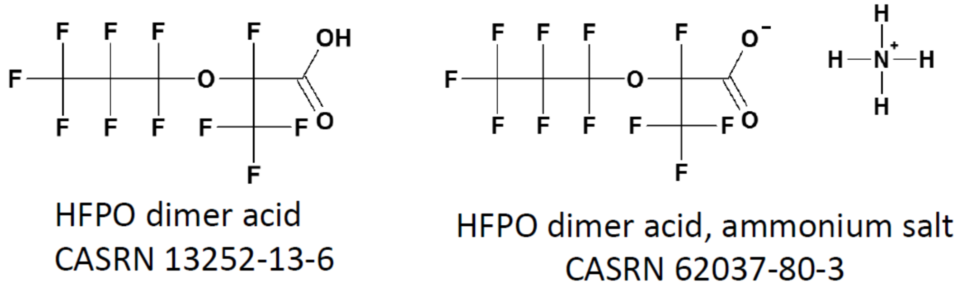

Figure 1. Chemical structure of the GenX chemicals.

In response to reports of this and other per- and polyfluoroalkyl substances in the Cape Fear River, N.C. DHHS began to compile and review available toxicological information and consult with federal partners such as the U.S. Environmental Protection Agency (EPA). In July 2017, N.C. DHHS issued a provisional health goal for GenX in drinking water of 140 nanograms per liter (ng/L, or parts per trillion (ppt)). The provisional health goal was based on a point of departure from a No Observed Adverse Effects Level (NOAEL) of 0.1 mg/kg/day from two sub-chronic studies in mice provided by the chemical manufacturer (a 28-day repeat oral dose study and a reproductive and developmental toxicity screen). Sensitive adverse effects observed at doses higher than 0.1 mg/kg/day included liver effects such as single cell hepatocellular necrosis.

In the fall of 2017, the provisional health goal was brought before the SAB for their review. The SAB recommended benchmark dose modeling using the EPA's Benchmark Dose Software to better refine the point of departure. The following report presents the efforts of OEEB staff to conduct benchmark dose modeling for SAB consideration in their review of GenX in North Carolina.

Toxicity Study and Endpoint Selection

OEEB focused on studies provided by the registrant (i.e. the chemical manufacturer) because the reports provided sufficient information on dosing levels (controls + 3 treated dose levels) and responses (incidence numbers or means and standard deviations). Currently, there is limited information in the published peer-reviewed literature regarding the toxicity of GenX that provides the level of detail necessary for benchmark dose modeling[1]. Full reports of the studies provided by the registrant are available online in the N.C. Department of Environmental Quality electronic document repository[2].

The registrant provided seven repeat oral dose studies in rodents with exposure durations of 28-days or longer. These studies are as follows:

- 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery (28-day mice)
- 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery (28-day rats)
- H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice (90-day mice)
- 90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery (90-day rats)
- H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats (2-year rats)
- Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice (Reproductive screen mice)
- Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats (Prenatal and developmental rats)

OEEB first compiled all dose-response data for endpoints that showed a statistically significant response between the control and treated animals in all seven studies (OEEB 2018). OEEB relied on the registrant's statistical analysis in compiling these endpoints. Additionally, endpoints for which no statistical analysis was performed (i.e. pathology data) were included if an apparent dose-response trend existed. Some of these endpoints were deemed by the registrant to be either non-adverse or not considered related to the test substance. OEEB considered all statistically significant endpoints in its review, regardless of registrant determinations of relevance.

OEEB then reviewed the previously compiled data for the following to narrow down the endpoints to be modeled:

- an apparent dose-response trend,
- sensitivity and adversity of the endpoint,
- the endpoint's relevance to human health,
- the magnitude of response for each endpoint, and;
- consistency in the response for each endpoint across studies.

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[1] Primary literature on toxic effects of GenX that are not based on data provided in the seven registrant studies include Wang et al 2017, Rushing et al 2017, and Sheng et al 2018. Wang et al 2017 only used one dose group, which is insufficient for benchmark dose modeling. Sheng et al 2018 is an in vitro study and chemical specific information to translate in vitro exposure levels to external doses for modeling is unavailable. Rushing et al 2017 uses three dose groups plus a control group, but the identified NOAEL for liver effects from that study is 1 mg/kg/day, which is an order of magnitude higher than the most sensitive effects seen in the registrant provided literature. Rushing et al 2017 also looked at immune effects, with a NOAEL of 10 mg/kg/day for these effects.

[2] https://edocs.deq.nc.gov/WaterResources/Browse.aspx?dbid=0&startid=624254&row=1&cr=1

During this process, OEEB consulted with a member of the SAB and partners at the U.S. Environmental Protection Agency (EPA) regarding interpretation of toxic endpoints, relevance of endpoints to human health, and benchmark dose guidance.

This detailed review led OEEB to further narrow its modeling efforts to a subset of hepatic, hematological, and developmental endpoints. Hepatic and hematological endpoints were chosen because these effects were consistently observed at similar dose levels across studies, and often at lower doses than other endpoints. Hepatic effects chosen for modeling include hepatocellular necrosis and increases in liver enzymes and liver weights. Hematological effects chosen for modeling include changes in red blood cell parameters such as decreases in hemoglobin and hematocrit. Developmental endpoints were included in modeling to address concerns about the potential for GenX to cause adverse developmental effects in exposed infants and children. This age group is considered to be a sensitive population due to physiological and behavioral differences from adults. Developmental effects chosen for modeling include decreased offspring weight and an increase in skeletal variations in offspring exposed to high doses of GenX in utero.

A few other considerations were taken into account for narrowing the endpoints to be modeled. For endpoints where clear sex-specific differences were observed, response data for the more sensitive sex was used for modeling. Sex-specific differences were considered to be present if statistically significant effects were seen in only one sex, or if the effect was seen at lower doses in one sex. Additionally, in the two-year rat study some endpoints were measured at multiple time points throughout the study. Only the latest time point with a statistically significant difference between the control and treatment animals was used in modeling to be more representative of long term exposure. In the two-year rat study, some hematological effects appeared to be transient, in that they appeared significant at earlier timepoints but not at later timepoints. In these cases, the latest timepoint with statically significant changes was used for modeling. Appendix A includes data tables for all modeled data.

It is worth noting that other adverse effects were observed in toxicity studies but not selected for modeling in this analysis. Hepatocellular hypertrophy was not modeled because single cell hepatocellular necrosis was chosen as a more representative adverse effect on the liver. Other liver histopathology endpoints, such as focal hepatocellular necrosis, were not observed consistently across studies and therefore were not modeled. Increased kidney weight was observed in several studies, but this was not modeled because increased liver weight was observed at lower doses in those studies and was determined to be a more sensitive endpoint. Histopathology changes in the kidney and increased adrenal gland weight were only observed in one study and therefore were not modeled.

Benchmark Dose Modeling Methods

Staff from OEEB used EPA's Benchmark Dose Software (BMDS), version 2.7.0.4, which is available for free download at https://www.epa.gov/bmds. The BMDS Wizard is available as part of this download. The BMDS Wizard is an Excel-based tool that allows for multiple modeling session to be run in BMDS at one time. The BMDS Wizard (version 1.11) was used for all modeling and analysis and to create the output reports presented in Appendix B. The standard benchmark response (BMR) was chosen for each endpoint based on guidance from the SAB and the EPA BMDS guidance document (EPA 2012). For dichotomous data, the standard BMR is 10% extra risk. For continuous data, the standard BMR is a one standard deviation change from the control mean. The benchmark dose lower bound (BMDL) is the lower end of a one-sided confidence limit on the benchmark dose, with the standard confidence level of 95%. OEEB did not alter any model parameters in the BMDS Wizard.

To review the BMDS Wizard results, OEEB used the BMD decision tree (Figure 2) found in the EPA Benchmark Dose Technical Guidance (EPA 2012).

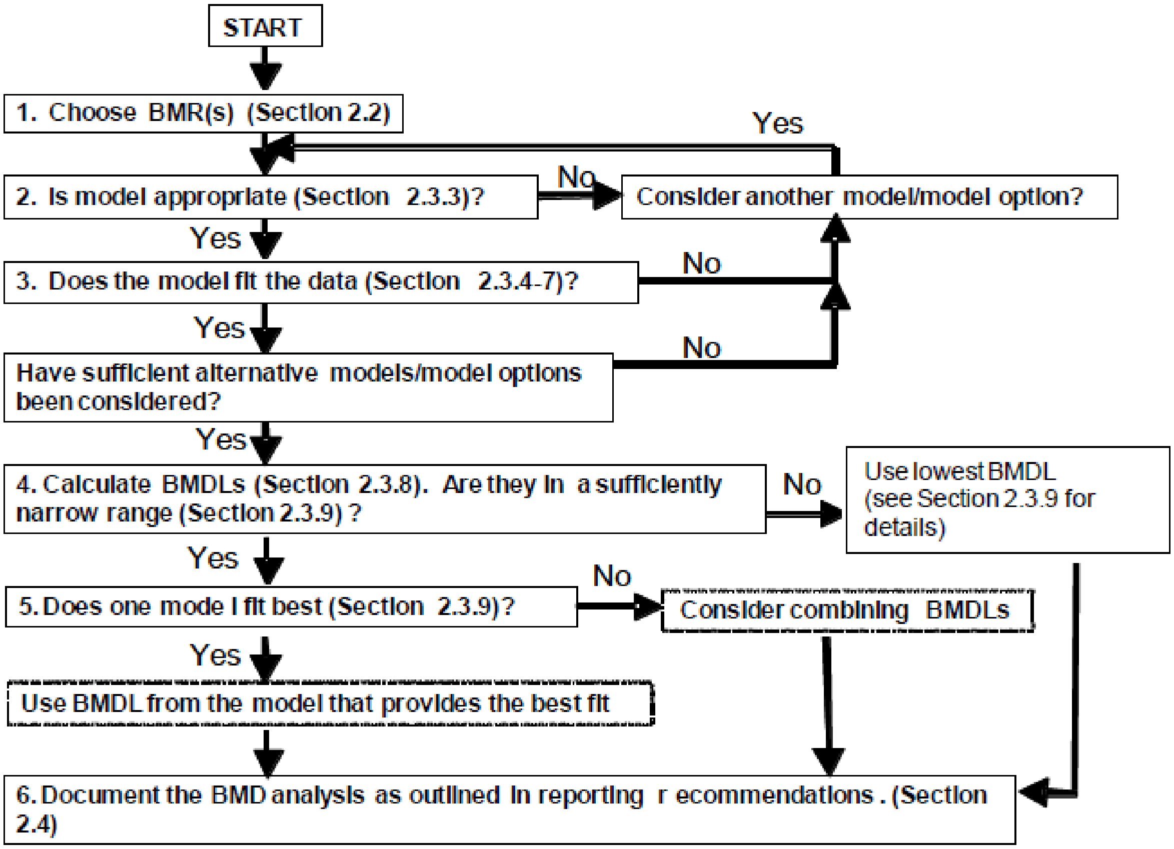

Figure 2. EPA Benchmark Dose Technical Guidance Decision Tree (EPA 2012)

When reviewing model fit, OEEB looked at the following criteria per the BMD technical guidance:

- Goodness-of-fit p-value: models with a goodness-of-fit p-value <0.1 were discarded
- Local measurement: Models with scaled residuals with absolute values > 2.0 were discarded
- Variance modeling (continuous data only):
    - If the Test 2 p-value > 0.1, then the variance of the data is constant and models using constant variance were chosen.
    - If the Test 2 p-value is <0.1 and the Test 3 p-value is >0.1, then the variance of the data is not constant and models using modeled variance were chosen.
    - If the Test 2 p-value is <0.1 and the Test 3 p-value is <0.1, then OEEB determined the data was not adequate for modeling and no BMDL could be calculated.
- Visual inspection of the model results

Only models meeting all model fit criteria were included for selection of the BMDL. The models included in the output reports in Appendix B are only those meeting the above model fit criteria. All models that fit the data were then compared to select a BMDL for each endpoint modeled. If the BMDLs from each model were sufficiently close (< 3-fold difference), then the BMDL from the least complex model, or model with the lowest Akaike's Information Criterion (AIC), was selected. If the BMDLs were not sufficiently close (> 3-fold difference), then the lowest BMDL was selected.

Output reports were created using the report function in the BMDS Wizard. BMD-to-BMDL ratios were added to these reports to illustrate the size of the confidence intervals. A large BMD-to-BMDL ratio may indicate poor data quality for modeling purposes.

Benchmark Dose Modeling Results

Table 1 below summarizes the selected BMDLs for modeled endpoints across all seven studies with NOAELs for each endpoint included for comparison. BMDs, BMD-to-BMDL ratio, and model visualizations for each modeled endpoint can be found in the Wizard output reports in Appendix B. BMDLs from selected endpoints ranged from 0.00589 to 635 mg/kg/day across studies and endpoints. It is important to note that several endpoints, including the three endpoints with the lowest BMDLs, have very large BMD-to-BMDL ratios, indicating a large confidence interval on the BMD and perhaps inadequate data for modeling these endpoints. The BMDS Wizard automatically flags any BMDL that has a BMD-to-BMDL ratio greater than five.

For hematological effects, BMDLs ranged from 0.00589 to 25.3 mg/kg/day across studies. Decreased hematocrit in males from the 28-day mice study resulted in the lowest BMDL of 0.00589 mg/kg/day, but the BMD-to-BMDL ratio for this endpoint from this study is 20.7. The lowest hematological BMDL without a flag is 0.357 mg/kg/day for decreased hematocrit in males from the 28-day rat study.

BMDLs for hepatic effects ranged from 0.0741 to 5.55 mg/kg/day across studies. The BMDL of 0.0741 mg/kg/day for increased albumin to globulin ratio in males from the 90-day rat study was the lowest for hepatic endpoints but had a BMD-to-BMDL ratio of 45.8. The lowest hepatic BMDL without a flag is 0.151 mg/kg/day for single cell hepatocellular necrosis in males from the reproductive study in mice.

Finally, BMDLs for developmental effects ranged from 3.06 to 635 mg/kg/day across studies. The lowest developmental BMDL was for decreased offspring weight on postnatal day 21 in male offspring from the reproductive study in mice.

Table 1. No observed adverse effects levels (NOAELs) and proposed benchmark dose lower bound (BMDL) for selected endpoints from seven repeat oral dose studies in rodents dosed with GenX. BMDS Wizard output reports, which include BMD, BMD-to-BMDL ratio, and model visualizations for each modeled endpoint, can be found in Appendix B.

	28-day Mice		**28-day Rats**		**90-day Mice**		**90-day Rats**	
Study dose groups (mg/kg/day)	**0, 0.1, 3, 30**		**M - 0, 0.3, 3, 30 F - 0, 3, 30, 300**		**0, 0.1, 0.5, 5**		**M - 0, 0.1, 10, 100 F - 0, 10, 100, 1000**	
	NOAEL (mg/kg/day)	**Proposed BMDL (mg/kg/day)**	**NOAEL (mg/kg/day)**	**Proposed BMDL (mg/kg/day)**	**NOAEL (mg/kg/day)**	**Proposed BMDL (mg/kg/day)**	**NOAEL (mg/kg/day)**	**Proposed BMDL (mg/kg/day)**
Hematology								
Hemoglobin	0.1 (M)	0.0492*	0.3 (M)	1.19	NS		0.1 (M)	2.12
Hematocrit	0.1 (M)	0.00589*	0.3 (M)	0.357	NS		0.1 (M)	--
Hepatotoxicity								
Albumin/Globulin ratio	0.1 (M&F)	0.464 (M); 0.595 (F)	0.3 (M)	0.945	NS		0.1 (M)	0.0741*
Alkaline Phosphatase	3 (M&F)	-- (M); 5.55 (F)	NS		0.5 (M&F)	0.480 (M); 0.859* (F)	10 (M)	1.43
Alanine Aminotransferase	3 (M)	--	NS		0.5 (M&F)	-- (M&F)	NS	
Aspartate Aminotransferase	3 (M)	1.18	NS		0.5 (M)	0.169	NS	
Sorbitol dehydrogenase	3 (M&F)	-- (M); 6.29 (F)	NS		0.5 (M&F)	-- (M&F)	NS	
Hepatocellular necrosis (single cell)	0.1 (M)^	0.299*	3 (M)^	2.70*	0.5 (M)^	0.126$^{\#}$	▨	▨
Liver weight to brain weight	0.1 (M&F)	0.194 (M); 0.751 (F)	0.3 (M)	0.611	0.5 (M&F)	0.300 (M); 0.929 (F)	0.1 (M)	--
Developmental								
Combined fetal weights	▨	▨	▨	▨	▨	▨	▨	▨
Skeletal variations	▨	▨	▨	▨	▨	▨	▨	▨
Offspring weight PND 21	▨	▨	▨	▨	▨	▨	▨	▨
F1 body weight PND 40	▨	▨	▨	▨	▨	▨	▨	▨

* = BMD-to-BMDL ratio > 5 for the selected model, indicating the data may be of poor quality for modeling purposes
\# = selected model has a questionable visual fit
^ = NOAEL estimated based on visual inspection of data, no statistical analysis provided
-- = No models met all criteria for model fit, so no BMDL was selected
NOAEL = No Observed Adverse Effect Level
BMDL = Benchmark Dose Lower Bound

mg/kg/day = milligrams of GenX per kilogram of body weight per day
M = Males
F = Females
NS = effect not statistically significant in the study
mo = months
PND = postnatal day
Cells shaded dark grey denote that the endpoint was not measured in that study

Table 1 Continued. No observed adverse effects levels (NOAELs) and proposed benchmark dose lower bound (BMDL) for selected endpoints from seven repeat oral dose studies in rodents dosed with GenX. BMDS Wizard output reports, which include BMD, BMD-to-BMDL ratio, and model visualizations for each modeled endpoint, can be found in Appendix B.

	2-year Rats		**Reproductive Screen Mice**		**Prenatal and Developmental Rats**	
Study dose groups (mg/kg/day)	**M - 0, 0.1, 1, 50 F - 0, 1, 50, 500**		**0, 0.1, 0.5, 5**		**0, 10, 100, 1000**	
	NOAEL (mg/kg/day)	**Proposed BMDL (mg/kg/day)**	**NOAEL (mg/kg/day)**	**Proposed BMDL (mg/kg/day)**	**NOAEL (mg/kg/day)**	**Proposed BMDL (mg/kg/day)**
Hematology						
Hemoglobin	1 (M 3&6mo)	3.55*# (6mo)				
Hematocrit	1 (M 3 and 6 mo)	25.3 (6mo)				
Hepatotoxicity						
Albumin/Globulin ratio	0.1 (M 3&12mo)	-- (12 mo)				
Alkaline Phosphatase	1 (M 3,6,12mo)	-- (12 mo)				
Alanine Aminotransferase	1 (M 12mo)	-- (12 mo)				
Aspartate Aminotransferase	NS					
Sorbitol dehydrogenase	1 (M 12mo)	1.21* (12mo)				
Hepatocellular necrosis (single cell)	50 (F)	Not modeled (high NOAEL)	0.1 (M)^	0.151		
Liver weight to brain weight	50 (F)	Not modeled (high NOAEL)	0.1 (M&F)	0.165 (M); -- (F)		
Developmental						
Combined fetal weights					10	--
Skeletal variations					100	635
Offspring weight PND 21			0.5 (M&F)	3.06 (M); 3.66 (F)		
F1 body weight PND 40			0.5 (M)	3.36 (M)		

* = BMD-to-BMDL ratio > 5 for the selected model, indicating the data may be of poor quality for modeling purposes
\# = selected model has a questionable visual fit
^ = NOAEL estimated based on visual inspection of data, no statistical analysis provided
-- = No models met all criteria for model fit, so no BMDL was selected
NOAEL = No Observed Adverse Effect Level
BMDL = Benchmark Dose Lower Bound

mg/kg/day = milligrams of GenX per kilogram of body weight per day
M = Males
F = Females
NS = effect not statistically significant in the study
mo = months
PND = postnatal day
Cells shaded dark grey denote that the endpoint was not measured in that study

Limitations

This report is not intended as a comprehensive review of all scientific information available for GenX. Not all statistically significant endpoints were modeled for this report. Rather, this report focuses on those endpoints that were seen at the lowest doses and observed consistently across studies, as well as developmental endpoints given the special concerns for exposure to infants and children. This report does not address the factors used to calculate a provisional health goal for drinking water, such as uncertainty factors or exposure parameters.

Conclusions

This report provides the results of benchmark dose modeling of certain priority endpoints for GenX in response to a request from the North Carolina SAB made during their review of the DHHS provisional health goal for GenX in drinking water. OEEB has completed benchmark dose modeling on select hematological, hepatic, and developmental endpoints from seven repeat oral dose studies in rodents. NOAELs from these endpoints range from 0.1 to 100 mg/kg/day, and proposed BMDLs for these endpoints range from 0.00589 to 635 mg/kg/day. N.C. DHHS asks that the SAB consider this information when making recommendations regarding health or regulatory levels for GenX in the state of North Carolina.

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Appendix A

Data Tables for Endpoints Selected for Benchmark Dose Modeling

<u>Contents</u>

Introduction

Data tables for all statistically significant endpoints from all seven repeat oral dose studies can be found in a separate document previously provided to the North Carolina Secretaries’ Science Advisory Board (OEEB 2018). Data tables presented here are for endpoints selected for benchmark dose modeling.

The following tables are organized by endpoint. For endpoints where clear sex-specific differences were observed, the more sensitive sex was used for modeling, and only that data is shown here. For endpoints that were measured at multiple time points in the same study, the latest time point with a statistically significant difference between the control and treatment animals was used to be more representative of long term exposure, and only that data is shown here.

Table A-1. Hemoglobin data from repeat oral dose studies used for benchmark dose modeling.

Hemoglobin (g/dL)					
28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	14.1	0.53	
	0.1	8	13.8	0.45	
	3	8	13.4	0.46	significant at p=0.05
	30	9	13.1	0.53	significant at p=0.01
28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	16.3	0.36	
	0.3	10	16.3	0.47	
	3	10	15.8	0.42	significant at p=0.05
	30	10	15.2	0.61	significant at p=0.01
90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	16.4	0.59	
	0.1	10	16.3	0.81	
	10	10	15.3	0.94	significant at p=0.01
	100	10	14.3	0.56	significant at p=0.01
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats 6-month timepoint					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	15.99	0.645	
	0.1	10	15.76	1.082	
	1	10	16.22	0.587	
	50	10	14.86	1.064	significant at p=0.05

Table A-2. Hematocrit data from repeat oral dose studies used for benchmark dose modeling.

Hematocrit (%)					
28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	40.1	1.72	
	0.1	8	38.8	1.06	
	3	8	38.1	1.36	significant at p=0.05
	30	9	37.5	1.54	significant at p=0.01
28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	45.6	1.66	
	0.3	10	44.9	1.37	
	3	10	43.4	1.4	significant at p=0.01
	30	10	42	1.6	significant at p=0.01
90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	46.8	1.5	
	0.1	10	46.3	2.53	
	10	10	43.5	2.64	significant at p=0.01
	100	10	41.2	1.36	significant at p=0.01
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats 6-month timepoint					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	48.15	1.706	
	0.1	10	47.61	2.762	
	1	10	48.98	2.836	
	50	10	44.85	2.974	significant at p=0.05

Table A-3. Albumin to globulin ratio data from repeat oral dose studies used for benchmark dose modeling.

Albumin/Globulin Ratio					
28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery					
	Dose (mg/kg/day)	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	1.54	0.134	
	0.1	10	1.56	0.128	
	3	10	1.92	0.222	significant at p=0.01
	30	10	2.32	0.241	significant at p=0.01
Females	0	10	1.93	0.159	
	0.1	10	1.98	0.134	
	3	10	2.2	0.087	significant at p=0.01
	30	10	2.46	0.19	significant at p=0.01
28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	1.84	0.196	
	0.3	10	1.93	0.17	
	3	10	2.13	0.224	significant at p=0.01
	30	10	2.59	0.232	significant at p=0.01
90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	1.64	0.179	
	0.1	10	1.73	0.195	
	10	10	2.06	0.289	significant at p=0.01
	100	10	2.22	0.357	significant at p=0.01
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats 12-month timepoint					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	0.88	0.063	
	0.1	10	0.94	0.135	
	1	10	1.02	0.092	significant at p=0.05
	50	10	1.13	0.125	significant at p=0.01

Table A-4. Alkaline phosphatase data from repeat oral dose studies used for benchmark dose modeling.

Alkaline Phosphatase (U/L)					
28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	88	29.5	
	0.1	10	73	18.2	
	3	10	144	51.2	
	30	10	1163	682.4	significant at p=0.01
Females	0	10	90	21.9	
	0.1	10	97	22.1	
	3	10	96	19.7	
	30	10	216	51.3	significant at p=0.01
H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	50	12	
	0.1	10	55	22	
	0.5	10	70	30	
	5	10	617	339	significant at p=0.05
Females	0	10	65	19	
	0.1	10	77	25	
	0.5	9	72	18	
	5	9	158	38	significant at p=0.05
90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	80	12.9	
	0.1	10	79	15.4	
	10	10	118	30.9	
	100	10	165	41.5	significant at p=0.01
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats 12-month timepoint					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	73	15.06	
	0.1	10	93.5	26.22	
	1	10	107	31.7	
	50	10	204.7	67.12	significant at p=0.01

Table A-5. Alanine aminotransferase data from repeat oral dose studies used for benchmark dose modeling.

Alanine Aminotransferase (U/L)					
28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	52	37.2	
	0.1	10	38	11	
	3	10	82	30.8	
	30	10	704	311.9	significant at p=0.01
H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	49	16	
	0.1	10	62	22	
	0.5	10	66	48	
	5	10	255	114	significant at p=0.05
Females	0	10	36	12	
	0.1	10	36	8	
	0.5	9	32	6	
	5	9	51	20	significant at p=0.05
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats 12-month timepoint					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	39.7	12.97	
	0.1	10	34.8	5.2	
	1	10	37.4	8.51	
	50	10	130.3	85.73	significant at p=0.05

Table A-6. Aspartate aminotransferase data from repeat oral dose studies used for benchmark dose modeling.

Aspartate Aminotransferase (U/L)					
28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	72	18.5	
	0.1	10	72	13.3	
	3	10	90	38	
	30	10	416	218.3	significant at p=0.01
H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	62	11	
	0.1	10	67	21	
	0.5	10	84	21	
	5	10	128	80	significant at p=0.05

Table A-7. Sorbitol dehydrogenase data from repeat oral dose studies used for benchmark dose modeling.

Sorbitol Dehydrogenase (U/L)					
28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	24	5.4	
	0.1	10	22	3.4	
	3	10	46	20.4	
	30	9	456	225.2	significant at p=0.01
Females	0	10	14	5.1	
	0.1	10	16	4.8	
	3	10	16	5.5	
	30	10	40	20.2	significant at p=0.01
H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	26.6	2.5	
	0.1	10	26	2.4	
	0.5	10	25.8	5.4	
	5	10	108.5	47.2	significant at p=0.05
Females	0	10	25.3	11.7	
	0.1	9	22.9	2	
	0.5	9	23.6	3.6	
	5	9	33.5	9.3	significant at p=0.05
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats 12-month timepoint					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	13.32	6.006	
	0.1	10	14.47	3.873	
	1	10	15.7	4.848	
	50	10	32.08	26.424	significant at p=0.05

Table A-8. Single cell hepatocellular necrosis data from repeat oral dose studies used for benchmark dose modeling.

<table>
<tr><th colspan="5">Liver Necrosis, Single Cell</th></tr>
<tr><th colspan="5">28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery</th></tr>
<tr><th>Sex</th><th>Dose (mg/kg/day)</th><th>N</th><th>Incidence (#)</th><th>Notes</th></tr>
<tr><td rowspan="4">Males</td><td>0</td><td>10</td><td>0</td><td></td></tr>
<tr><td>0.1</td><td>10</td><td>0</td><td></td></tr>
<tr><td>3</td><td>10</td><td>4</td><td>4 minimal</td></tr>
<tr><td>30</td><td>10</td><td>10</td><td>10 minimal</td></tr>
<tr><td rowspan="4">Females</td><td>0</td><td>10</td><td>0</td><td></td></tr>
<tr><td>0.1</td><td>10</td><td>0</td><td></td></tr>
<tr><td>3</td><td>10</td><td>0</td><td></td></tr>
<tr><td>30</td><td>10</td><td>4</td><td>4 minimal</td></tr>
<tr><th colspan="5">28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery</th></tr>
<tr><th>Sex</th><th>Dose (mg/kg/day)</th><th>N</th><th>Incidence #</th><th>Notes</th></tr>
<tr><td rowspan="4">Males</td><td>0</td><td>10</td><td>0</td><td></td></tr>
<tr><td>0.3</td><td>10</td><td>0</td><td></td></tr>
<tr><td>3</td><td>10</td><td>0</td><td></td></tr>
<tr><td>30</td><td>10</td><td>3</td><td>3 minimal</td></tr>
<tr><th colspan="5">H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice</th></tr>
<tr><th>Sex</th><th>Dose (mg/kg/day)</th><th>N</th><th>Incidence (#)</th><th>Notes</th></tr>
<tr><td rowspan="4">Males</td><td>0</td><td>10</td><td>0</td><td></td></tr>
<tr><td>0.1</td><td>10</td><td>0</td><td></td></tr>
<tr><td>0.5</td><td>10</td><td>0</td><td></td></tr>
<tr><td>5</td><td>10</td><td>10</td><td>10 minimal</td></tr>
<tr><th colspan="5">Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice</th></tr>
<tr><th>Sex</th><th>Dose (mg/kg/day)</th><th>N</th><th>Incidence (#)</th><th>Notes</th></tr>
<tr><td rowspan="4">Males</td><td>0</td><td>25</td><td>1</td><td>1 minimal</td></tr>
<tr><td>0.1</td><td>24</td><td>1</td><td>1 minimal</td></tr>
<tr><td>0.5</td><td>24</td><td>5</td><td>5 minimal</td></tr>
<tr><td>5</td><td>24</td><td>24</td><td>4 minimal, 17 mild, 3 moderate</td></tr>
</table>

Table A-9. Liver weight to brain weight data from repeat oral dose studies used for benchmark dose modeling.

Liver Weight to Brain Weight (g/100g brain)					
28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	347.314	35.9339	
	0.1	10	365.446	37.5748	
	3	10	611.951	119.6603	significant at p=0.01
	30	10	948.956	204.0532	significant at p=0.01
Females	0	10	270.582	31.8333	
	0.1	10	285.47	29.77	
	3	10	347.618	38.6819	significant at p=0.01
	30	10	554.315	65.5015	significant at p=0.01
28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	546.486	62.2678	
	0.3	10	560.332	49.3673	
	3	10	679.305	74.8864	significant at p=0.01
	30	10	867.076	121.2461	significant at p=0.01
H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	386.366	45.011	
	0.1	10	407.101	36.407	
	0.5	10	437.1	69.385	
	5	9	935.966	193.179	significant at p=0.05
Females	0	10	332.826	66.34	
	0.1	10	334.248	30.441	
	0.5	9	350.216	59.323	
	5	9	555.33	193.239	significant at p=0.05
90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	657.943	47.9593	
	0.1	10	682.492	66.4246	
	10	10	825.582	161.3767	significant at p=0.01
	100	10	1060.36	136.53	significant at p=0.01

Table A-9 continued. Liver weight to brain weight data from repeat oral dose studies used for benchmark dose modeling.

Liver Weight to Brain Weight (g/100g brain)					
Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	25	372.934	41.0786	
	0.1	24	396.618	54.4874	
	0.5	24	465.278	63.5695	significant at p=0.01
	5	24	893.709	169.7741	significant at p=0.01
Females	0	21	427.097	51.1989	
	0.1	18	455.91	46.8862	
	0.5	23	526.053	94.2293	significant at p=0.01
	5	20	863.983	93.4767	significant at p=0.01

Table A-10. Offspring weight postnatal day 21 data from the Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice study used for benchmark dose modeling.

Offspring Weight (litter as experimental unit) - PND21 (g)					
Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	21	13.52	1.376	
	0.1	18	13.78	1.37	
	0.5	23	13.87	1.284	
	5	20	10.56	1.908	significant at p=0.01
Females	0	21	13.04	1.149	
	0.1	18	13.22	1.258	
	0.5	23	13.45	1.127	
	5	18	10.73	1.54	significant at p=0.01

Table A-11. F1 Body weight postnatal day 40 data from the Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice study used for benchmark dose modeling.

F1 Body Weight - PND40 (g)					
Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	21	29.6	2.77	
	0.1	18	29.8	2.07	
	0.5	23	30	2.86	
	5	19	27.2	2.3	significant at p=0.01

Table A-12. Combined fetal weight data from the Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats study used for benchmark dose modeling.

Combined Fetal Weights (g)				
Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats				
Dose (mg/kg/day)	**N (# of litters)**	**Mean**	**St. Dev**	**Notes**
0	22	5.7	0.38	
10	21	5.6	0.24	
100	21	5.2	0.24	significant at p=0.01
1000	21	4.1	0.29	significant at p=0.01

Table A-13. Percent per litter with skeletal variations data from the Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats study used for benchmark dose modeling.

Percent Per Litter with Skeletal Variations (%)				
Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats				
Dose (mg/kg/day)	**N (# of litters)**	**Mean**	**St. Dev**	**Notes**
0	22	10.6	14.17	
10	21	11.6	10.9	
100	21	14.7	10.42	
1000	21	30.3	27.49	significant at p=0.05, 14th rudimentary rib, 7th cervical rib

Appendix B

BMDS Wizard Output Reports for Endpoints Selected for Benchmark Dose Modeling

Contents

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Hemoglobin (g/dL) in Males

1.1. BMDS Summary of Hemoglobin in Males (28-Day Mice)

Table 1. Summary of BMD Modeling Results for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M4) Exponential (M5)[b]	0.241	-8.5015	2.08	0.0607	24.2	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from model with lowest AIC and lowest BMDL.
Hill	0.287	-8.7441	0.343	0.0492	6.97	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.933, BMDS Test 3 *p*-value = 0.933), no model was selected as a best-fitting model.

[b] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

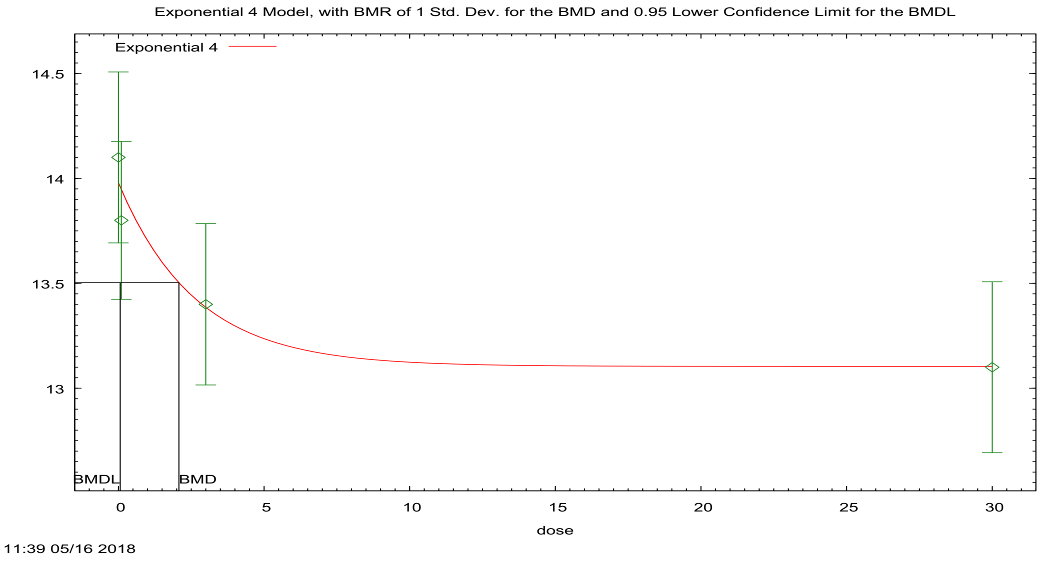

Figure 1. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.07626

BMDL at the 95% confidence level = 0.0606788

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.48534	-1.52581
rho	n/a	0
a	13.9789	14.805
b	0.378088	0.0465873
c	0.937413	0.842701
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	13.98	0.53	0.48	0.7637
0.1	8	13.8	13.95	0.45	0.48	-0.8702
3	8	13.4	13.39	0.46	0.48	0.08685
30	9	13.1	13.1	0.53	0.48	-0.0251

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655
A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
R	-0.03421454	2	4.068429

4	8.250725	4	-8.50145

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.38	6	0.005347
Test 2	0.4351	3	0.9329
Test 3	0.4351	3	0.9329
Test 6a	1.376	1	0.2407

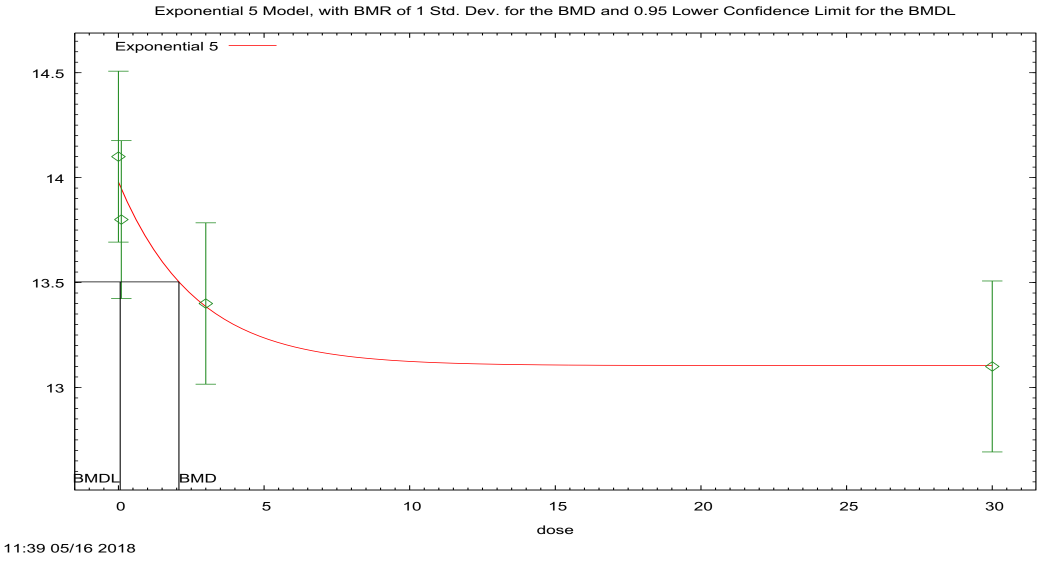

Figure 2. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.07626

BMDL at the 95% confidence level = 0.0606788

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.48534	-1.52581
rho	n/a	0
a	13.9789	14.805
b	0.378087	0.0465873
c	0.937413	0.842701
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	13.98	0.53	0.48	0.7637
0.1	8	13.8	13.95	0.45	0.48	-0.8702
3	8	13.4	13.39	0.46	0.48	0.08685
30	9	13.1	13.1	0.53	0.48	-0.0251

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655
A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
R	-0.03421454	2	4.068429
5	8.250725	4	-8.50145

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.38	6	0.005347
Test 2	0.4351	3	0.9329

Test 3	0.4351	3	0.9329
Test 7a	1.376	1	0.2407

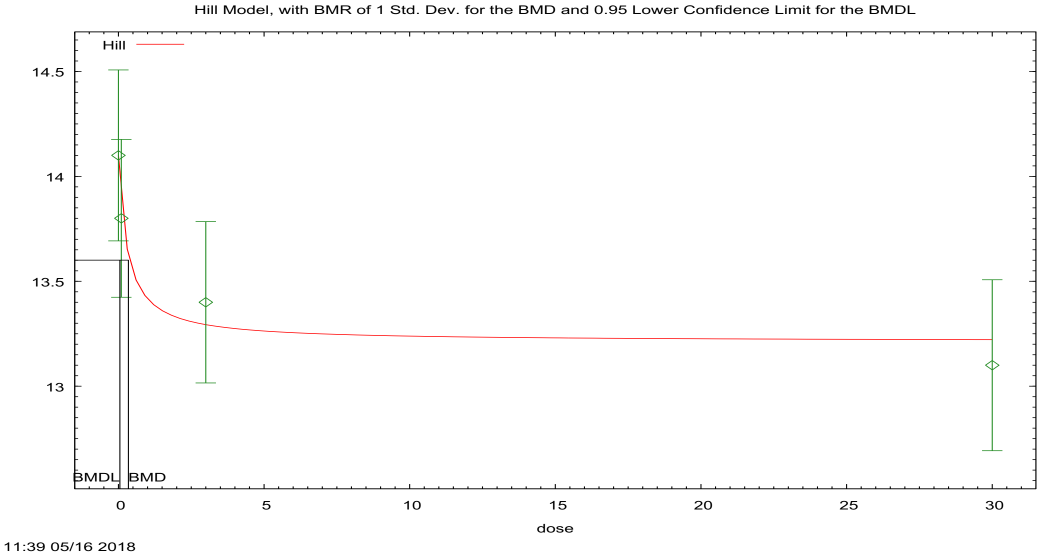

Figure 3. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.342989

BMDL at the 95% confidence level = 0.0491937

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.224816	0.246437

rho	n/a	0
intercept	14.0748	14.1
v	-0.887431	-1
n	1	0.796114
k	0.298961	1.55

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	14.1	0.53	0.47	0.159
0.1	8	13.8	13.9	0.45	0.47	-0.312
3	8	13.4	13.3	0.46	0.47	0.789
30	9	13.1	13.2	0.53	0.47	-0.608

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655
A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
fitted	8.372034	4	-8.744068
R	-0.034215	2	4.068429

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.3812	6	0.005347
Test 2	0.435143	3	0.9329
Test 3	0.435143	3	0.9329
Test 4	1.13359	1	0.287

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery – Hemoglobin (g/dL) in Males

1.2. BMDS Summary of Hemoglobin in Males (28-Day Rats)

Table 2. Summary of BMD Modeling Results for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M4)	**0.731**	**-15.807**	**2.44**	**1.19**	**2.06**	**Only one model met inclusion criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)).**

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.383), selected model in bold; scaled residuals for selected model for doses 0, 0.3, 3, and 30 mg/kg/day were -0.22, 0.26, -0.05, 0.01, respectively.

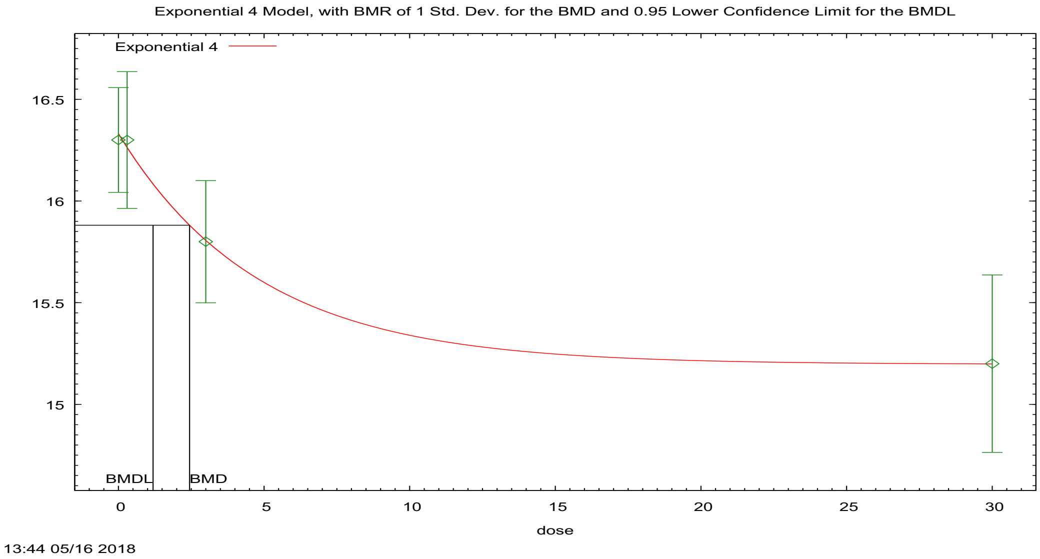

Figure 4. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.4439

BMDL at the 95% confidence level = 1.18907

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.59517	-1.59813
rho	n/a	0
a	16.3313	17.115
b	0.207026	0.0450856
c	0.930541	0.845819
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.3	16.33	0.36	0.45	-0.2197
0.3	10	16.3	16.26	0.47	0.45	0.2599
3	10	15.8	15.81	0.42	0.45	-0.04565
30	10	15.2	15.2	0.61	0.45	0.005483

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	11.96254	5	-13.92508
A2	13.49192	8	-10.98384
A3	11.96254	5	-13.92508
R	-2.034667	2	8.069334

4	11.90349	4	-15.80699

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.05	6	<0.0001
Test 2	3.059	3	0.3827
Test 3	3.059	3	0.3827
Test 6a	0.1181	1	0.7311

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery – Hemoglobin (g/dL) in Males

1.3. BMDS Summary of Hemoglobin in Males (90-Day Rats)

Table 3. Summary of BMD Modeling Results for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	**Goodness of fit**		**BMD$_{1SD}$ (mg/kg/day)**	**BMDL$_{1SD}$ (mg/kg/day)**	**BMD/BMDL**	**Basis for model selection**
	***p*-value**	**AIC**				
Exponential (M4) Exponential (M5)[b]	0.787	19.971	5.80	3.23	1.80	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from model with lowest AIC and lowest BMDL.
Hill	**0.798**	**19.963**	**5.15**	**2.12**	**2.42**	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.294), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 10, and 100 mg/kg/day were 0.18, -0.18, 0.01, 0, respectively.

[b] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

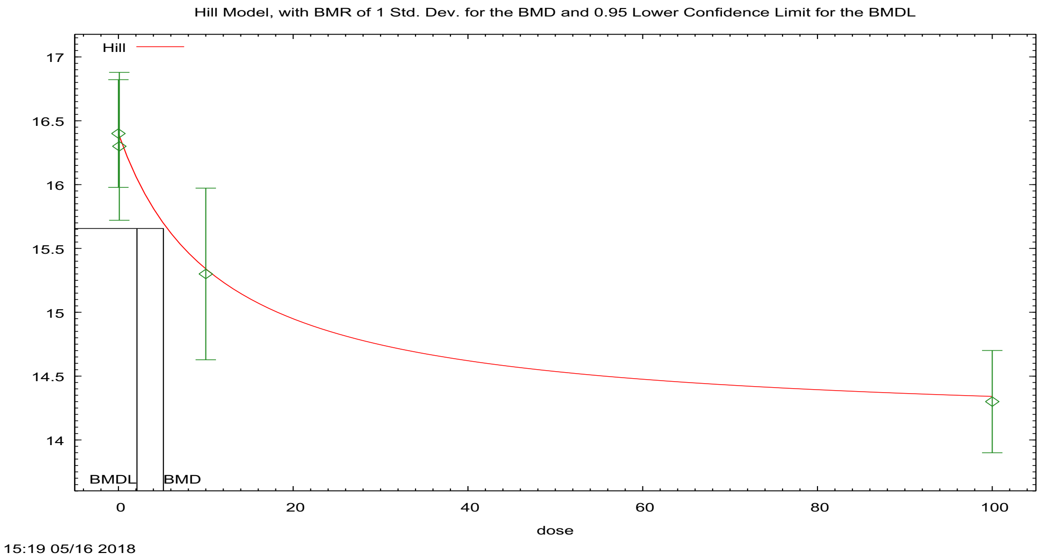

Figure 5. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 5.14707

BMDL at the 95% confidence level = 2.12258

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.496125	0.55035
rho	n/a	0
intercept	16.3603	16.4
v	-2.30015	-2.1
n	1	1.26758
k	11.6611	9.505

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.4	0.59	0.7	0.178
0.1	10	16.3	16.3	0.81	0.7	-0.183
10	10	15.3	15.3	0.94	0.7	0.00689
100	10	14.3	14.3	0.56	0.7	-0.00182

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-5.948773	5	21.897546
A2	-4.092313	8	24.184626
A3	-5.948773	5	21.897546
fitted	-5.981439	4	19.962879

R	-24.012887	2	52.025773

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	39.8411	6	<0.0001
Test 2	3.71292	3	0.2942
Test 3	3.71292	3	0.2942
Test 4	0.0653329	1	0.7983

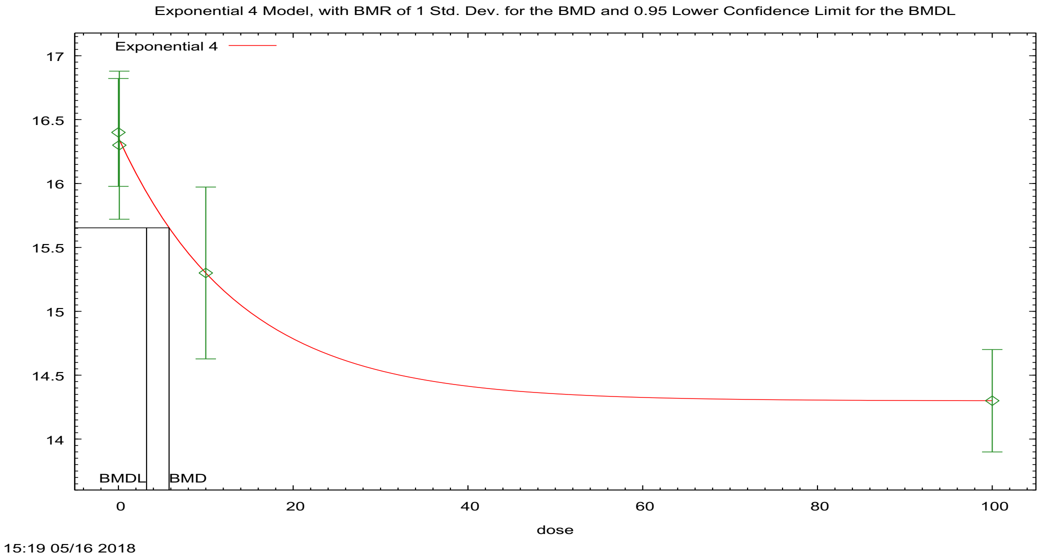

Figure 6. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 5.80078

BMDL at the 95% confidence level = 3.22524

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.700731	-0.702561
rho	n/a	0
a	16.3578	17.22
b	0.0721802	0.0172469
c	0.874119	0.790885
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.36	0.59	0.7	0.1896
0.1	10	16.3	16.34	0.81	0.7	-0.1929
10	10	15.3	15.3	0.94	0.7	0.003951
100	10	14.3	14.3	0.56	0.7	-0.0006445

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-5.948773	5	21.89755
A2	-4.092313	8	24.18463
A3	-5.948773	5	21.89755
R	-24.01289	2	52.02577
4	-5.985381	4	19.97076

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	39.84	6	<0.0001
Test 2	3.713	3	0.2942

Test 3	3.713	3	0.2942
Test 6a	0.07322	1	0.7867

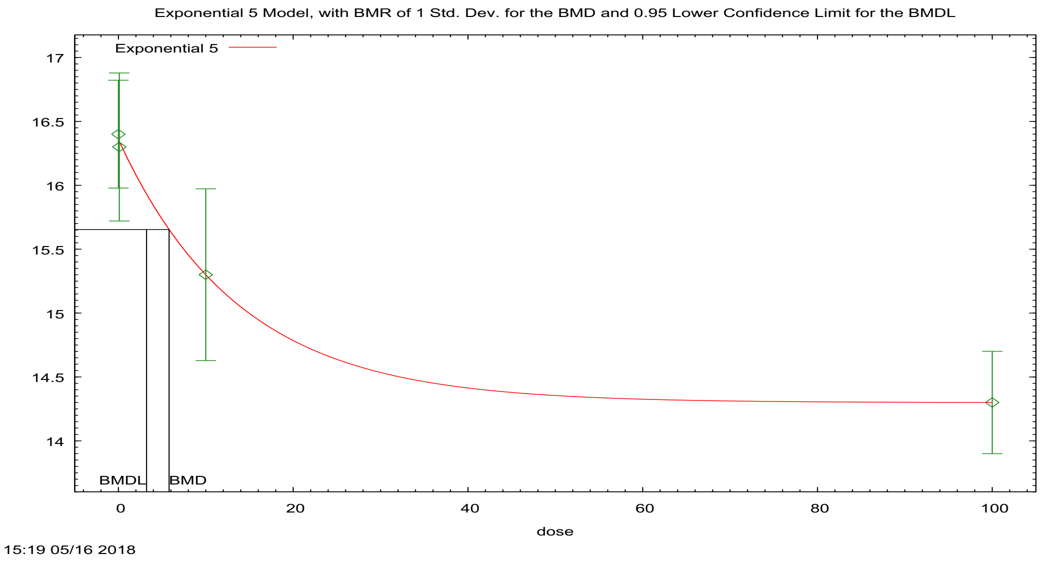

Figure 7. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 5.80078

BMDL at the 95% confidence level = 3.22524

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.700731	-0.702561

rho	n/a	0
a	16.3578	17.22
b	0.0721802	0.0172469
c	0.874119	0.790885
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.36	0.59	0.7	0.1896
0.1	10	16.3	16.34	0.81	0.7	-0.1929
10	10	15.3	15.3	0.94	0.7	0.003951
100	10	14.3	14.3	0.56	0.7	-0.0006443

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-5.948773	5	21.89755
A2	-4.092313	8	24.18463
A3	-5.948773	5	21.89755
R	-24.01289	2	52.02577
5	-5.985381	4	19.97076

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	39.84	6	<0.0001
Test 2	3.713	3	0.2942
Test 3	3.713	3	0.2942
Test 7a	0.07322	1	0.7867

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats – Hemoglobin (g/dL) at 6-month timepoint in Males

1.4. BMDS Summary of Hemoglobin in Males at 6 months (2-Year Rats)

Table 4. Summary of BMD Modeling Results for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.439	32.762	37.1	24.5	1.51	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were not sufficiently close (> 3-fold difference), so the lowest BMDL was selected.
Exponential (M3)	0.220	34.621	46.9	24.7	1.90	
Exponential (M4)	**0.439**	**32.762**	**37.1**	**3.55**	**10.4**	
Power	0.220	34.621	46.7	25.3	1.84	
Polynomial 3°	0.471	32.621	45.4	39.8	1.14	
Polynomial 2°	0.470	32.624	43.3	25.3	1.71	
Linear	0.440	32.757	37.4	25.1	1.49	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.115), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 1, and 50 mg/kg/day were -0.03, -0.88, 0.92, -0.02, respectively.

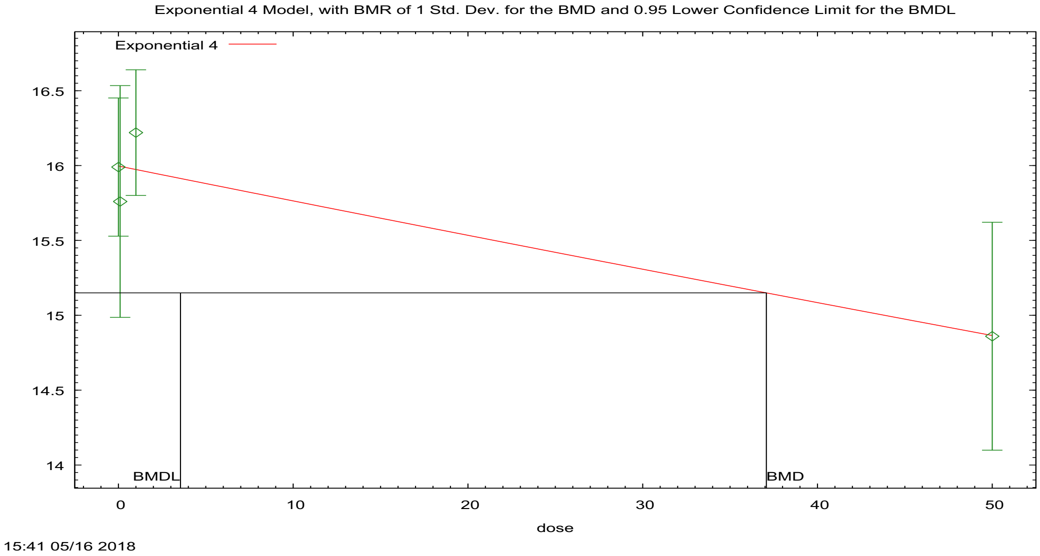

Figure 8. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 37.0764

BMDL at the 95% confidence level = 3.55258

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.330954	-0.372125
rho	n/a	0
a	15.997	17.031
b	0.00146813	0.0282075
c	0	0.830978
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	15.99	16	0.64	0.85	-0.02616
0.1	10	15.76	15.99	1.08	0.85	-0.8756
1	10	16.22	15.97	0.59	0.85	0.9196
50	10	14.86	14.86	1.06	0.85	-0.01788

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.5575	5	35.115
A2	-9.588901	8	35.1778
A3	-12.5575	5	35.115
R	-19.08199	2	42.16398

4	-13.38092	3	32.76184

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.99	6	0.004187
Test 2	5.937	3	0.1147
Test 3	5.937	3	0.1147
Test 6a	1.647	2	0.4389

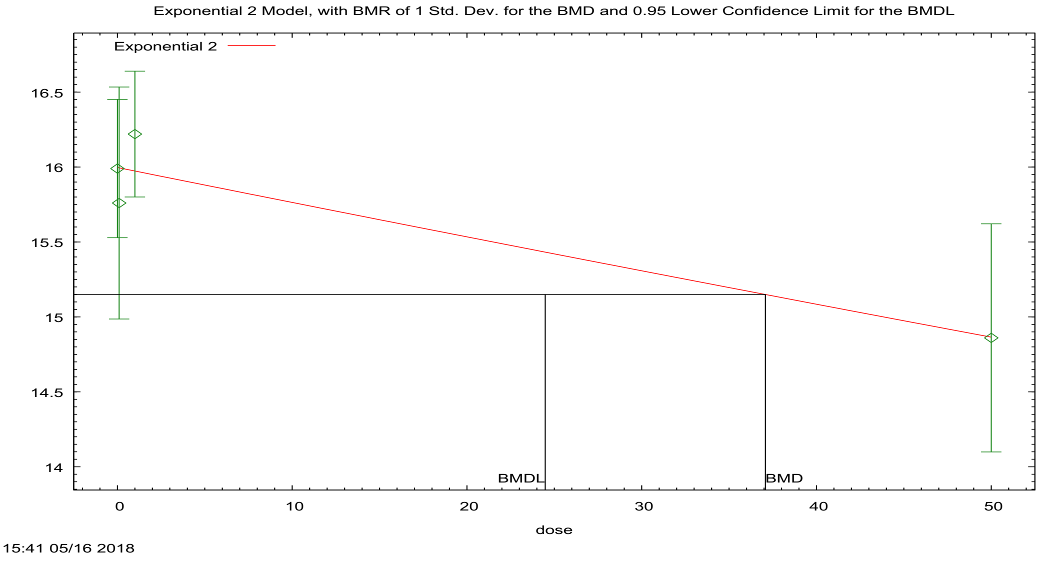

Figure 9. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 37.0764

BMDL at the 95% confidence level = 24.4798

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.330954	-0.372125
rho	n/a	0
a	15.997	15.4073
b	0.00146813	0.00146778
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	15.99	16	0.64	0.85	-0.02617
0.1	10	15.76	15.99	1.08	0.85	-0.8756
1	10	16.22	15.97	0.59	0.85	0.9196
50	10	14.86	14.86	1.06	0.85	-0.01788

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.5575	5	35.115
A2	-9.588901	8	35.1778
A3	-12.5575	5	35.115
R	-19.08199	2	42.16398
2	-13.38092	3	32.76184

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.99	6	0.004187
Test 2	5.937	3	0.1147

Test 3	5.937	3	0.1147
Test 4	1.647	2	0.4389

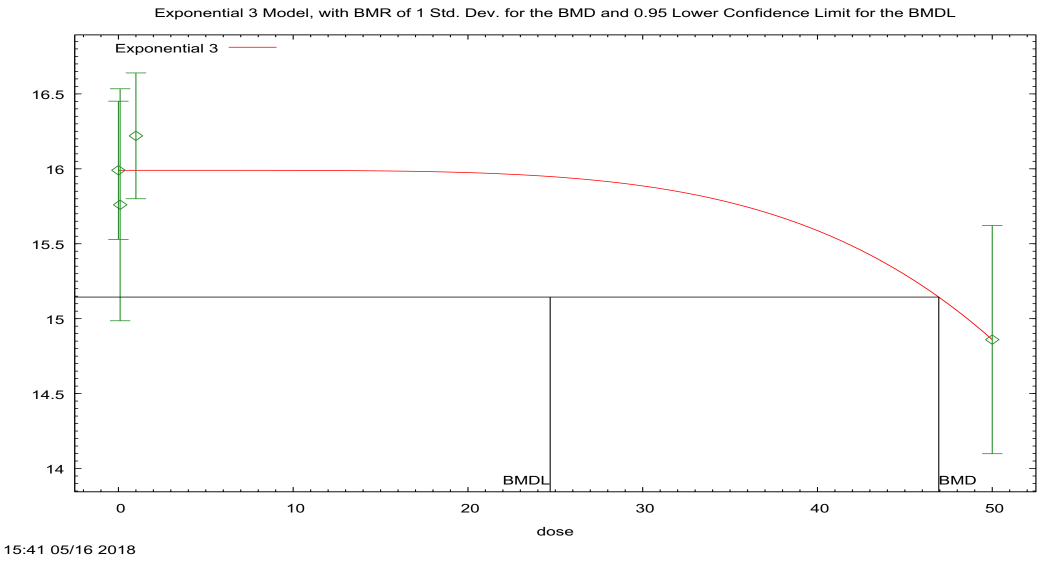

Figure 10. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 46.9404

BMDL at the 95% confidence level = 24.704

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.334469	-0.372125

rho	n/a	0
a	15.99	15.4073
b	0.0115132	0.00146778
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	15.99	15.99	0.64	0.85	-0.000000004659
0.1	10	15.76	15.99	1.08	0.85	-0.8597
1	10	16.22	15.99	0.59	0.85	0.8597
50	10	14.86	14.86	1.06	0.85	0.00000003753

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.5575	5	35.115
A2	-9.588901	8	35.1778
A3	-12.5575	5	35.115
R	-19.08199	2	42.16398
3	-13.31062	4	34.62125

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.99	6	0.004187
Test 2	5.937	3	0.1147
Test 3	5.937	3	0.1147
Test 5a	1.506	1	0.2197

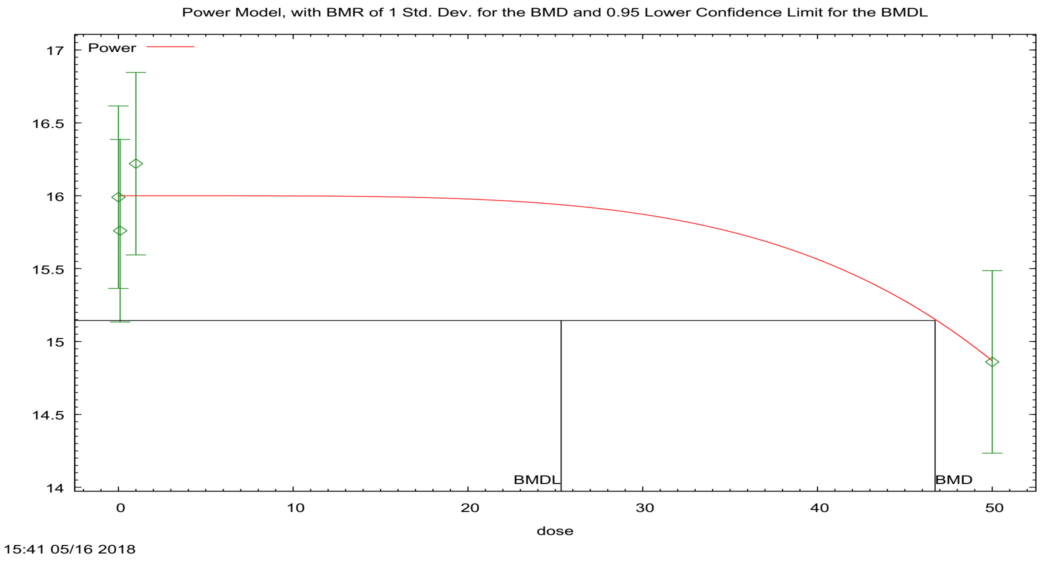

Figure 11. Plot of mean response by dose with fitted curve for Power model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 46.7298

BMDL at the 95% confidence level = 25.3338

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.715718	0.765854
rho	n/a	0
control	15.99	14.86
slope	-0.0000000606318	1.36

power	4.27929	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16	16	0.64	0.85	-0.0000000602
0.1	10	15.8	16	1.08	0.85	-0.86
1	10	16.2	16	0.59	0.85	0.86
50	10	14.9	14.9	1.06	0.85	-0.0000000458

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.557502	5	35.115004
A2	-9.588901	8	35.177802
A3	-12.557502	5	35.115004
fitted	-13.310623	4	34.621247
R	-19.081988	2	42.163976

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.9862	6	0.004187
Test 2	5.9372	3	0.1147
Test 3	5.9372	3	0.1147
Test 4	1.50624	1	0.2197

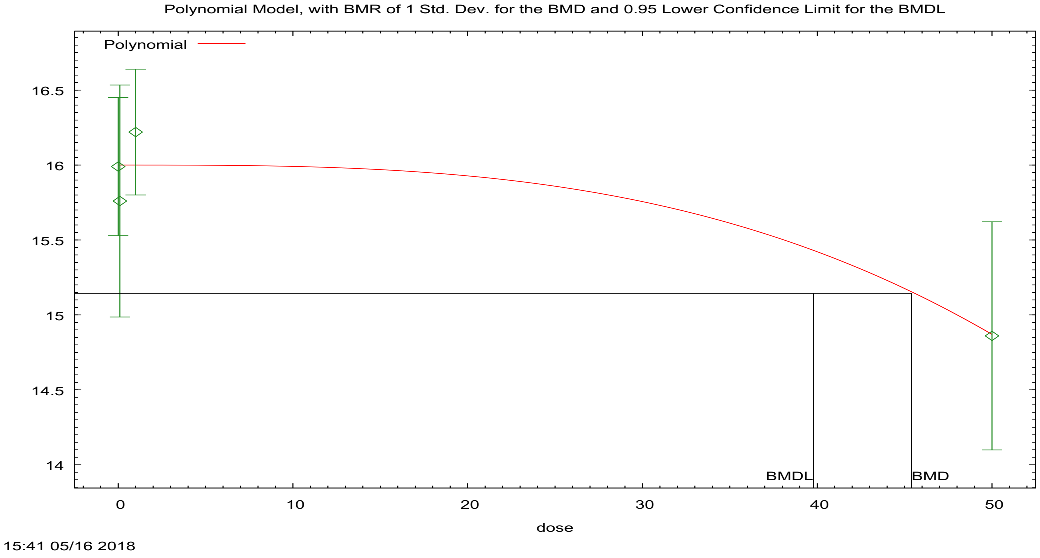

Figure 12. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 45.4012

BMDL at the 95% confidence level = 39.7802

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.715719	0.765854
rho	n/a	0
beta_0	15.99	15.99
beta_1	-8.20886E-24	-2.58676

beta_2	-9.65457E-27	0
beta_3	-0.00000904001	-0.0564382

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16	16	0.64	0.85	-0.00000858
0.1	10	15.8	16	1.08	0.85	-0.86
1	10	16.2	16	0.59	0.85	0.86
50	10	14.9	14.9	1.06	0.85	-0.00000577

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.557502	5	35.115004
A2	-9.588901	8	35.177802
A3	-12.557502	5	35.115004
fitted	-13.310652	3	32.621305
R	-19.081988	2	42.163976

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.9862	6	0.004187
Test 2	5.9372	3	0.1147
Test 3	5.9372	3	0.1147
Test 4	1.5063	2	0.4709

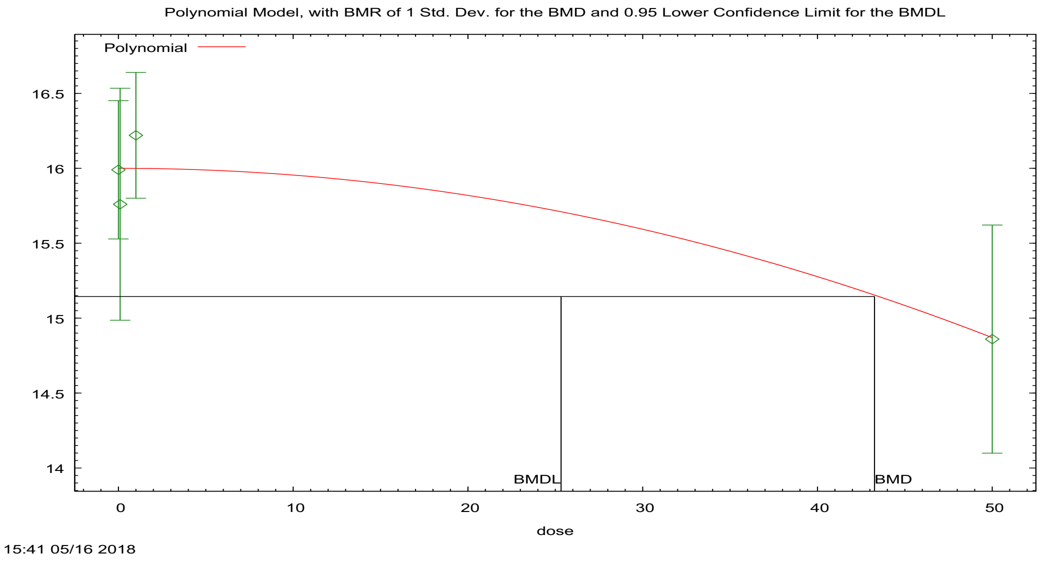

Figure 13. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 43.2632

BMDL at the 95% confidence level = 25.3293

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.71577	0.765854
rho	n/a	0
beta_0	15.9901	15.8647
beta_1	0	0

beta_2	-0.000452012	-0.00737093

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16	16	0.64	0.85	-0.000454
0.1	10	15.8	16	1.08	0.85	-0.86
1	10	16.2	16	0.59	0.85	0.861
50	10	14.9	14.9	1.06	0.85	-0.00034

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.557502	5	35.115004
A2	-9.588901	8	35.177802
A3	-12.557502	5	35.115004
fitted	-13.312062	3	32.624125
R	-19.081988	2	42.163976

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.9862	6	0.004187
Test 2	5.9372	3	0.1147
Test 3	5.9372	3	0.1147
Test 4	1.50912	2	0.4702

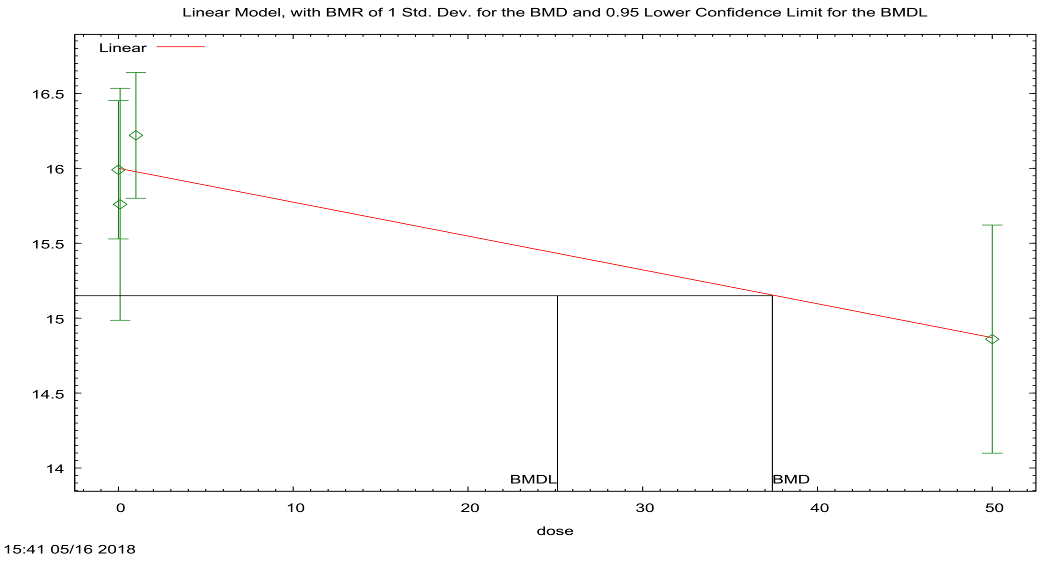

Figure 14. Plot of mean response by dose with fitted curve for Linear model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 37.4185

BMDL at the 95% confidence level = 25.1224

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.718147	0.765854
rho	n/a	0
beta_0	15.9968	15.9968
beta_1	-0.0226475	-0.0226475

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16	16	0.64	0.85	-0.0255
0.1	10	15.8	16	1.08	0.85	-0.875
1	10	16.2	16	0.59	0.85	0.917
50	10	14.9	14.9	1.06	0.85	-0.0166

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.557502	5	35.115004
A2	-9.588901	8	35.177802
A3	-12.557502	5	35.115004
fitted	-13.378368	3	32.756735
R	-19.081988	2	42.163976

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.9862	6	0.004187
Test 2	5.9372	3	0.1147
Test 3	5.9372	3	0.1147
Test 4	1.64173	2	0.4401

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Hematocrit (%) in Males

1.5. BMDS Summary of Hematocrit in Males (28-Day Mice)

Table 5. Summary of BMD Modeling Results for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	**Goodness of fit**		**BMD_{1SD} (mg/kg/day)**	**$BMDL_{1SD}$ (mg/kg/day)**	**BMD/BMDL**	**Basis for model selection**
	***p*-value**	**AIC**				
Hill	**0.416**	**63.876**	**0.122**	**0.00589**	**20.7**	**Only one model met inclusion criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)).**

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.555), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were 0.01, -0.06, 0.61, -0.53, respectively.

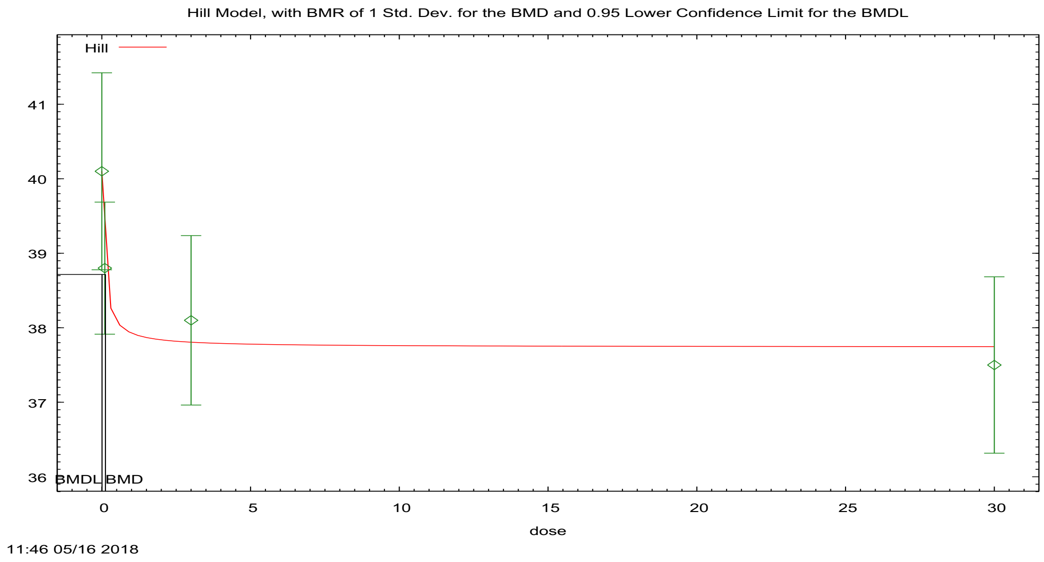

Figure 15. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.121759

BMDL at the 95% confidence level = 0.00588873

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	1.90295	2.11508
rho	n/a	0
intercept	40.0946	40.1
v	-2.35783	-2.6
n	1	0.176992
k	0.0863544	0.1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	40.1	40.1	1.72	1.38	0.0117
0.1	8	38.8	38.8	1.06	1.38	-0.0602
3	8	38.1	37.8	1.36	1.38	0.609
30	9	37.5	37.7	1.54	1.38	-0.53

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-27.606801	5	65.213603
A2	-26.564691	8	69.129382
A3	-27.606801	5	65.213603
fitted	-27.937879	4	63.875758

R	-34.799167	2	73.598334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.469	6	0.01145
Test 2	2.08422	3	0.5551
Test 3	2.08422	3	0.5551
Test 4	0.662155	1	0.4158

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery – Hematocrit (%) in Males

1.6. BMDS Summary of Hematocrit in Males (28-Day Rats)

Table 6. Summary of BMD Modeling Results for ; BMR = 1 std. dev. change from control mean

Model[a]	**Goodness of fit**		**BMD$_{1SD}$ (mg/kg/day)**	**BMDL$_{1SD}$ (mg/kg/day)**	**BMD/BMDL**	**Basis for model selection**
	***p*-value**	**AIC**				
Exponential (M4) Exponential (M5)[b]	0.53	77.289	1.76	0.738	2.39	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from model with lowest AIC and lowest BMDL.
Hill	**0.676**	**77.070**	**1.35**	**0.357**	**3.78**	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.908), selected model in bold; scaled residuals for selected model for doses 0, 0.3, 3, and 30 mg/kg/day were 0.22, -0.32, 0.15, -0.05, respectively.

[b] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

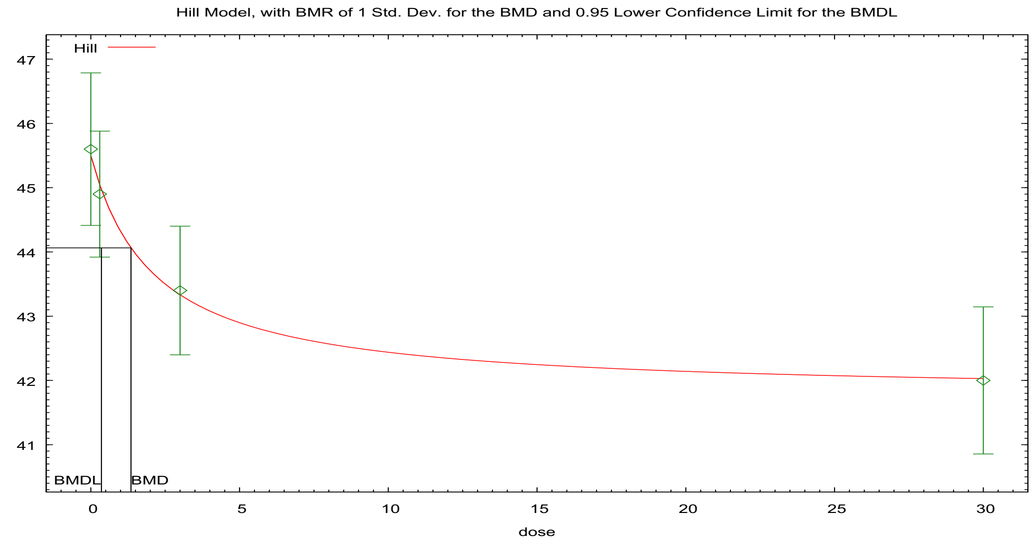
Hill Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

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Figure 16. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.35004

BMDL at the 95% confidence level = 0.357169

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.06835	2.28813
rho	n/a	0
intercept	45.501	45.6
v	-3.72485	-3.6
n	1	1.17389
k	2.14654	2.28

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	45.5	1.66	1.44	0.218
0.3	10	44.9	45	1.37	1.44	-0.317
3	10	43.4	43.3	1.4	1.44	0.154
30	10	42	42	1.6	1.44	-0.0548

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.447444	5	78.894888
A2	-34.173832	8	84.347664
A3	-34.447444	5	78.894888
fitted	-34.535063	4	77.070127

R	-47.681776	2	99.363552

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.0159	6	0.0001438
Test 2	0.547224	3	0.9084
Test 3	0.547224	3	0.9084
Test 4	0.175239	1	0.6755

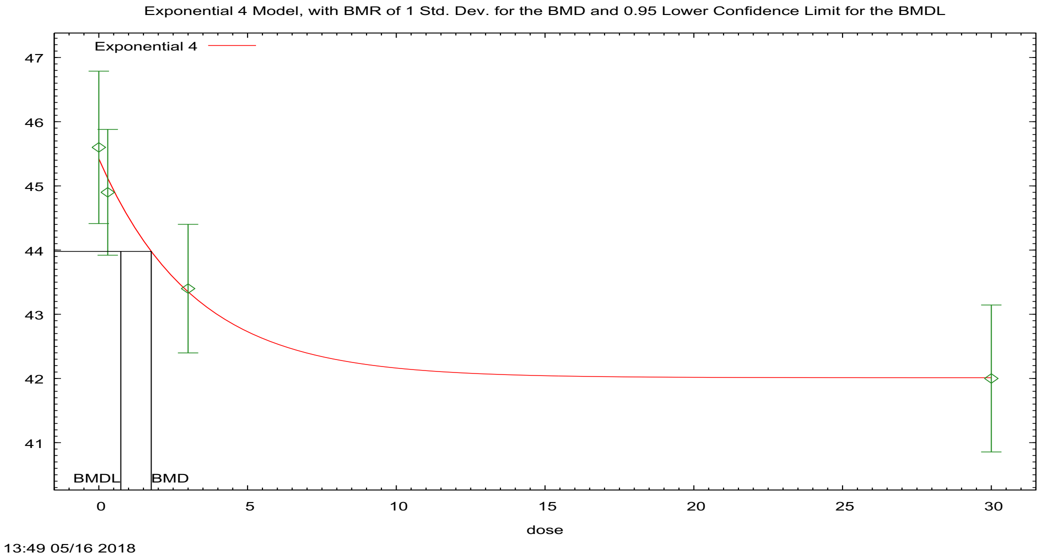

Figure 17. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.76258

BMDL at the 95% confidence level = 0.738122

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.732232	0.722372
rho	n/a	0
a	45.4219	47.88
b	0.31179	0.0481796
c	0.924905	0.835422
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	45.42	1.66	1.44	0.3906
0.3	10	44.9	45.12	1.37	1.44	-0.4765
3	10	43.4	43.35	1.4	1.44	0.1106
30	10	42	42.01	1.6	1.44	-0.02467

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.44744	5	78.89489
A2	-34.17383	8	84.34766
A3	-34.44744	5	78.89489
R	-47.68178	2	99.36355
4	-34.64464	4	77.28927

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.02	6	0.0001438
Test 2	0.5472	3	0.9084

Test 3	0.5472	3	0.9084
Test 6a	0.3944	1	0.53

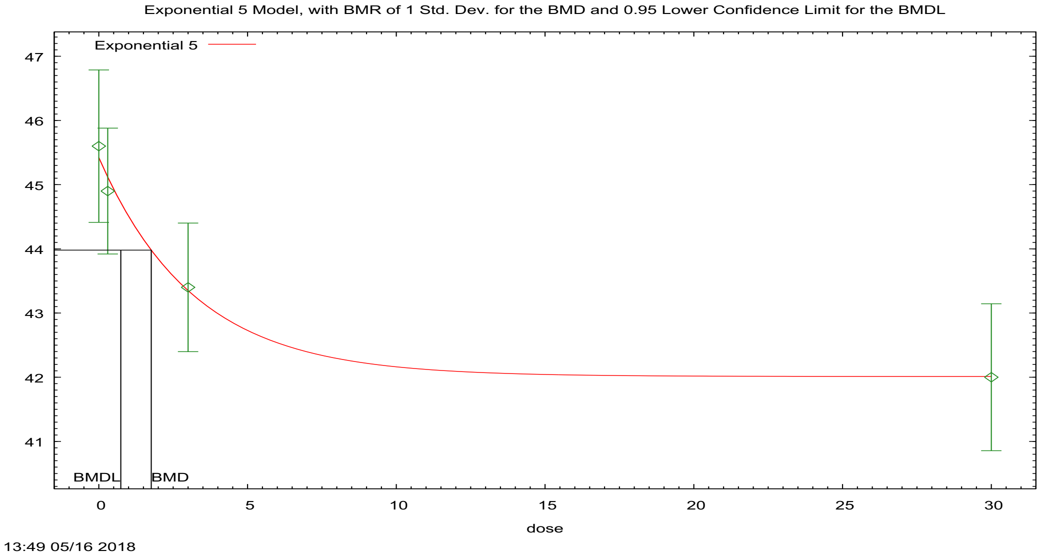

Figure 18. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.76258

BMDL at the 95% confidence level = 0.738122

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.732232	0.722372

rho	n/a	0
a	45.4219	47.88
b	0.31179	0.0481796
c	0.924905	0.835422
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	45.42	1.66	1.44	0.3906
0.3	10	44.9	45.12	1.37	1.44	-0.4765
3	10	43.4	43.35	1.4	1.44	0.1106
30	10	42	42.01	1.6	1.44	-0.02467

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.44744	5	78.89489
A2	-34.17383	8	84.34766
A3	-34.44744	5	78.89489
R	-47.68178	2	99.36355
5	-34.64464	4	77.28927

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.02	6	0.0001438
Test 2	0.5472	3	0.9084
Test 3	0.5472	3	0.9084
Test 7a	0.3944	1	0.53

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats – Hematocrit (%) at 6-month timepoint in Males

1.7. BMDS Summary of Hematocrit in Males at 6 months (2-Year Rats)

Table 7. Summary of BMD Modeling Results for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.435	120.46	36.9	24.4	1.51	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.219	122.31	46.8	24.7	1.90	
Exponential (M4)	0.197	122.46	36.9	24.4	1.51	
Power	0.219	122.31	46.4	25.3	1.84	
Polynomial 3°	**0.469**	**120.31**	**45.3**	**25.3**	**1.79**	
Polynomial 2°	0.468	120.31	43.2	35.4	1.22	
Linear	0.436	120.46	37.3	25.1	1.49	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.339), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 1, and 50 mg/kg/day were -0.12, -0.8, 0.92, 0, respectively.

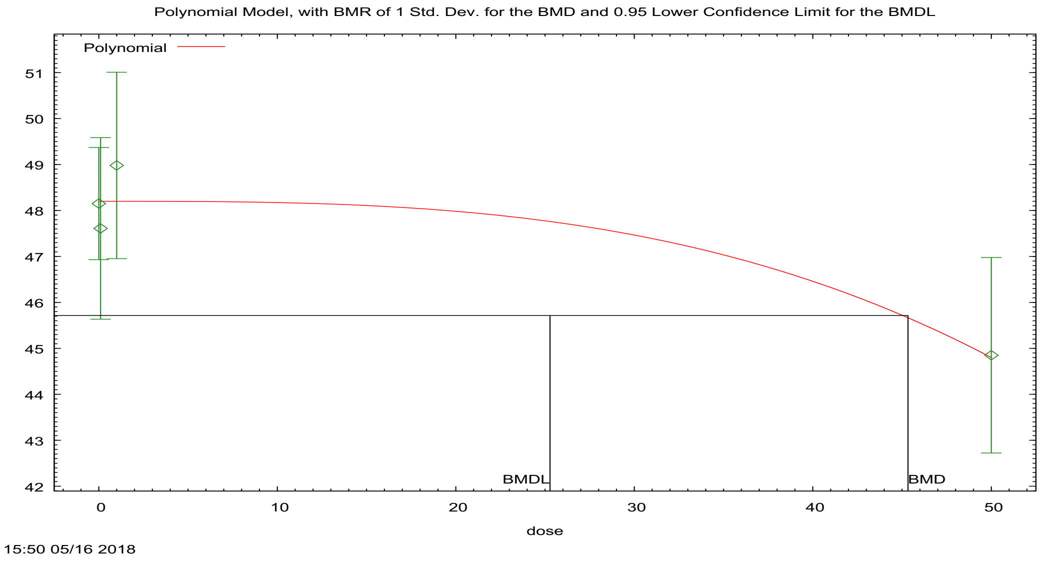

Figure 19. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 45.3334

BMDL at the 95% confidence level = 25.279

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.40912	6.85666
rho	n/a	0
beta_0	48.2467	48.15
beta_1	0	-6.10613
beta_2	-5.6392E-25	0
beta_3	-0.0000271733	-0.139088

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.1	48.2	1.71	2.53	-0.121
0.1	10	47.6	48.2	2.76	2.53	-0.795
1	10	49	48.2	2.84	2.53	0.916
50	10	44.9	44.9	2.97	2.53	-0.00000696

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.397207	5	122.794415
A2	-54.716879	8	125.433759
A3	-56.397207	5	122.794415
fitted	-57.15445	3	120.3089

R	-62.970874	2	129.941748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.508	6	0.01127
Test 2	3.36066	3	0.3393
Test 3	3.36066	3	0.3393
Test 4	1.51449	2	0.469

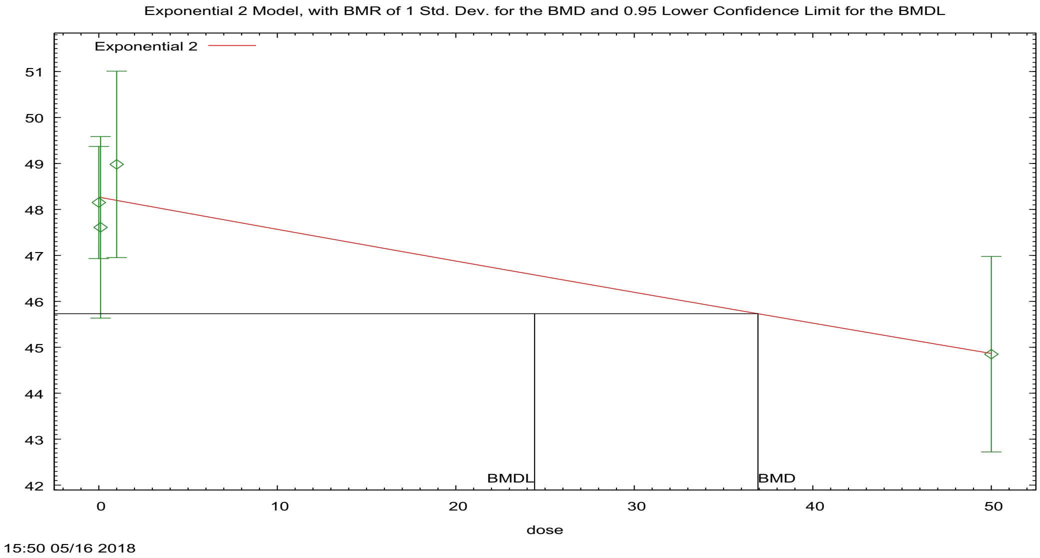

Figure 20. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 36.9284

BMDL at the 95% confidence level = 24.4126

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.86153	1.81986
rho	n/a	0
a	48.2674	46.4954
b	0.00146177	0.00146151
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.15	48.27	1.71	2.54	-0.1464
0.1	10	47.61	48.26	2.76	2.54	-0.8108
1	10	48.98	48.2	2.84	2.54	0.9763
50	10	44.85	44.87	2.97	2.54	-0.01923

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.39721	5	122.7944
A2	-54.71688	8	125.4338
A3	-56.39721	5	122.7944
R	-62.97087	2	129.9417
2	-57.23054	3	120.4611

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.51	6	0.01127
Test 2	3.361	3	0.3393

Test 3	3.361	3	0.3393
Test 4	1.667	2	0.4346

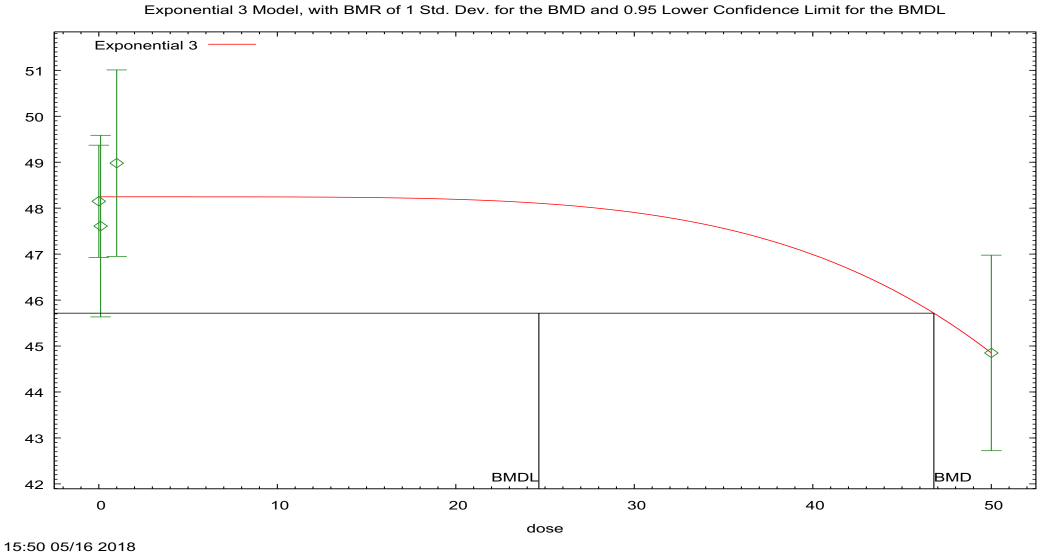

Figure 21. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 46.7835

BMDL at the 95% confidence level = 24.6546

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.85772	1.81986

rho	n/a	0
a	48.2467	46.4954
b	0.0112697	0.00146151
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.15	48.25	1.71	2.53	-0.1207
0.1	10	47.61	48.25	2.76	2.53	-0.7953
1	10	48.98	48.25	2.84	2.53	0.916
50	10	44.85	44.85	2.97	2.53	-0.0000000655

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.39721	5	122.7944
A2	-54.71688	8	125.4338
A3	-56.39721	5	122.7944
R	-62.97087	2	129.9417
3	-57.15442	4	122.3088

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.51	6	0.01127
Test 2	3.361	3	0.3393
Test 3	3.361	3	0.3393
Test 5a	1.514	1	0.2185

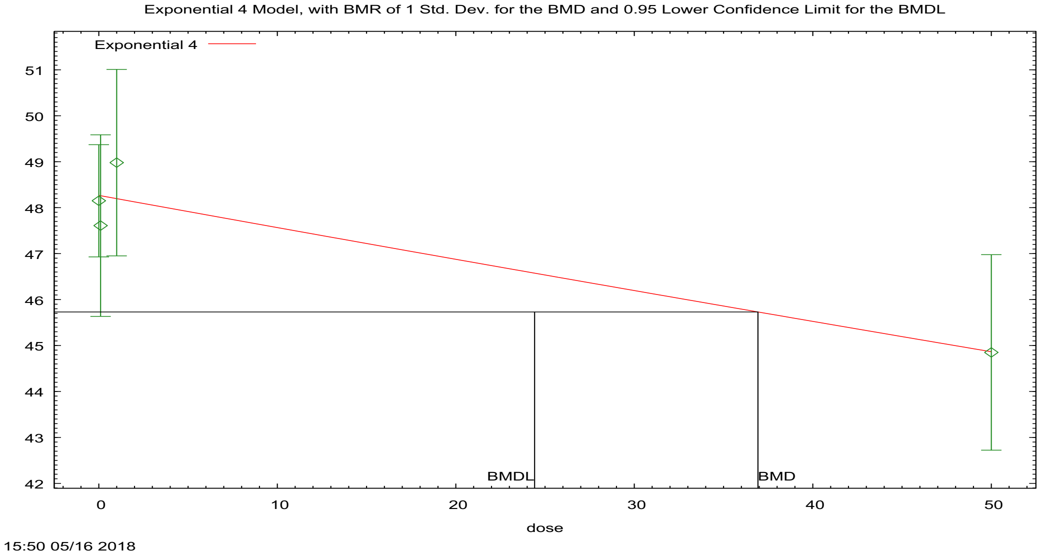

Figure 22. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 36.9284

BMDL at the 95% confidence level = 24.4126

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.86153	1.81986
rho	n/a	0
a	48.2674	51.429
b	0.00146177	0.0282678

c	0.000000000174759	0.830549
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.15	48.27	1.71	2.54	-0.1464
0.1	10	47.61	48.26	2.76	2.54	-0.8108
1	10	48.98	48.2	2.84	2.54	0.9763
50	10	44.85	44.87	2.97	2.54	-0.01923

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.39721	5	122.7944
A2	-54.71688	8	125.4338
A3	-56.39721	5	122.7944
R	-62.97087	2	129.9417
4	-57.23054	4	122.4611

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.51	6	0.01127
Test 2	3.361	3	0.3393
Test 3	3.361	3	0.3393
Test 6a	1.667	1	0.1967

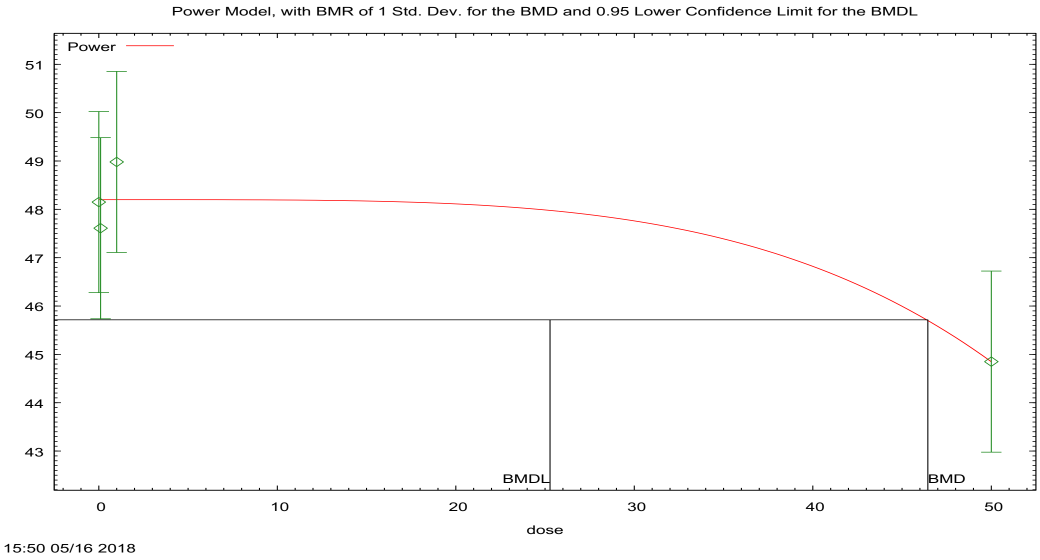

Figure 23. Plot of mean response by dose with fitted curve for Power model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 46.4432

BMDL at the 95% confidence level = 25.2791

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.40911	6.85666
rho	n/a	0
control	48.2467	44.85
slope	-0.000000580442	4.13

power	3.98317	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.1	48.2	1.71	2.53	-0.121
0.1	10	47.6	48.2	2.76	2.53	-0.795
1	10	49	48.2	2.84	2.53	0.916
50	10	44.9	44.9	2.97	2.53	-0.000000144

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.397207	5	122.794415
A2	-54.716879	8	125.433759
A3	-56.397207	5	122.794415
fitted	-57.154419	4	122.308839
R	-62.970874	2	129.941748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.508	6	0.01127
Test 2	3.36066	3	0.3393
Test 3	3.36066	3	0.3393
Test 4	1.51442	1	0.2185

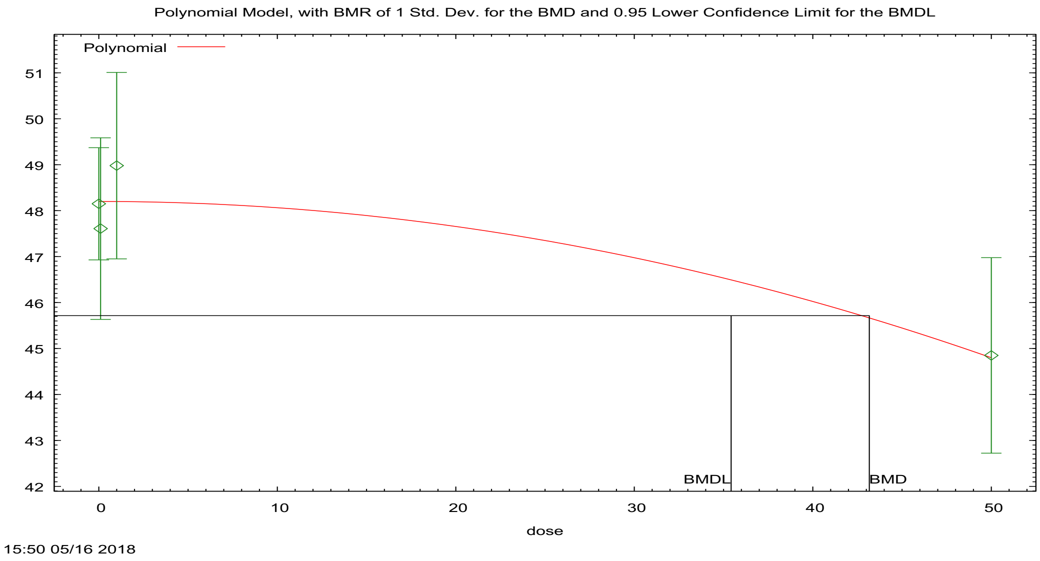

Figure 24. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 43.1665

BMDL at the 95% confidence level = 35.4249

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.40961	6.85666
rho	n/a	0
beta_0	48.247	47.8412
beta_1	-9.04729E-26	0

beta_2	-0.00135869	-0.0237465

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.1	48.2	1.71	2.53	-0.121
0.1	10	47.6	48.2	2.76	2.53	-0.796
1	10	49	48.2	2.84	2.53	0.917
50	10	44.9	44.9	2.97	2.53	-0.000364

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.397207	5	122.794415
A2	-54.716879	8	125.433759
A3	-56.397207	5	122.794415
fitted	-57.155961	3	120.311922
R	-62.970874	2	129.941748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.508	6	0.01127
Test 2	3.36066	3	0.3393
Test 3	3.36066	3	0.3393
Test 4	1.51751	2	0.4682

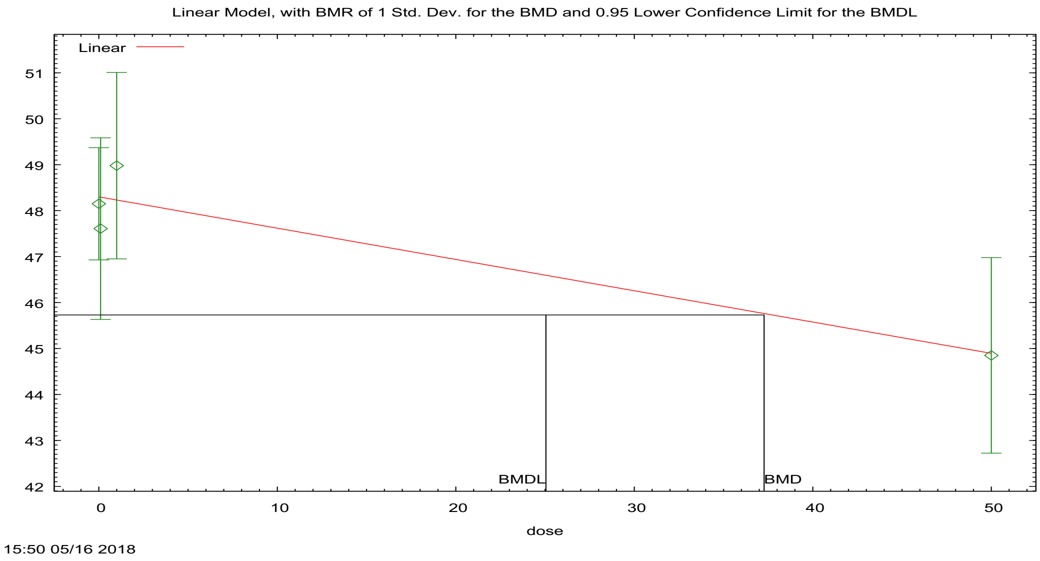

Figure 25. Plot of mean response by dose with fitted curve for Linear model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 37.2705

BMDL at the 95% confidence level = 25.0508

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.43267	6.85666
rho	n/a	0
beta_0	48.2668	48.2668
beta_1	-0.0680504	-0.0680504

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.1	48.3	1.71	2.54	-0.146
0.1	10	47.6	48.3	2.76	2.54	-0.81
1	10	49	48.2	2.84	2.54	0.974
50	10	44.9	44.9	2.97	2.54	-0.0179

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.397207	5	122.794415
A2	-54.716879	8	125.433759
A3	-56.397207	5	122.794415
fitted	-57.227793	3	120.455586
R	-62.970874	2	129.941748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.508	6	0.01127
Test 2	3.36066	3	0.3393
Test 3	3.36066	3	0.3393
Test 4	1.66117	2	0.4358

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Albumin to Globulin Ratio in Males

1.8. BMDS Summary of Albumin to Globulin Ratio in Males (28-Day Mice)

Table 8. Summary of BMD Modeling Results for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M4) **Exponential (M5)[b]**	**0.999**	**-93.451**	**0.775**	**0.464**	**1.67**	**Only one model met inclusion criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)).**

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0996), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were 0, 0.06, -0.15, 0.09, respectively.

[b] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

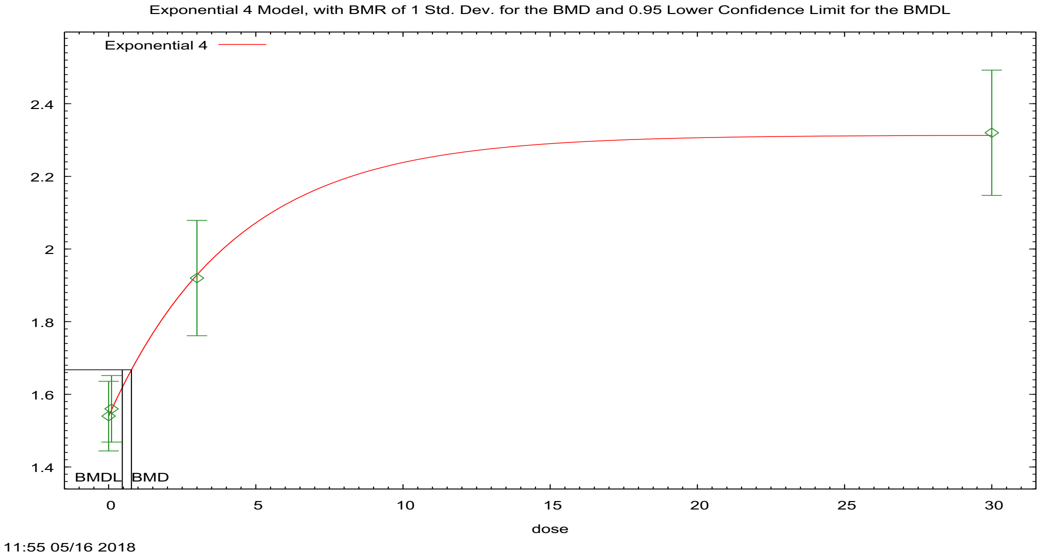

Figure 26. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.774566

BMDL at the 95% confidence level = 0.464264

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.54159	-5.41198
rho	3.29978	3.23182
a	1.53988	1.463
b	0.232774	0.0722953
c	1.50243	1.66507
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.54	0.13	0.13	0.003022
0.1	10	1.56	1.56	0.13	0.13	0.05642
3	10	1.92	1.93	0.22	0.19	-0.1489
30	10	2.32	2.31	0.24	0.25	0.09068

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.91325	5	-87.82651
A2	52.04398	8	-88.08796
A3	51.72568	6	-91.45137
R	20.32428	2	-36.64857

4	51.72568	5	-93.45137

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.44	6	<0.0001
Test 2	6.261	3	0.09956
Test 3	0.6366	2	0.7274
Test 6a	0.0000004765	1	0.9994

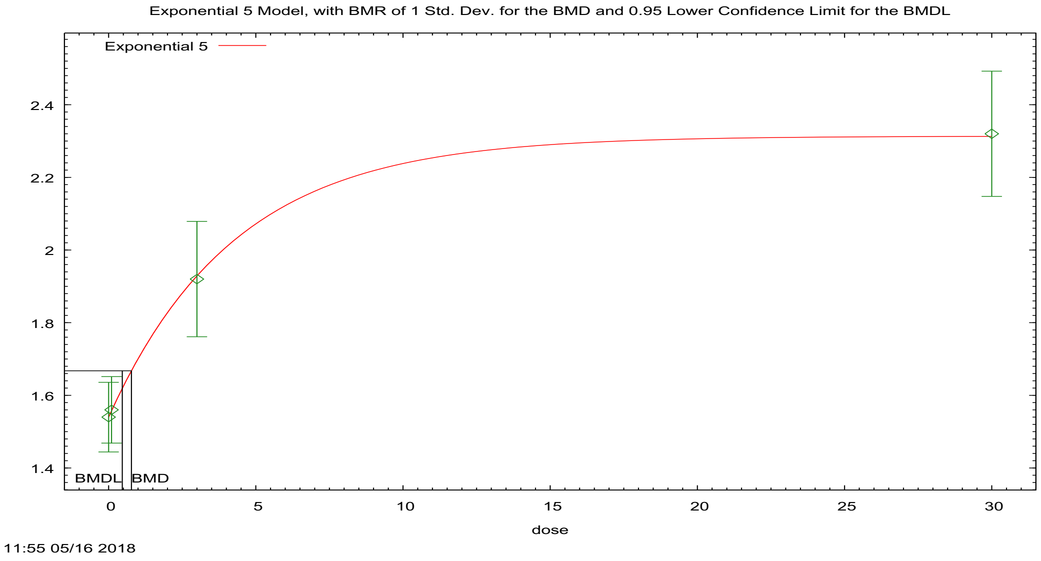

Figure 27. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.774566

BMDL at the 95% confidence level = 0.464264

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.54159	-5.41198
rho	3.29978	3.23182
a	1.53988	1.463
b	0.232774	0.0722953
c	1.50243	1.66507
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.54	0.13	0.13	0.003022
0.1	10	1.56	1.56	0.13	0.13	0.05642
3	10	1.92	1.93	0.22	0.19	-0.1489
30	10	2.32	2.31	0.24	0.25	0.09068

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.91325	5	-87.82651
A2	52.04398	8	-88.08796
A3	51.72568	6	-91.45137
R	20.32428	2	-36.64857
5	51.72568	5	-93.45137

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.44	6	<0.0001
Test 2	6.261	3	0.09956

Test 3	0.6366	2	0.7274
Test 7a	0.0000004765	1	0.9994

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Albumin to Globulin Ratio in Females

1.9. BMDS Summary of Albumin to Globulin Ratio in Females (28-Day Mice)

Table 9. Summary of BMD Modeling Results for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M4) Exponential (M5)[b]	0.538	-109.00	1.42	0.863	1.64	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from model with lowest AIC and lowest BMDL.
Hill	**0.573**	**-109.07**	**1.22**	**0.595**	**2.04**	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.119), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were -0.38, 0.41, -0.05, 0.01, respectively.

[b] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

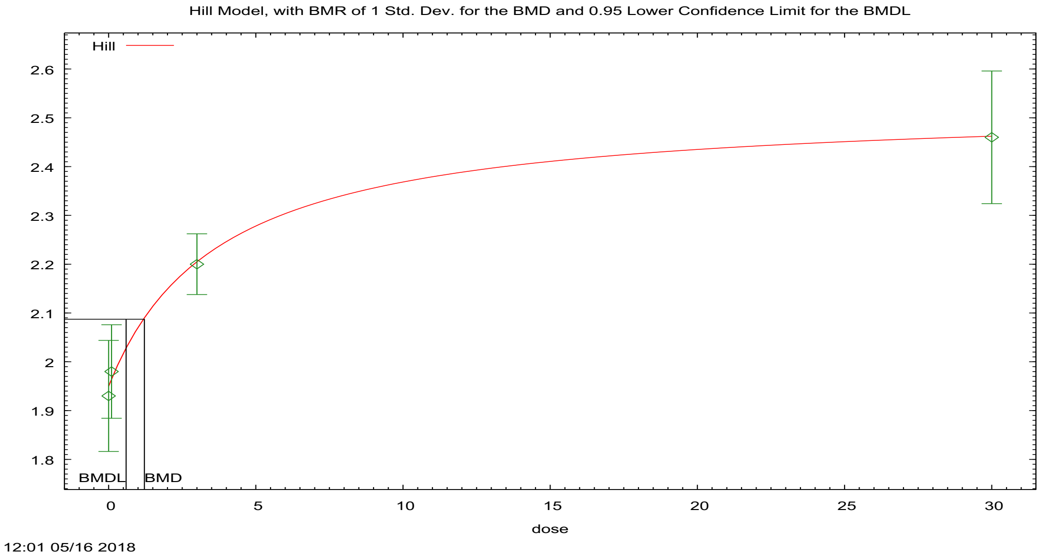

Figure 28. Plot of mean response by dose with fitted curve for Hill model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.21611

BMDL at the 95% confidence level = 0.595276

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0197096	0.0217265
rho	n/a	0
intercept	1.94679	1.93
v	0.577417	0.53
n	1	0.330384
k	3.78567	3.06591

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	1.95	0.16	0.14	-0.378
0.1	10	1.98	1.96	0.13	0.14	0.413
3	10	2.2	2.2	0.09	0.14	-0.0465
30	10	2.46	2.46	0.19	0.14	0.0112

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	58.691662	5	-107.383323
A2	61.62066	8	-107.241319
A3	58.691662	5	-107.383323
fitted	58.532951	4	-109.065902

R	35.142939	2	-66.285878

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.9554	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 4	0.317422	1	0.5732

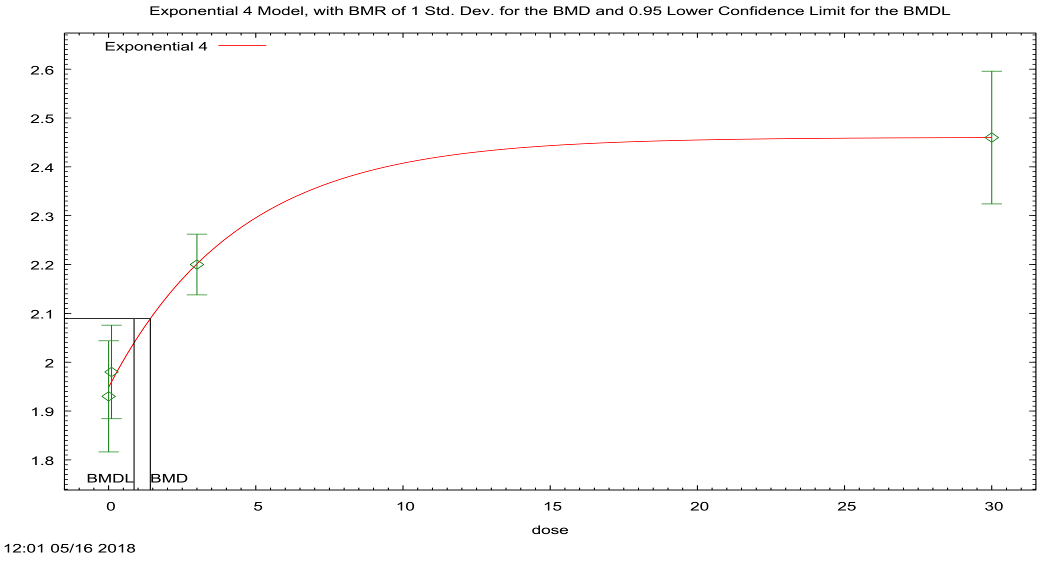

Figure 29. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.41534

BMDL at the 95% confidence level = 0.863474

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.92511	-3.93458
rho	n/a	0
a	1.94872	1.8335
b	0.226816	0.0618833
c	1.26256	1.40878
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	1.95	0.16	0.14	-0.4213
0.1	10	1.98	1.96	0.13	0.14	0.4458
3	10	2.2	2.2	0.09	0.14	-0.02878
30	10	2.46	2.46	0.19	0.14	0.004218

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	58.69166	5	-107.3833
A2	61.62066	8	-107.2413
A3	58.69166	5	-107.3833
R	35.14294	2	-66.28588
4	58.50222	4	-109.0044

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.96	6	<0.0001
Test 2	5.858	3	0.1187

Test 3	5.858	3	0.1187
Test 6a	0.3789	1	0.5382

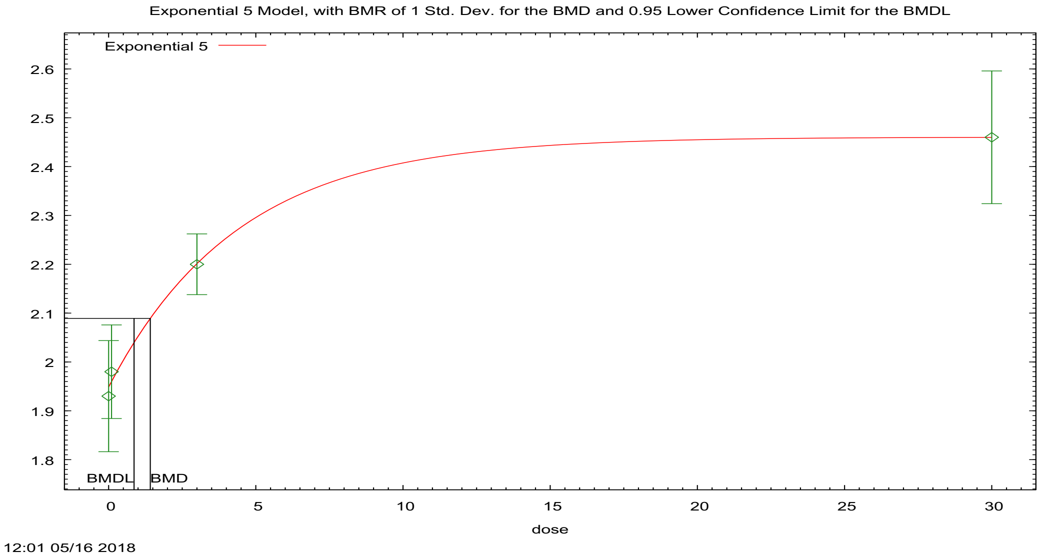

Figure 30. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.41534

BMDL at the 95% confidence level = 0.863474

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.92511	-3.93458

rho	n/a	0
a	1.94872	1.8335
b	0.226816	0.0618833
c	1.26256	1.40878
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	1.95	0.16	0.14	-0.4213
0.1	10	1.98	1.96	0.13	0.14	0.4458
3	10	2.2	2.2	0.09	0.14	-0.02878
30	10	2.46	2.46	0.19	0.14	0.004213

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	58.69166	5	-107.3833
A2	61.62066	8	-107.2413
A3	58.69166	5	-107.3833
R	35.14294	2	-66.28588
5	58.50222	4	-109.0044

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.96	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 7a	0.3789	1	0.5382

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery – Albumin to Globulin Ratio in Males

1.10. BMDS Summary of Albumin to Globulin Ratio in Males (28-Day Rats)

Table 10. Summary of BMD Modeling Results for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	**Goodness of fit**		**BMD$_{1SD}$ (mg/kg/day)**	**BMDL$_{1SD}$ (mg/kg/day)**	**BMD/BMDL**	**Basis for model selection**
	***p*-value**	**AIC**				
Exponential (M4) Exponential (M5)[b]	0.511	-81.804	2.07	1.17	1.76	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from model with lowest AIC and lowest BMDL.
Hill	**0.544**	**-81.868**	**1.94**	**0.945**	**2.05**	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.764), selected model in bold; scaled residuals for selected model for doses 0, 0.3, 3, and 30 mg/kg/day were -0.38, 0.46, -0.1, 0.01, respectively.

[b] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

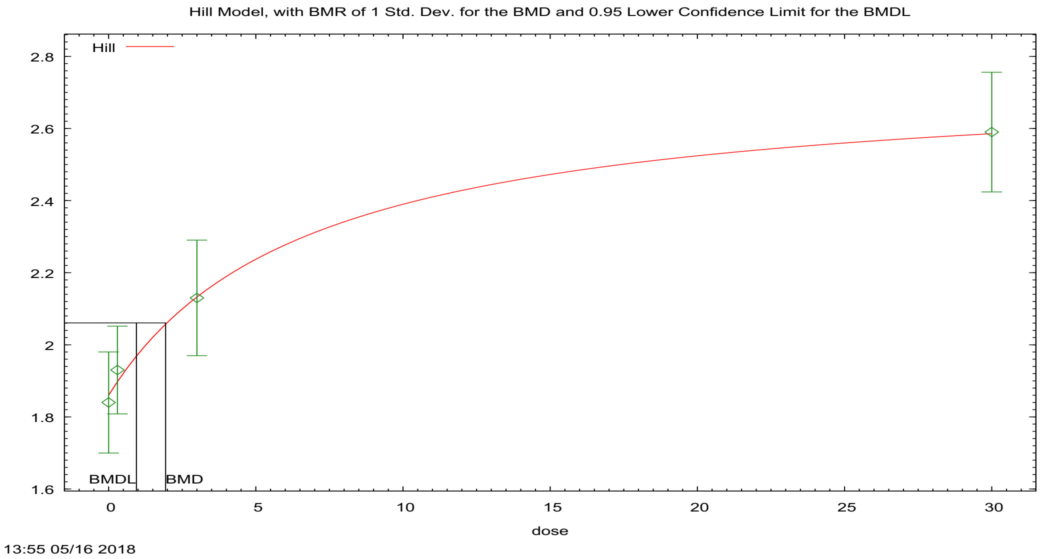

Figure 31. Plot of mean response by dose with fitted curve for Hill model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.93577

BMDL at the 95% confidence level = 0.944663

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0389019	0.042829
rho	n/a	0
intercept	1.86356	1.84
v	0.890165	0.75
n	1	0.274093
k	6.80075	52.0109

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.86	0.2	0.2	-0.378
0.3	10	1.93	1.9	0.17	0.2	0.462
3	10	2.13	2.14	0.22	0.2	-0.0969
30	10	2.59	2.59	0.23	0.2	0.0124

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.118007	5	-80.236014
A2	45.694456	8	-75.388913
A3	45.118007	5	-80.236014
fitted	44.934219	4	-81.868439

R	22.006792	2	-40.013584

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	47.3753	6	<0.0001
Test 2	1.1529	3	0.7643
Test 3	1.1529	3	0.7643
Test 4	0.367575	1	0.5443

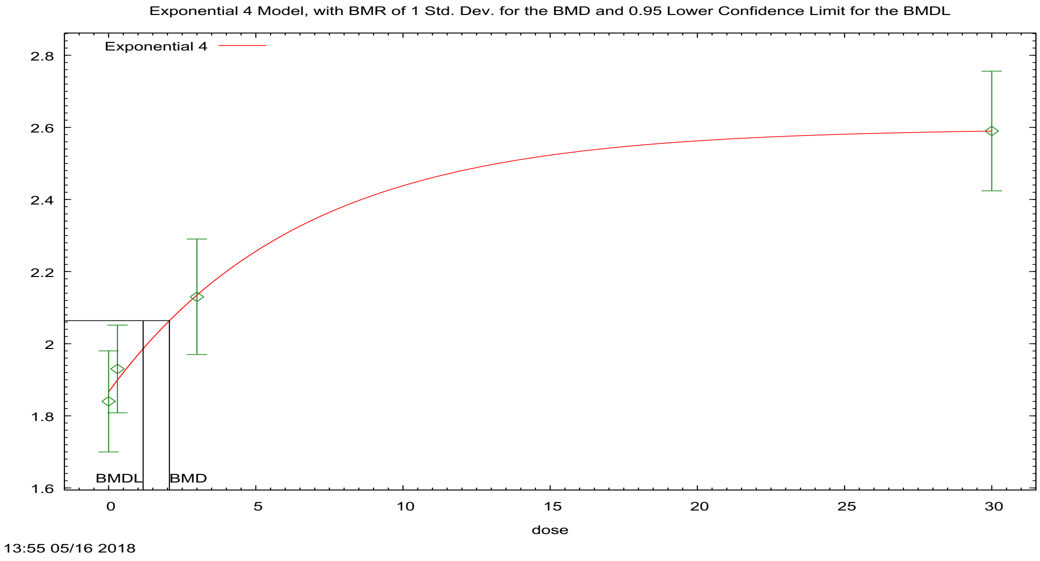

Figure 32. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.06536

BMDL at the 95% confidence level = 1.1729

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.24509	-3.2559
rho	n/a	0
a	1.86649	1.748
b	0.152473	0.0682174
c	1.39148	1.55578
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.87	0.2	0.2	-0.4243
0.3	10	1.93	1.9	0.17	0.2	0.4941
3	10	2.13	2.13	0.22	0.2	-0.07551
30	10	2.59	2.59	0.23	0.2	0.005683

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.11801	5	-80.23601
A2	45.69446	8	-75.38891
A3	45.11801	5	-80.23601
R	22.00679	2	-40.01358
4	44.90188	4	-81.80377

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	47.38	6	<0.0001
Test 2	1.153	3	0.7643

Test 3	1.153	3	0.7643
Test 6a	0.4322	1	0.5109

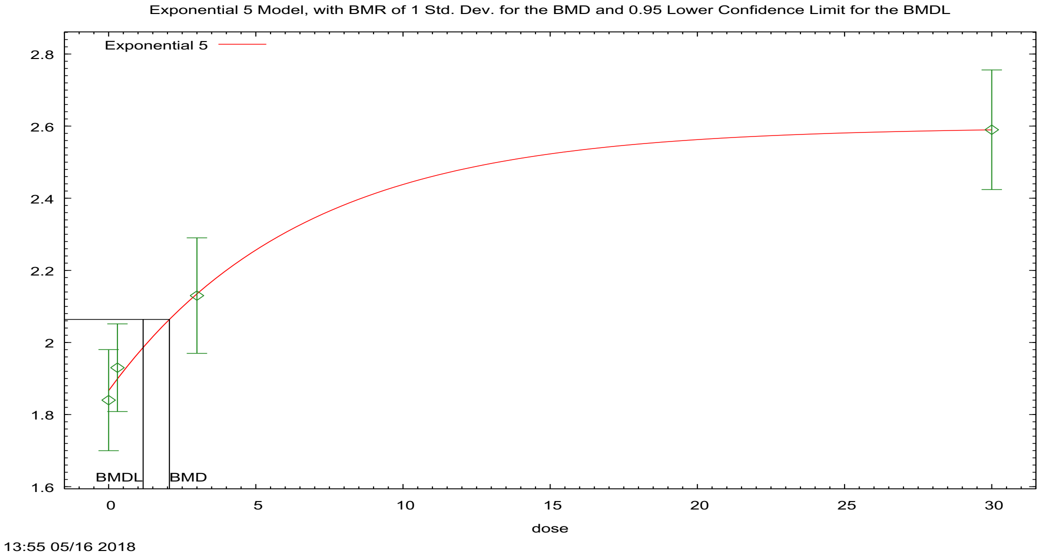

Figure 33. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.06536

BMDL at the 95% confidence level = 1.1729

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.24509	-3.2559

rho	n/a	0
a	1.86649	1.748
b	0.152473	0.0682174
c	1.39148	1.55578
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.87	0.2	0.2	-0.4243
0.3	10	1.93	1.9	0.17	0.2	0.4941
3	10	2.13	2.13	0.22	0.2	-0.07551
30	10	2.59	2.59	0.23	0.2	0.005683

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.11801	5	-80.23601
A2	45.69446	8	-75.38891
A3	45.11801	5	-80.23601
R	22.00679	2	-40.01358
5	44.90188	4	-81.80377

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	47.38	6	<0.0001
Test 2	1.153	3	0.7643
Test 3	1.153	3	0.7643
Test 7a	0.4322	1	0.5109

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery – Albumin to Globulin Ratio in Males

1.11. BMDS Summary of Albumin to Globulin Ratio in Males (90-Day Rats)

Table 11. Summary of BMD Modeling Results for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	**Goodness of fit**		**BMD_{1SD} (mg/kg/day)**	**BMDL_{1SD} (mg/kg/day)**	**BMD/BMDL**	**Basis for model selection**
	***p*-value**	**AIC**				
Exponential (M4) Exponential (M5)[b]	**0.287**	**-65.584**	**3.39**	**0.0741**	**45.8**	**Only one model met inclusion criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)).**

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0976), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 10, and 100 mg/kg/day were -0.72, 0.73, 0.01, -0.02, respectively.

[b] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

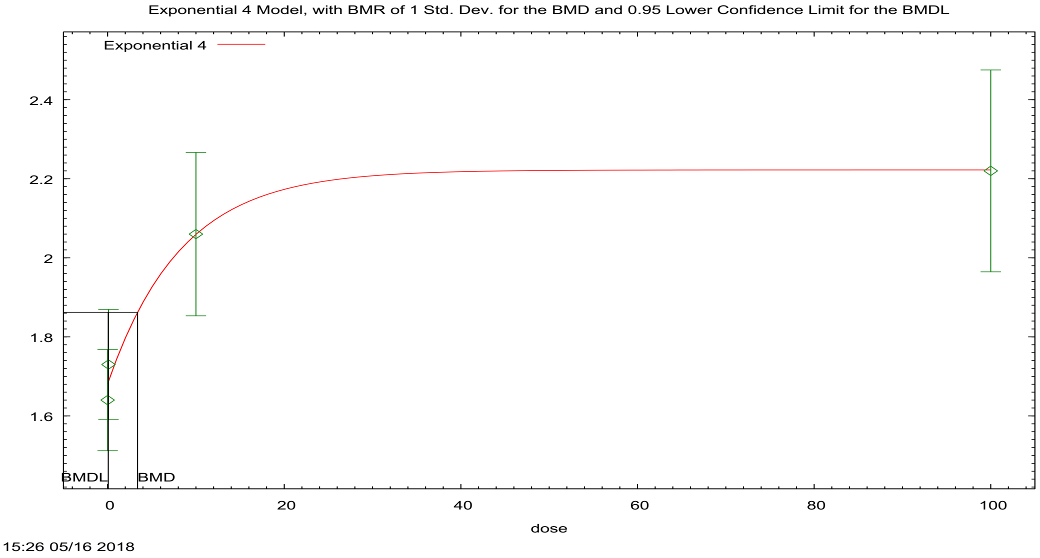

Figure 34. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 3.39438

BMDL at the 95% confidence level = 0.0740762

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.68779	-5.73506
rho	4.36573	4.55995
a	1.68125	1.558
b	0.119894	0.0202556
c	1.32183	1.49615
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.68	0.18	0.18	-0.7212
0.1	10	1.73	1.69	0.2	0.18	0.7332
10	10	2.06	2.06	0.29	0.28	0.0091
100	10	2.22	2.22	0.36	0.33	-0.02215

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.21855	5	-60.4371
A2	38.37194	8	-60.74389
A3	38.35916	6	-64.71831
R	22.53874	2	-41.07748

4	37.79209	5	-65.58419

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.67	6	<0.0001
Test 2	6.307	3	0.0976
Test 3	0.02558	2	0.9873
Test 6a	1.134	1	0.2869

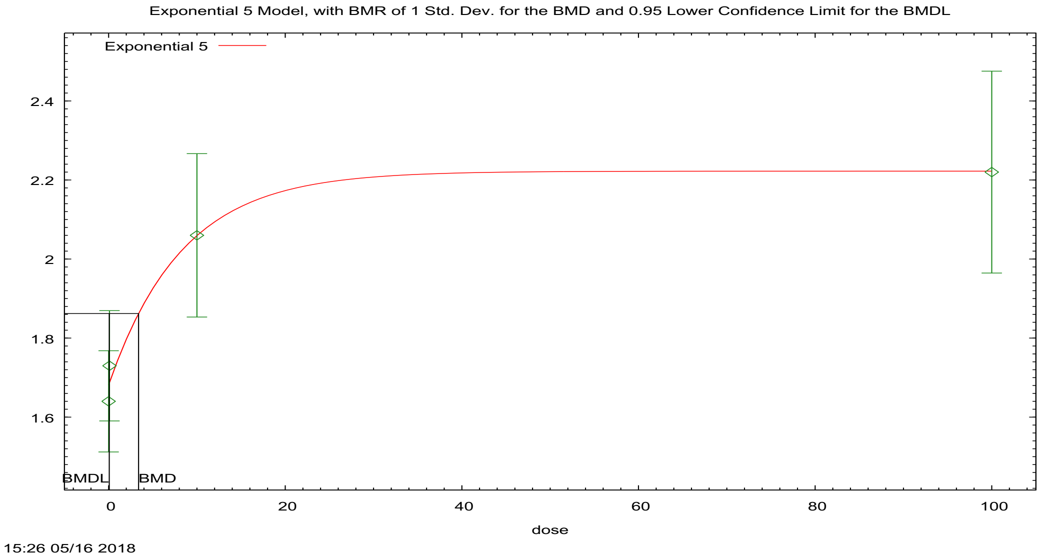

Figure 35. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 3.39438

BMDL at the 95% confidence level = 0.0740762

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.68779	-5.73506
rho	4.36573	4.55995
a	1.68125	1.558
b	0.119894	0.0202556
c	1.32183	1.49615
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.68	0.18	0.18	-0.7212
0.1	10	1.73	1.69	0.2	0.18	0.7332
10	10	2.06	2.06	0.29	0.28	0.0091
100	10	2.22	2.22	0.36	0.33	-0.02215

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.21855	5	-60.4371
A2	38.37194	8	-60.74389
A3	38.35916	6	-64.71831
R	22.53874	2	-41.07748
5	37.79209	5	-65.58419

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.67	6	<0.0001
Test 2	6.307	3	0.0976

Test 3	0.02558	2	0.9873
Test 7a	1.134	1	0.2869

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Alkaline Phosphatase (U/L) in Females

1.12. BMDS Summary of Alkaline Phosphatase in Females (28-Day Mice)

Table 12. Summary of BMD Modeling Results for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	**0.535**	**307.32**	**6.97**	**5.55**	**1.26**	**Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.**
Exponential (M3)	0.458	308.62	13.3	5.72	2.32	
Exponential (M4)	0.128	310.38	4.97	3.73	1.33	
Power	0.458	308.62	12.1	4.18	2.89	
Polynomial 3°	0.461	308.61	15.0	4.18	3.58	
Polynomial 2°	0.458	308.62	12.0	4.18	2.88	
Linear	0.315	308.38	4.97	3.73	1.33	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.00267), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were -0.27, 0.78, -0.56, 0.05, respectively.

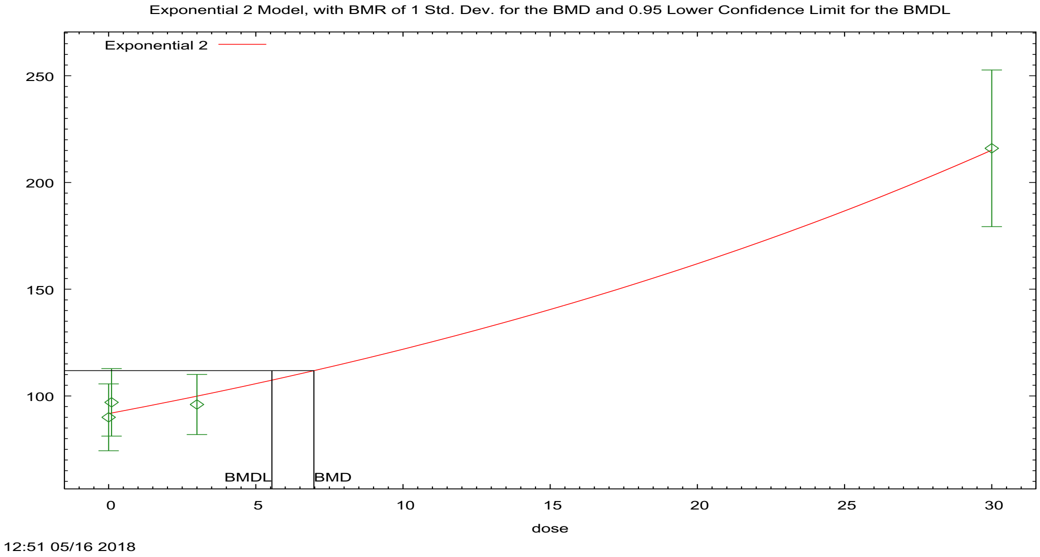

Figure 36. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 6.97274

BMDL at the 95% confidence level = 5.54681

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.25046	-3.48696
rho	2.04737	2.11151
a	91.7451	91.6649
b	0.0284134	0.0284468
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	91.75	21.9	20.1	-0.2745
0.1	10	97	92.01	22.1	20.16	0.7833
3	10	96	99.91	19.7	21.94	-0.5635
30	10	216	215.2	51.3	48.11	0.05472

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.9868	5	321.9736
A2	-148.8965	8	313.7931
A3	-149.0341	6	310.0682
R	-184.213	2	372.4261

2	-149.6606	4	307.3212

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.63	6	<0.0001
Test 2	14.18	3	0.002669
Test 3	0.2752	2	0.8715
Test 4	1.253	2	0.5345

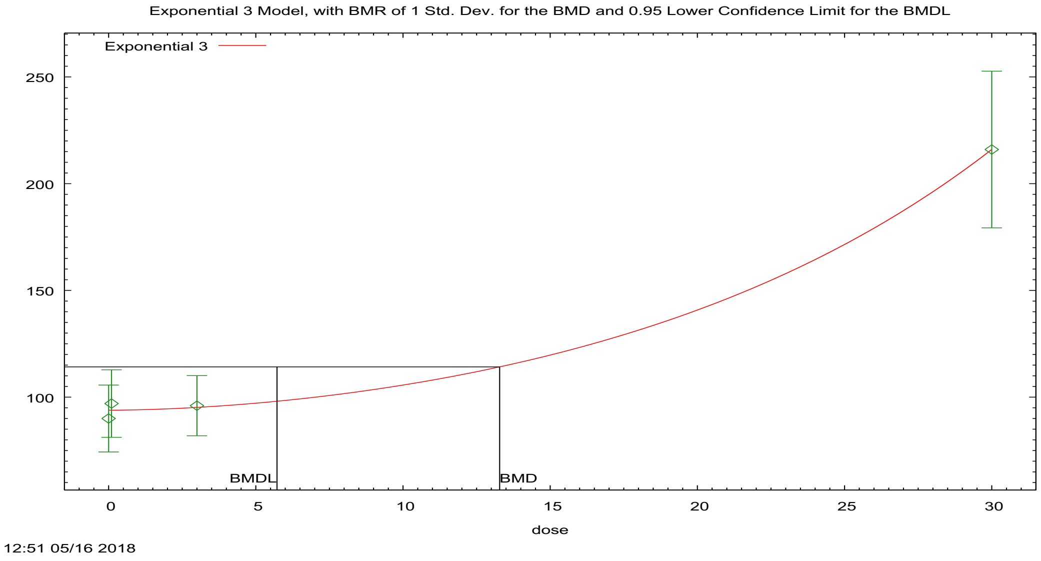

Figure 37. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 13.2823

BMDL at the 95% confidence level = 5.72002

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.49022	-3.48696
rho	2.09422	2.11151
a	93.8856	91.6649
b	0.0300844	0.0284468
c	n/a	0
d	1.77762	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	93.89	21.9	20.31	-0.6051
0.1	10	97	93.89	22.1	20.31	0.4845
3	10	96	95.2	19.7	20.6	0.1227
30	10	216	216	51.3	48.6	-0.002149

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.9868	5	321.9736
A2	-148.8965	8	313.7931
A3	-149.0341	6	310.0682
R	-184.213	2	372.4261
3	-149.3095	5	308.6191

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.63	6	<0.0001
Test 2	14.18	3	0.002669

Test 3	0.2752	2	0.8715
Test 5a	0.5508	1	0.458

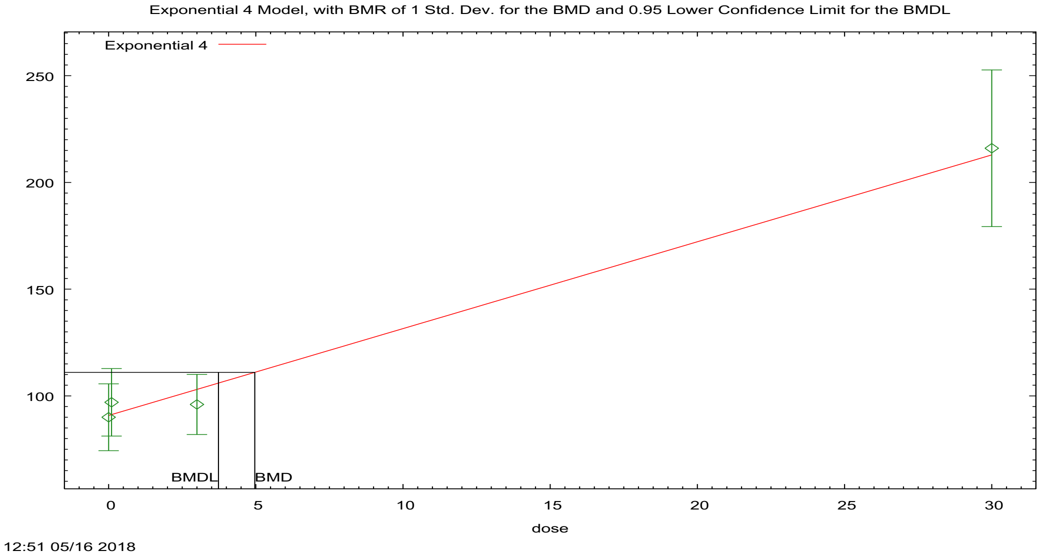

Figure 38. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.96504

BMDL at the 95% confidence level = 3.73159

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.13899	-3.48696

rho	2.02929	2.11151
a	90.8386	85.5
b	0.000000267161	0.0000201196
c	167634	2526.32
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	90.84	21.9	20.2	-0.1313
0.1	10	97	91.25	22.1	20.29	0.8968
3	10	96	103	19.7	22.95	-0.9703
30	10	216	212.9	51.3	47.93	0.2055

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.9868	5	321.9736
A2	-148.8965	8	313.7931
A3	-149.0341	6	310.0682
R	-184.213	2	372.4261
4	-150.1908	5	310.3816

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.63	6	<0.0001
Test 2	14.18	3	0.002669
Test 3	0.2752	2	0.8715
Test 6a	2.313	1	0.1283

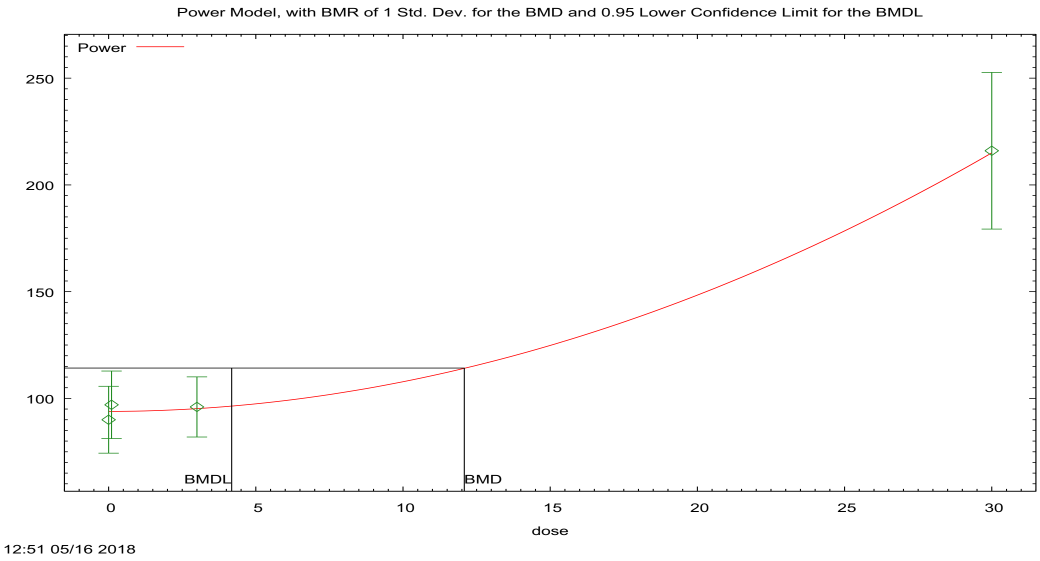

Figure 39. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 12.0822

BMDL at the 95% confidence level = 4.181

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.49043	6.9047
rho	2.09426	0
control	93.8909	90
slope	0.148867	12.3966

power	1.9728	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	93.9	21.9	20.3	-0.606
0.1	10	97	93.9	22.1	20.3	0.484
3	10	96	95.2	19.7	20.6	0.124
30	10	216	216	51.3	48.6	-0.00214

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.986802	5	321.973604
A2	-148.896526	8	313.793052
A3	-149.034119	6	310.068237
fitted	-149.30965	5	308.619299
R	-184.213048	2	372.426096

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.633	6	<0.0001
Test 2	14.1806	3	0.002669
Test 3	0.275185	2	0.8715
Test 4	0.551062	1	0.4579

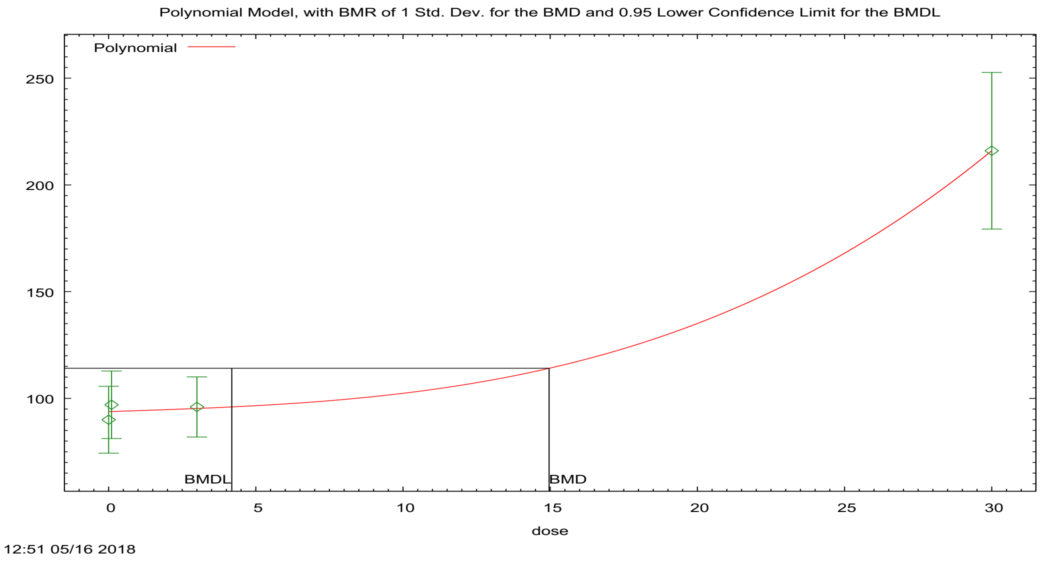

Figure 40. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 14.9627

BMDL at the 95% confidence level = 4.18359

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.48864	6.9047
rho	2.09385	0
beta_0	93.8164	90
beta_1	0.456035	0

beta_2	2.21944E-13	0
beta_3	0.00401997	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	93.8	21.9	20.3	-0.595
0.1	10	97	93.9	22.1	20.3	0.489
3	10	96	95.3	19.7	20.6	0.108
30	10	216	216	51.3	48.6	-0.00239

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.986802	5	321.973604
A2	-148.896526	8	313.793052
A3	-149.034119	6	310.068237
fitted	-149.306152	5	308.612304
R	-184.213048	2	372.426096

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.633	6	<0.0001
Test 2	14.1806	3	0.002669
Test 3	0.275185	2	0.8715
Test 4	0.544067	1	0.4608

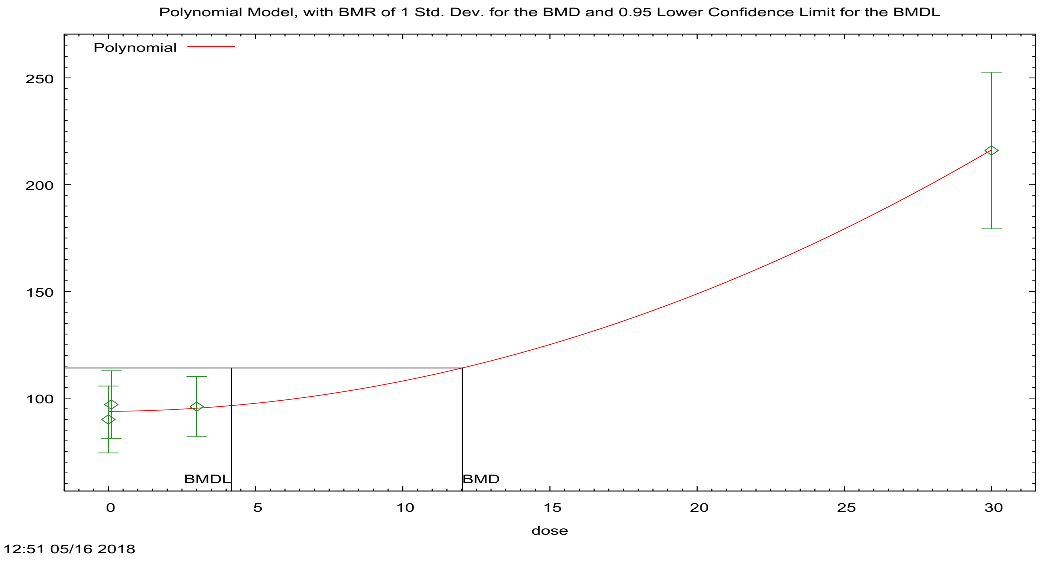

Figure 41. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 12.022

BMDL at the 95% confidence level = 4.18135

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.48753	6.9047
rho	2.09365	0
beta_0	93.8305	93.407
beta_1	0.0931736	0

beta_2	0.132672	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	93.8	21.9	20.3	-0.597
0.1	10	97	93.8	22.1	20.3	0.492
3	10	96	95.3	19.7	20.6	0.107
30	10	216	216	51.3	48.6	-0.00199

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.986802	5	321.973604
A2	-148.896526	8	313.793052
A3	-149.034119	6	310.068237
fitted	-149.309169	5	308.618338
R	-184.213048	2	372.426096

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.633	6	<0.0001
Test 2	14.1806	3	0.002669
Test 3	0.275185	2	0.8715
Test 4	0.550101	1	0.4583

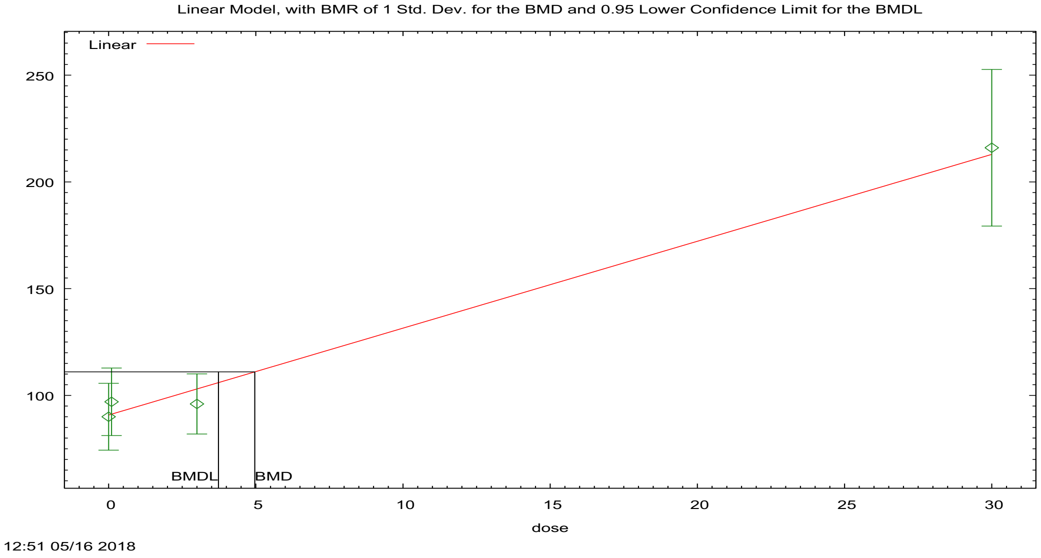

Figure 42. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.96506

BMDL at the 95% confidence level = 3.7316

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.13897	6.9047
rho	2.02929	0
beta_0	90.8386	90.2423
beta_1	4.0682	4.17012

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	90.8	21.9	20.2	-0.131
0.1	10	97	91.2	22.1	20.3	0.897
3	10	96	103	19.7	23	-0.97
30	10	216	213	51.3	47.9	0.206

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.986802	5	321.973604
A2	-148.896526	8	313.793052
A3	-149.034119	6	310.068237
fitted	-150.190806	4	308.381612
R	-184.213048	2	372.426096

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.633	6	<0.0001
Test 2	14.1806	3	0.002669
Test 3	0.275185	2	0.8715
Test 4	2.31338	2	0.3145

BMDS WIZARD OUTPUT REPORT

Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Alkaline Phosphatase (U/L) in Males

1.13. BMDS Summary of Alkaline Phosphatase in Males (90-Day Mice)

Table 13. Summary of BMD Modeling Results for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	**Goodness of fit**		**BMD_{1SD} (mg/kg/day)**	**BMDL_{1SD} (mg/kg/day)**	**BMD/BMDL**	**Basis for model selection**
	***p*-value**	**AIC**				
Exponential (M2) **Exponential (M3)**[b]	**0.384**	**344.14**	**0.596**	**0.480**	**1.24**	**Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.**
Power	0.314	345.24	0.383	0.190	2.02	
Polynomial 3°	0.502	344.68	0.329	0.173	1.90	
Polynomial 2°	0.452	344.79	0.343	0.176	1.95	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.38, 0.03, 0.41, -0.06, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

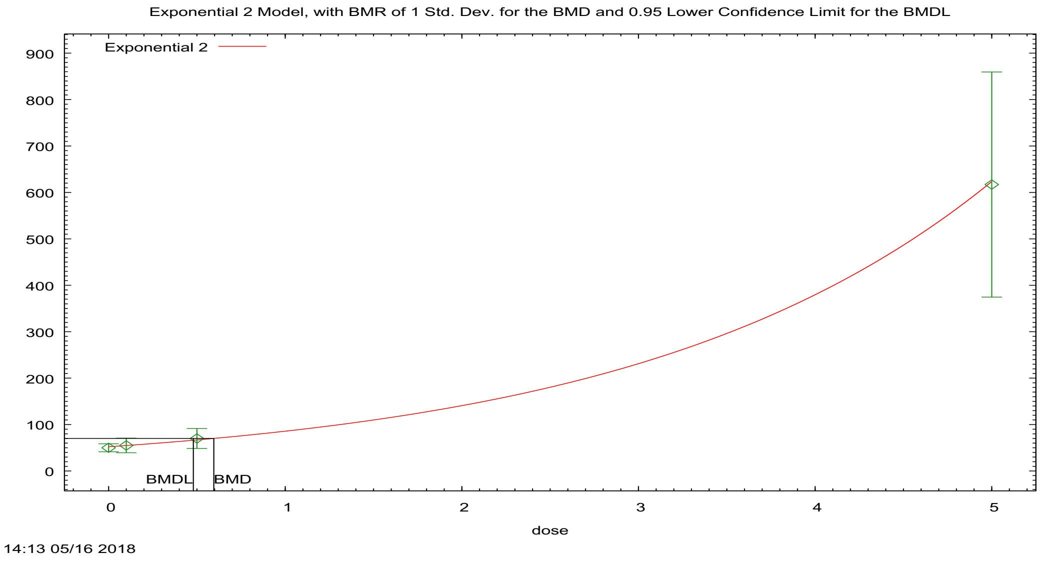

Figure 43. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.595588

BMDL at the 95% confidence level = 0.479579

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.50607	-3.88175
rho	2.34657	2.42747
a	52.176	52.2193
b	0.496121	0.494806
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	52.18	12	17.94	-0.3836
0.1	10	55	54.83	22	19.01	0.02831
0.5	10	70	66.87	30	24	0.4131
5	10	617	623.4	339	329.4	-0.06168

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.4711	5	456.9422
A2	-165.9243	8	347.8485
A3	-167.1141	6	346.2282
R	-246.9552	2	497.9105

2	-168.0715	4	344.143

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.1	6	<0.0001
Test 2	115.1	3	<0.0001
Test 3	2.38	2	0.3043
Test 4	1.915	2	0.3839

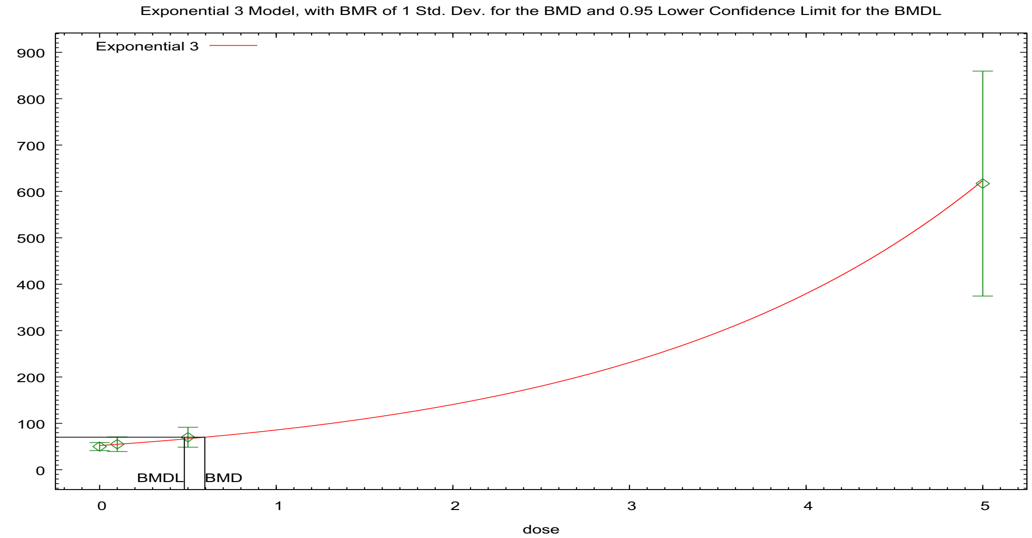

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Figure 44. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.595588

BMDL at the 95% confidence level = 0.479579

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.50607	-3.88175
rho	2.34657	2.42747
a	52.176	52.2193
b	0.496121	0.494806
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	52.18	12	17.94	-0.3836
0.1	10	55	54.83	22	19.01	0.02831
0.5	10	70	66.87	30	24	0.4131
5	10	617	623.4	339	329.4	-0.06168

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.4711	5	456.9422
A2	-165.9243	8	347.8485
A3	-167.1141	6	346.2282
R	-246.9552	2	497.9105
3	-168.0715	4	344.143

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.1	6	<0.0001
Test 2	115.1	3	<0.0001

Test 3	2.38	2	0.3043
Test 5a	1.915	2	0.3839

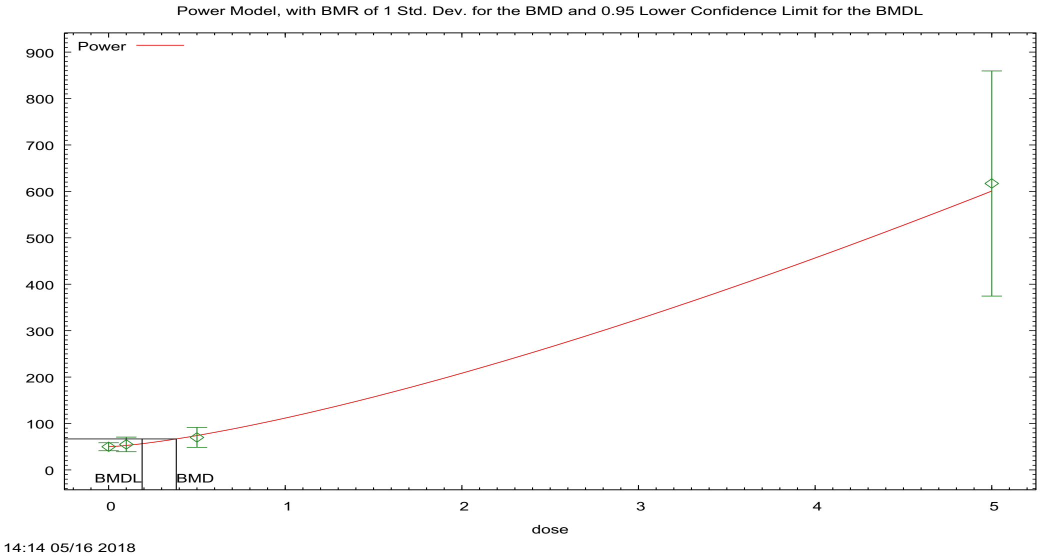

Figure 45. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.383064

BMDL at the 95% confidence level = 0.189838

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.74074	10.2789

rho	2.39323	0
control	50.1106	50
slope	61.6774	78.8136
power	1.36362	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	50.1	12	16.7	-0.021
0.1	10	55	52.8	22	17.7	0.396
0.5	10	70	74.1	30	26.6	-0.485
5	10	617	604	339	328	0.128

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.471076	5	456.942152
A2	-165.924256	8	347.848511
A3	-167.114116	6	346.228232
fitted	-167.62034	5	345.24068
R	-246.955243	2	497.910486

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.062	6	<0.0001
Test 2	115.094	3	<0.0001
Test 3	2.37972	2	0.3043
Test 4	1.01245	1	0.3143

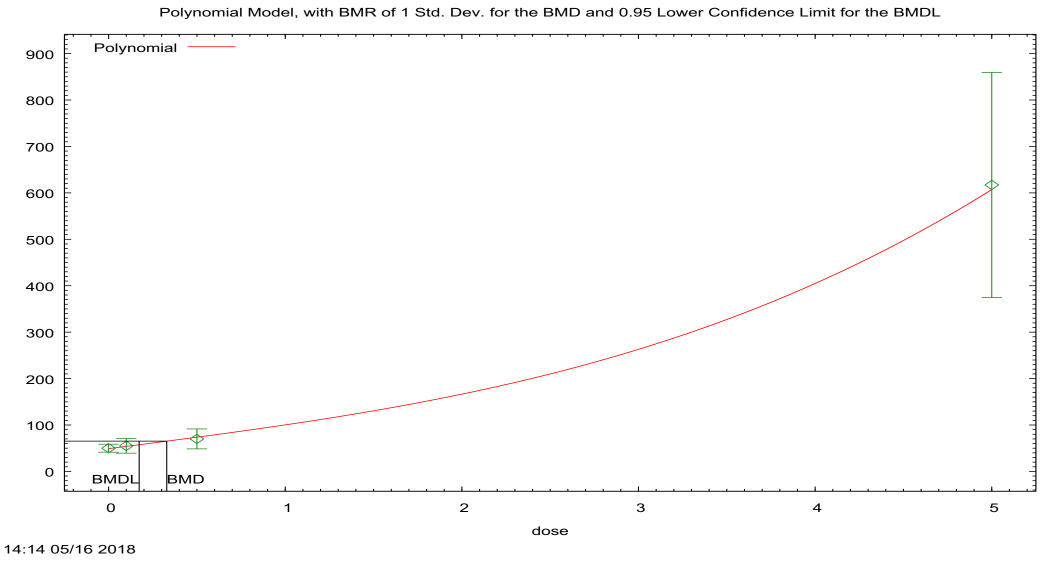

Figure 46. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.329181

BMDL at the 95% confidence level = 0.172959

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.78821	10.2789
rho	2.40012	0
beta_0	49.095	50
beta_1	48.6274	52.9215

beta_2	0	0
beta_3	2.51926	8.43084

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	49.1	12	16.1	0.178
0.1	10	55	54	22	18	0.182
0.5	10	70	73.7	30	26.2	-0.449
5	10	617	607	339	329	0.0947

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.471076	5	456.942152
A2	-165.924256	8	347.848511
A3	-167.114116	6	346.228232
fitted	-167.340021	5	344.680042
R	-246.955243	2	497.910486

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.062	6	<0.0001
Test 2	115.094	3	<0.0001
Test 3	2.37972	2	0.3043
Test 4	0.45181	1	0.5015

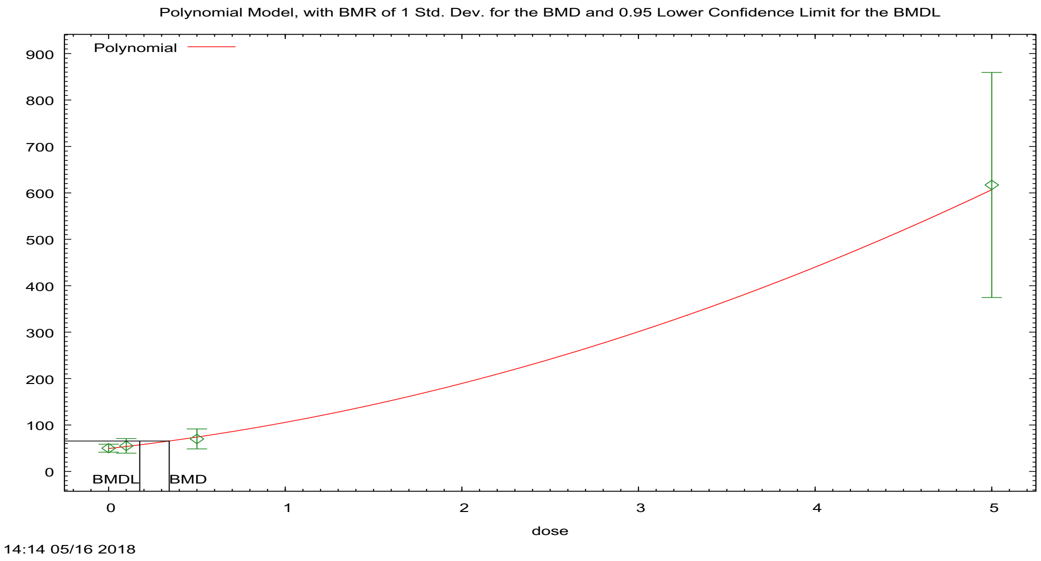

Figure 47. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.343149

BMDL at the 95% confidence level = 0.176227

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.78664	10.2789
rho	2.40053	0
beta_0	49.2818	50.7795
beta_1	42.4794	30.6108

beta_2	13.7541	16.5266

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	49.3	12	16.2	0.14
0.1	10	55	53.7	22	17.9	0.235
0.5	10	70	74	30	26.4	-0.475
5	10	617	606	339	329	0.11

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.471076	5	456.942152
A2	-165.924256	8	347.848511
A3	-167.114116	6	346.228232
fitted	-167.396602	5	344.793204
R	-246.955243	2	497.910486

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.062	6	<0.0001
Test 2	115.094	3	<0.0001
Test 3	2.37972	2	0.3043
Test 4	0.564972	1	0.4523

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Alkaline Phosphatase (U/L) in Females

1.14. BMDS Summary of Alkaline Phosphatase in Females (90-Day Mice)

Table 14. Summary of BMD Modeling Results for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.279	285.79	1.55	1.23	1.27	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.123	287.61	4.29	1.24	3.48	
Power	**0.305**	**285.61**	**4.62**	**0.859**	**5.37**	
Polynomial 3°	0.126	287.58	2.69	0.861	3.13	
Polynomial 2°	0.123	287.62	2.22	0.859	2.59	
Linear	0.233	286.15	1.13	0.833	1.36	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0751), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.97, 0.88, 0.1, 0, respectively.

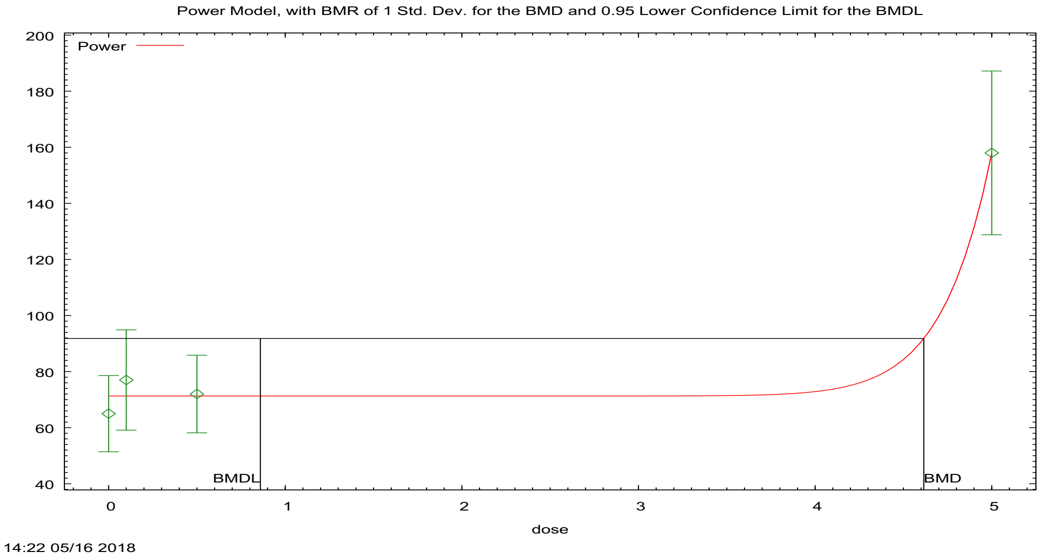

Figure 48. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.61514

BMDL at the 95% confidence level = 0.85933

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.0547528	6.51767
rho	1.40296	0
control	71.3103	65
slope	2.27252E-11	25.7584
power	18	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	71.3	19	20.5	-0.973
0.1	10	77	71.3	25	20.5	0.877
0.5	9	72	71.3	18	20.5	0.101
5	9	158	158	38	35.8	-0.0000000501

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.722467	5	291.444934
A2	-137.271117	8	290.542234
A3	-137.618003	6	287.236006
fitted	-138.80647	4	285.61294

R	-163.256735	2	330.513469

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.9712	6	<0.0001
Test 2	6.9027	3	0.07506
Test 3	0.693772	2	0.7069
Test 4	2.37693	2	0.3047

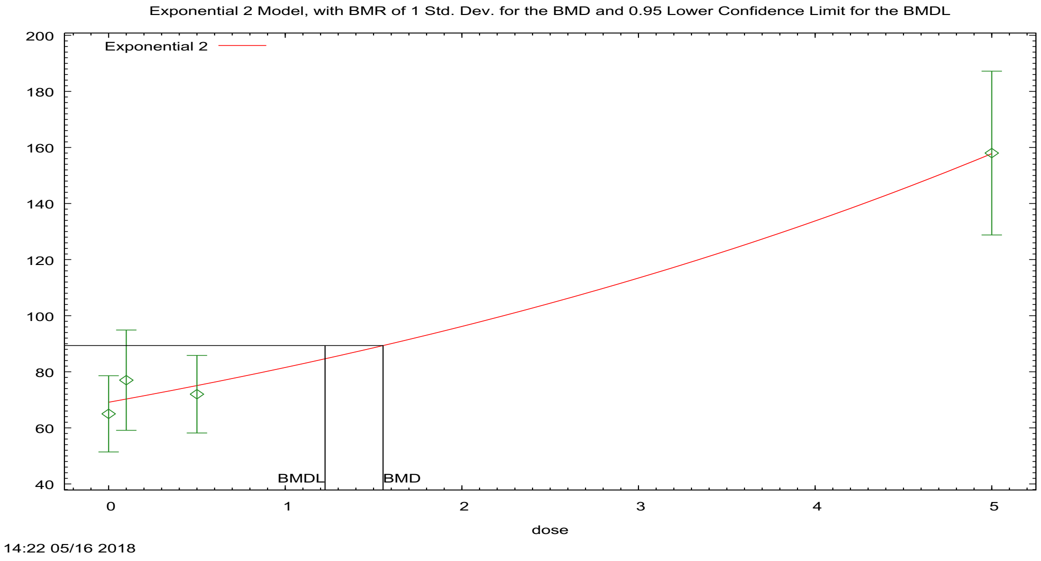

Figure 49. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.55374

BMDL at the 95% confidence level = 1.22565

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.261796	-0.767201
rho	1.35758	1.59325
a	69.1285	68.977
b	0.16507	0.165384
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	69.13	19	20.21	-0.646
0.1	10	77	70.28	25	20.44	1.04
0.5	9	72	75.08	18	21.38	-0.4317
5	9	158	157.8	38	35.39	0.0171

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.7225	5	291.4449
A2	-137.2711	8	290.5422
A3	-137.618	6	287.236
R	-163.2567	2	330.5135
2	-138.895	4	285.79

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.97	6	<0.0001
Test 2	6.903	3	0.07506

Test 3	0.6938	2	0.7069
Test 4	2.554	2	0.2789

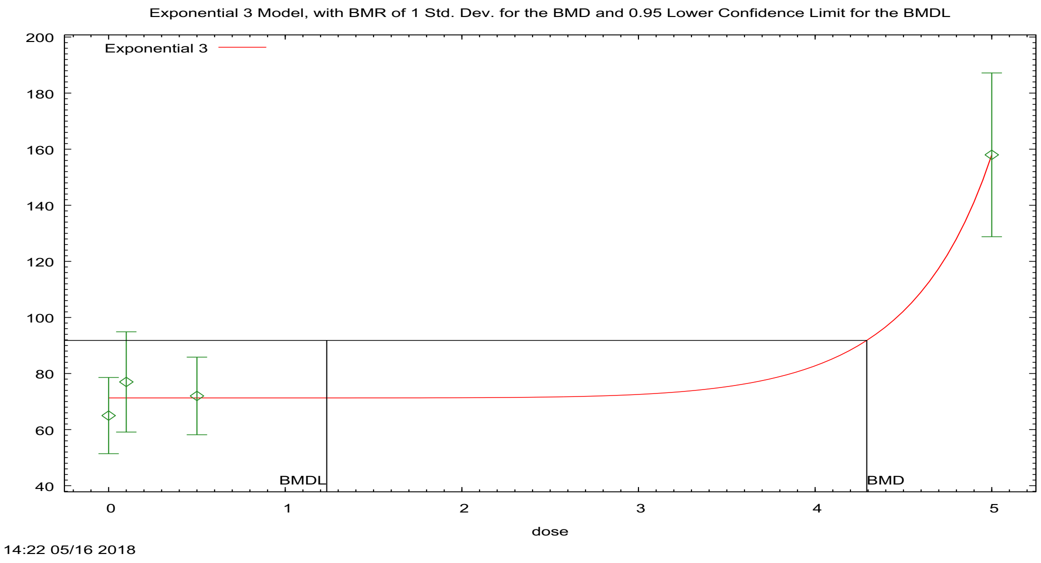

Figure 50. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.29214

BMDL at the 95% confidence level = 1.23501

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.0547497	-0.767201

rho	1.40296	1.59325
a	71.3103	68.977
b	0.194002	0.165384
c	n/a	0
d	7.51202	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	71.31	19	20.5	-0.9732
0.1	10	77	71.31	25	20.5	0.8775
0.5	9	72	71.31	18	20.5	0.1009
5	9	158	158	38	35.83	0.00000007256

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.7225	5	291.4449
A2	-137.2711	8	290.5422
A3	-137.618	6	287.236
R	-163.2567	2	330.5135
3	-138.8065	5	287.6129

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.97	6	<0.0001
Test 2	6.903	3	0.07506
Test 3	0.6938	2	0.7069
Test 5a	2.377	1	0.1231

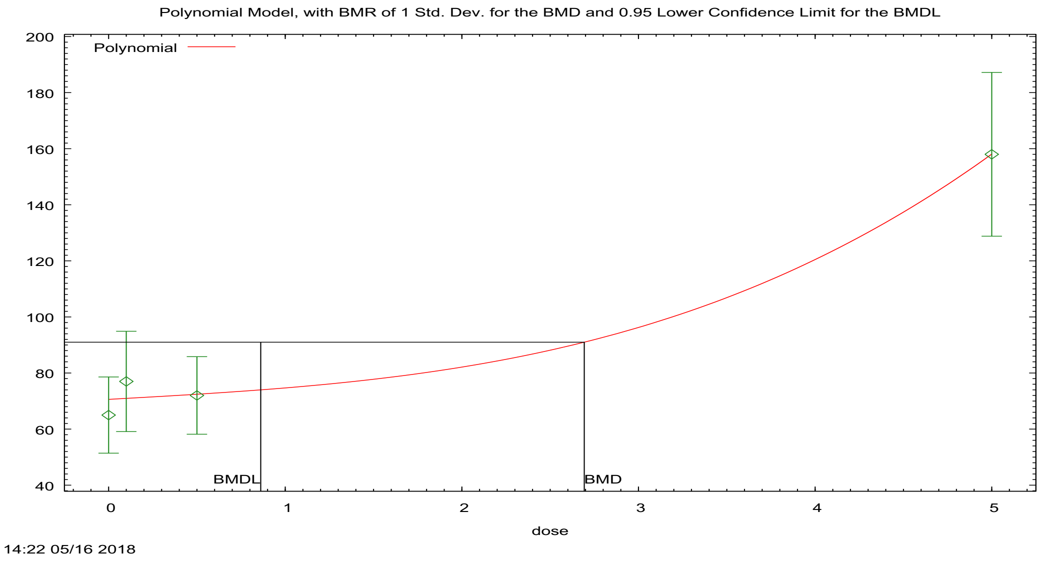

Figure 51. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.69286

BMDL at the 95% confidence level = 0.861199

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.10566	6.51767
rho	1.39137	0
beta_0	70.6107	65
beta_1	3.51553	0

beta_2	1.95415E-22	0
beta_3	0.55879	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	70.6	19	20.4	-0.871
0.1	10	77	71	25	20.4	0.934
0.5	9	72	72.4	18	20.7	-0.0634
5	9	158	158	38	35.7	-0.00311

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.722467	5	291.444934
A2	-137.271117	8	290.542234
A3	-137.618003	6	287.236006
fitted	-138.789061	5	287.578122
R	-163.256735	2	330.513469

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.9712	6	<0.0001
Test 2	6.9027	3	0.07506
Test 3	0.693772	2	0.7069
Test 4	2.34212	1	0.1259

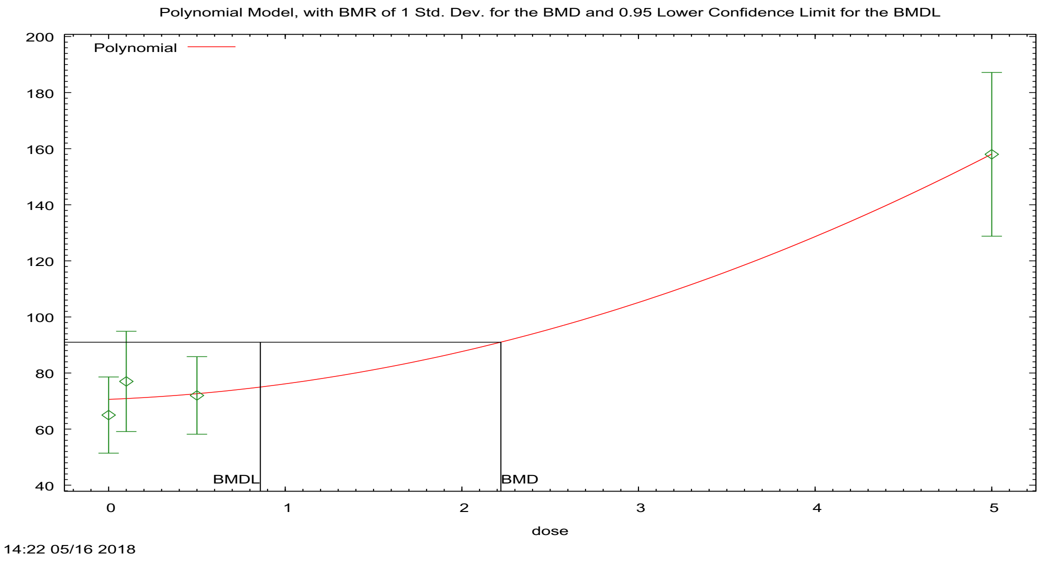

Figure 52. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.22069

BMDL at the 95% confidence level = 0.859021

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.124773	6.51767
rho	1.38731	0
beta_0	70.5826	70.0193
beta_1	2.54926	0

beta_2	2.98701	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	70.6	19	20.4	-0.866
0.1	10	77	70.9	25	20.4	0.948
0.5	9	72	72.6	18	20.8	-0.0871
5	9	158	158	38	35.7	-0.000349

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.722467	5	291.444934
A2	-137.271117	8	290.542234
A3	-137.618003	6	287.236006
fitted	-138.809366	5	287.618731
R	-163.256735	2	330.513469

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.9712	6	<0.0001
Test 2	6.9027	3	0.07506
Test 3	0.693772	2	0.7069
Test 4	2.38273	1	0.1227

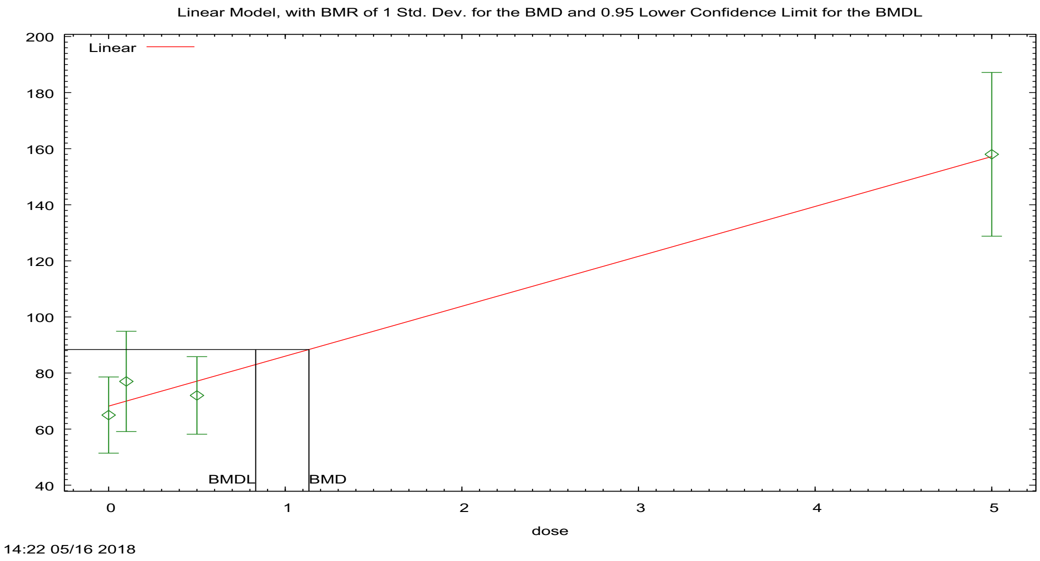

Figure 53. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.13426

BMDL at the 95% confidence level = 0.8326

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.359446	6.51767
rho	1.33766	0
beta_0	68.1984	67.853
beta_1	17.7756	17.9621

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	68.2	19	20.2	-0.502
0.1	10	77	70	25	20.5	1.08
0.5	9	72	77.1	18	21.9	-0.697
5	9	158	157	38	35.2	0.0787

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.722467	5	291.444934
A2	-137.271117	8	290.542234
A3	-137.618003	6	287.236006
fitted	-139.076002	4	286.152004
R	-163.256735	2	330.513469

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.9712	6	<0.0001
Test 2	6.9027	3	0.07506
Test 3	0.693772	2	0.7069
Test 4	2.916	2	0.2327

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery – Alkaline Phosphatase (U/L) in Males

1.15. BMDS Summary of Alkaline Phosphatase in Males (90-Day Rats)

Table 15. Summary of BMD Modeling Results for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	**Goodness of fit**		**BMD_{1SD} (mg/kg/day)**	**$BMDL_{1SD}$ (mg/kg/day)**	**BMD/BMDL**	**Basis for model selection**
	***p*-value**	**AIC**				
Exponential (M4)	**0.952**	**295.55**	**2.66**	**1.43**	**1.86**	**Only one model met inclusion criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)).**

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 7.40E-04), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 10, and 100 mg/kg/day were 0.22, -0.14, -0.25, 0.18, respectively.

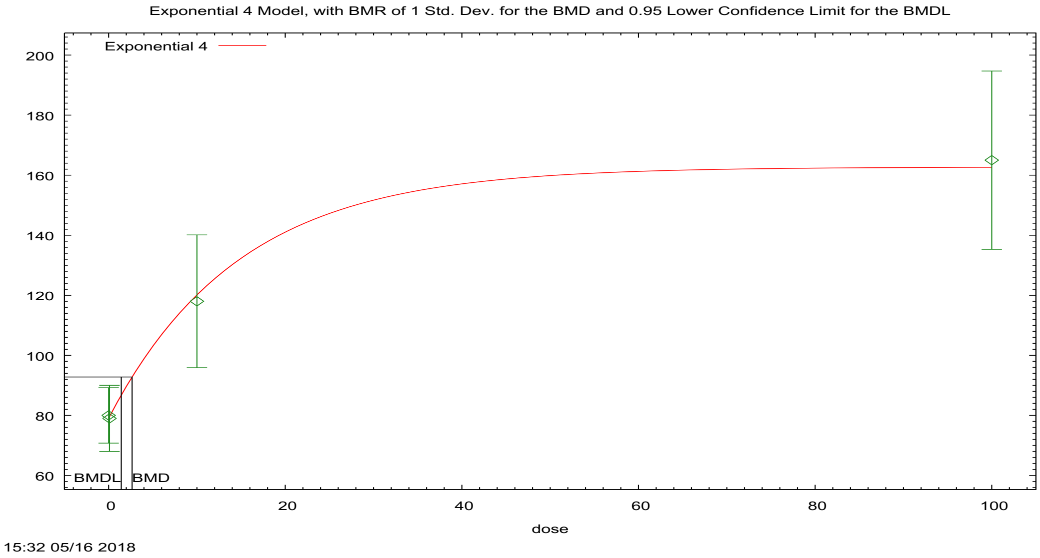

Figure 54. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.65934

BMDL at the 95% confidence level = 1.43235

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-8.41546	-8.09011
rho	3.12538	3.07366
a	79.043	75.05
b	0.0675108	0.0250925
c	2.05869	2.30846
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	80	79.04	12.9	13.75	0.2201
0.1	10	79	79.61	15.4	13.91	-0.1378
10	10	118	120.1	30.9	26.45	-0.2538
100	10	165	162.6	41.5	42.46	0.1767

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-150.8247	5	311.6494
A2	-142.3732	8	300.7465
A3	-142.7721	6	297.5442
R	-171.3096	2	346.6191

4	-142.7739	5	295.5478

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.87	6	<0.0001
Test 2	16.9	3	0.00074
Test 3	0.7977	2	0.6711
Test 6a	0.003674	1	0.9517

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Aspartate Aminotransferase (U/L) in Males

1.16. BMDS Summary of Aspartate Aminotransferase in Males (28-Day Mice)

Table 16. Summary of BMD Modeling Results for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.229	341.37	4.22	3.31	1.27	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from model with lowest AIC and lowest BMDL.
Exponential (M4)	0.538	340.80	1.69	1.18	1.44	
Power	0.657	340.61	1.99	1.19	1.67	
Polynomial 3°[c] Polynomial 2°	0.638	340.64	1.93	1.19	1.62	
Linear	**0.827**	**338.80**	**1.69**	**1.18**	**1.44**	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were 0.43, 0.24, -1.08, 0.56, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model.

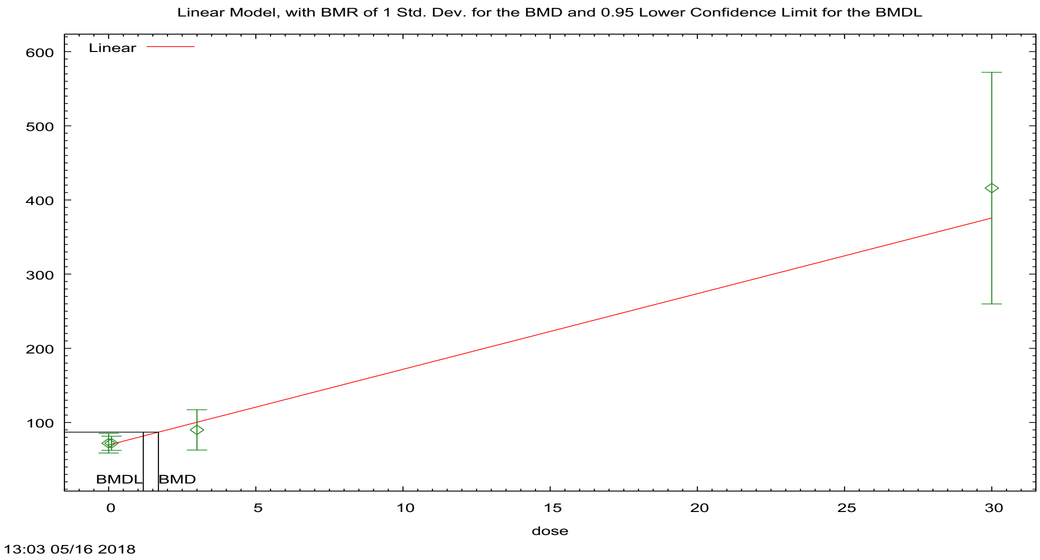

Figure 55. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.69171

BMDL at the 95% confidence level = 1.17843

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.18857	9.42582
rho	3.03741	0
beta_0	69.653	66.364
beta_1	10.223	11.6176

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	69.7	18.5	17.3	0.429
0.1	10	72	70.7	13.3	17.7	0.237
3	10	90	100	38	30.1	-1.08
30	10	416	376	218	224	0.559

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.409094	5	422.818187
A2	-163.182702	8	342.365403
A3	-165.208319	6	342.416637
fitted	-165.397938	4	338.795876
R	-227.865145	2	459.73029

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.365	6	<0.0001
Test 2	86.4528	3	<0.0001
Test 3	4.05123	2	0.1319
Test 4	0.379239	2	0.8273

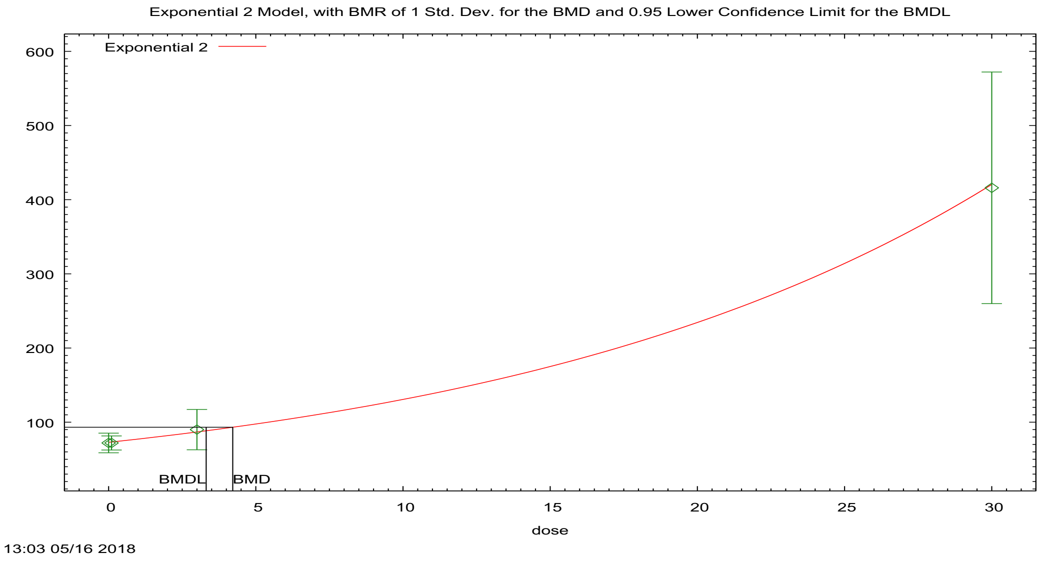

Figure 56. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.21632

BMDL at the 95% confidence level = 3.31493

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.56675	-6.39771
rho	2.70341	2.86362
a	72.8571	72.9518
b	0.0584388	0.058146
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	72.86	18.5	20.36	-0.1331
0.1	10	72	73.28	13.3	20.52	-0.1979
3	10	90	86.82	38	25.8	0.39
30	10	416	420.6	218.3	217.7	-0.06671

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.4091	5	422.8182
A2	-163.1827	8	342.3654
A3	-165.2083	6	342.4166
R	-227.8651	2	459.7303
2	-166.683	4	341.366

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.4	6	<0.0001
Test 2	86.45	3	<0.0001
Test 3	4.051	2	0.1319
Test 4	2.949	2	0.2289

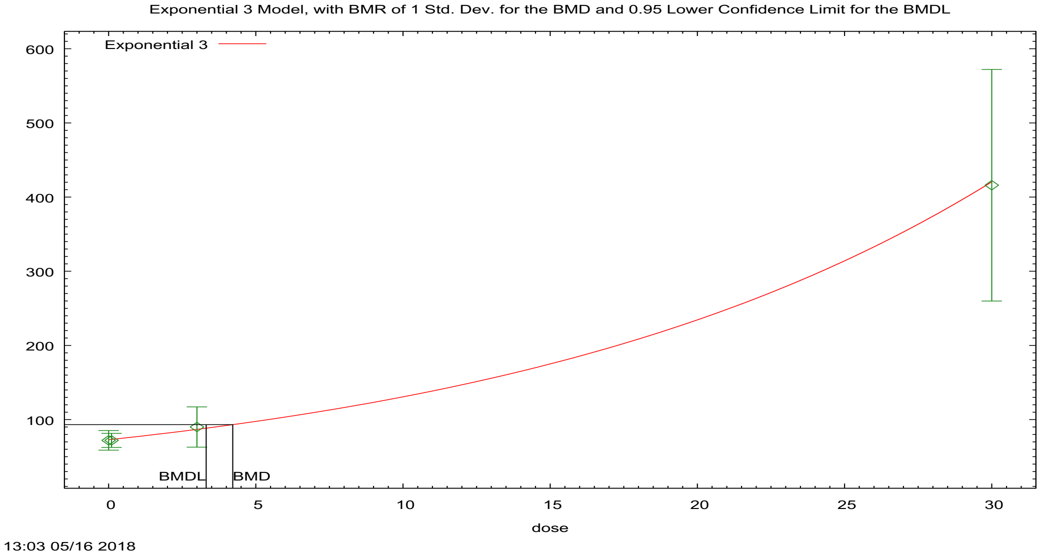

Figure 57. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.21632

BMDL at the 95% confidence level = 3.31493

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.56675	-6.39771
rho	2.70341	2.86362
a	72.8571	72.9518
b	0.0584388	0.058146

c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	72.86	18.5	20.36	-0.1331
0.1	10	72	73.28	13.3	20.52	-0.1979
3	10	90	86.82	38	25.8	0.39
30	10	416	420.6	218.3	217.7	-0.06671

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.4091	5	422.8182
A2	-163.1827	8	342.3654
A3	-165.2083	6	342.4166
R	-227.8651	2	459.7303
3	-166.683	4	341.366

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.4	6	<0.0001
Test 2	86.45	3	<0.0001
Test 3	4.051	2	0.1319
Test 5a	2.949	2	0.2289

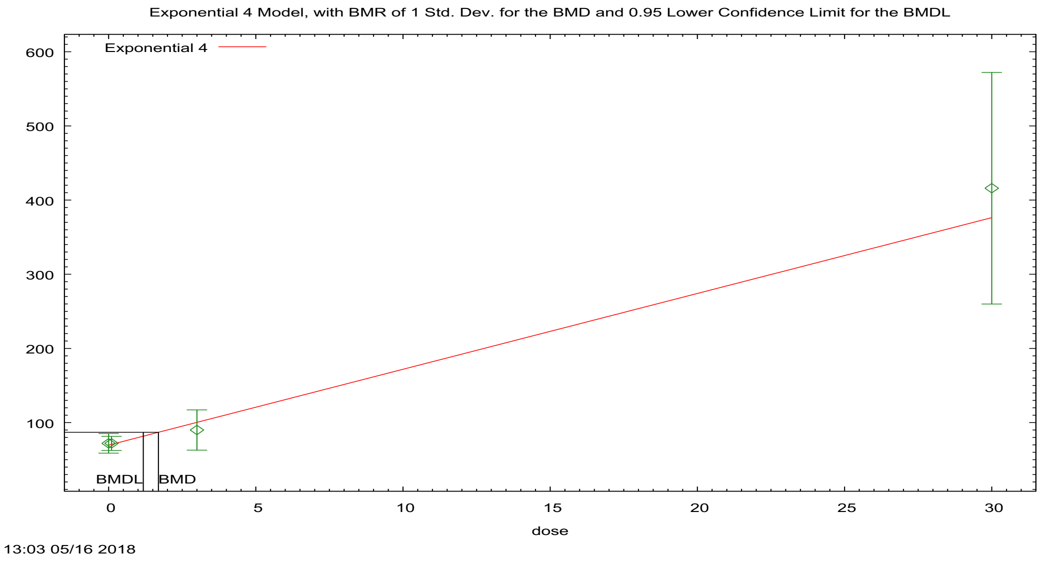

Figure 58. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.6917

BMDL at the 95% confidence level = 1.17843

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-7.18858	-6.39771
rho	3.03741	2.86362
a	69.653	68.4
b	0.000000376747	0.0000277649

c	389577	6081.87
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	69.65	18.5	17.29	0.4291
0.1	10	72	70.68	13.3	17.68	0.2369
3	10	90	100.3	38	30.1	-1.084
30	10	416	376.3	218.3	224.2	0.5594

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.4091	5	422.8182
A2	-163.1827	8	342.3654
A3	-165.2083	6	342.4166
R	-227.8651	2	459.7303
4	-165.3979	5	340.7959

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.4	6	<0.0001
Test 2	86.45	3	<0.0001
Test 3	4.051	2	0.1319
Test 6a	0.3792	1	0.538

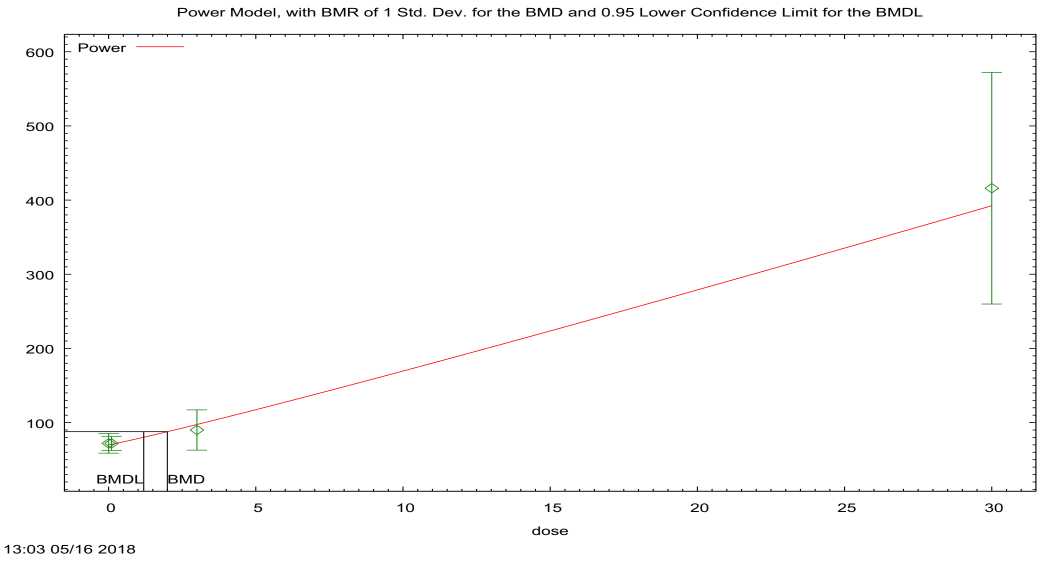

Figure 59. Plot of mean response by dose with fitted curve for Power model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.99497

BMDL at the 95% confidence level = 1.19209

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-6.63048	9.42582
rho	2.91504	0
control	70.0063	72
slope	8.46672	4.40498

power	1.07297	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	70	18.5	17.8	0.355
0.1	10	72	70.7	13.3	18	0.224
3	10	90	97.5	38	28.8	-0.826
30	10	416	396	218	222	0.292

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.409094	5	422.818187
A2	-163.182702	8	342.365403
A3	-165.208319	6	342.416637
fitted	-165.307186	5	340.614372
R	-227.865145	2	459.73029

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.365	6	<0.0001
Test 2	86.4528	3	<0.0001
Test 3	4.05123	2	0.1319
Test 4	0.197735	1	0.6566

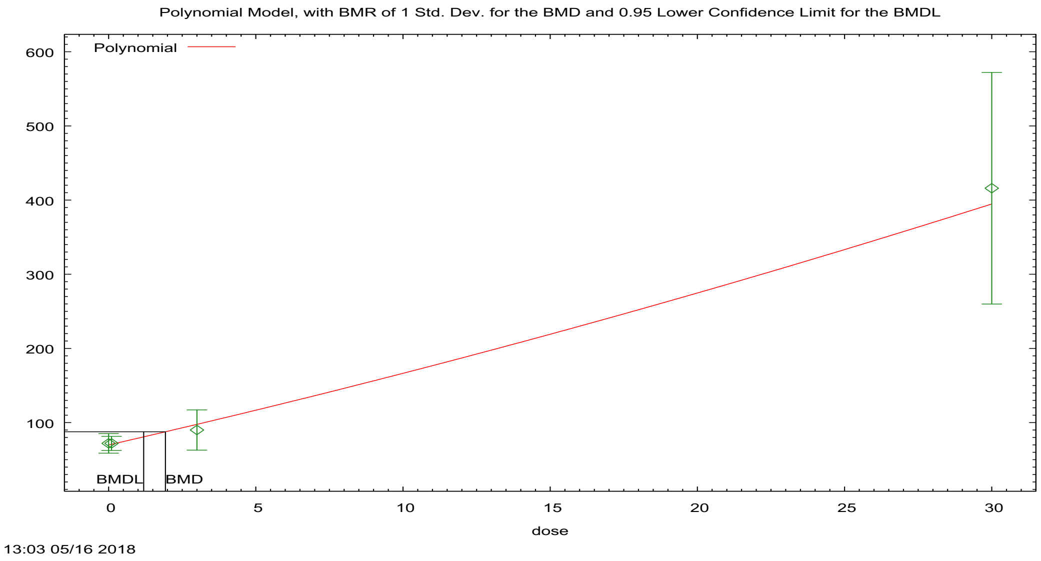

Figure 60. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.92984

BMDL at the 95% confidence level = 1.19025

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-6.64847	9.42582
rho	2.91913	0
beta_0	69.9046	72
beta_1	9.06936	0

beta_2	0.0585628	2.26248
beta_3	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	69.9	18.5	17.7	0.374
0.1	10	72	70.8	13.3	18.1	0.208
3	10	90	97.6	38	28.9	-0.837
30	10	416	395	218	222	0.304

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.409094	5	422.818187
A2	-163.182702	8	342.365403
A3	-165.208319	6	342.416637
fitted	-165.319127	5	340.638255
R	-227.865145	2	459.73029

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.365	6	<0.0001
Test 2	86.4528	3	<0.0001
Test 3	4.05123	2	0.1319
Test 4	0.221618	1	0.6378

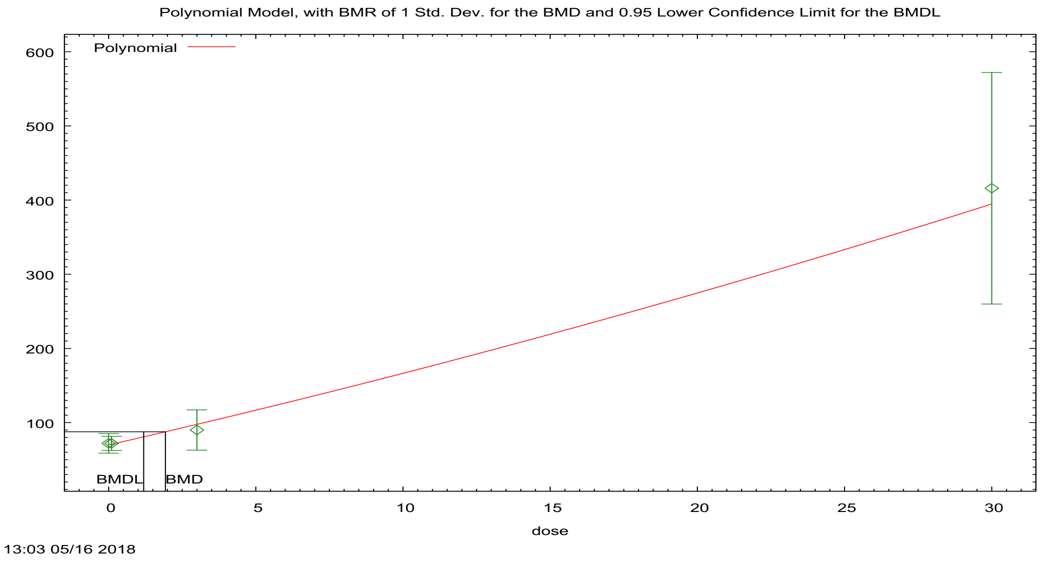

Figure 61. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.92984

BMDL at the 95% confidence level = 1.19025

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-6.64847	9.42582
rho	2.91913	0
beta_0	69.9045	71.7297
beta_1	9.06937	5.48785

beta_2	0.0585626	0.199594

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	69.9	18.5	17.7	0.374
0.1	10	72	70.8	13.3	18.1	0.208
3	10	90	97.6	38	28.9	-0.837
30	10	416	395	218	222	0.304

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.409094	5	422.818187
A2	-163.182702	8	342.365403
A3	-165.208319	6	342.416637
fitted	-165.319127	5	340.638255
R	-227.865145	2	459.73029

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.365	6	<0.0001
Test 2	86.4528	3	<0.0001
Test 3	4.05123	2	0.1319
Test 4	0.221618	1	0.6378

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Aspartate Aminotransferase (U/L) in Males

1.17. BMDS Summary of Aspartate Aminotransferase in Males (90-Day Mice)

Table 17. Summary of BMD Modeling Results for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M4) Exponential (M5)[b]	0.244	306.59	0.325	0.141	2.31	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Hill	**0.264**	**306.48**	**0.303**	**0.169**	**1.80**	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.08, -0.02, 0.23, -0.16, respectively.

[b] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

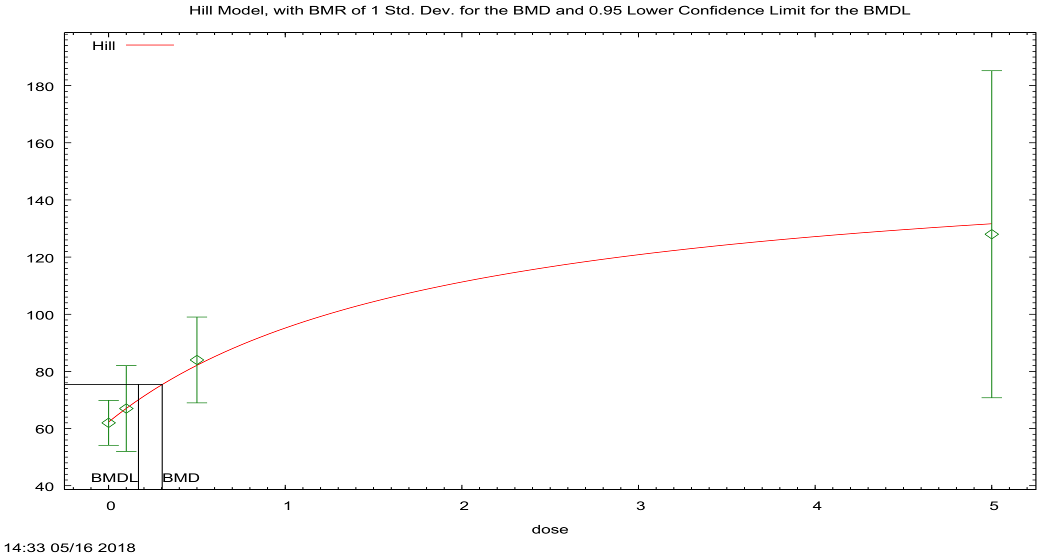

Figure 62. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.303154

BMDL at the 95% confidence level = 0.168638

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-13.9353	7.52335
rho	4.61691	0
intercept	62.3436	62
v	95.9827	66
n	1	0.405435
k	1.9185	8.375

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	62.3	11	13.1	-0.083
0.1	10	67	67.1	21	15.5	-0.0201
0.5	10	84	82.2	21	24.8	0.231
5	10	128	132	80	73.6	-0.159

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.359715	5	346.719429
A2	-146.582458	8	309.164915
A3	-147.613821	6	307.227642
fitted	-148.237838	5	306.475676

R	-175.169766	2	354.339532

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.1746	6	<0.0001
Test 2	43.5545	3	<0.0001
Test 3	2.06273	2	0.3565
Test 4	1.24803	1	0.2639

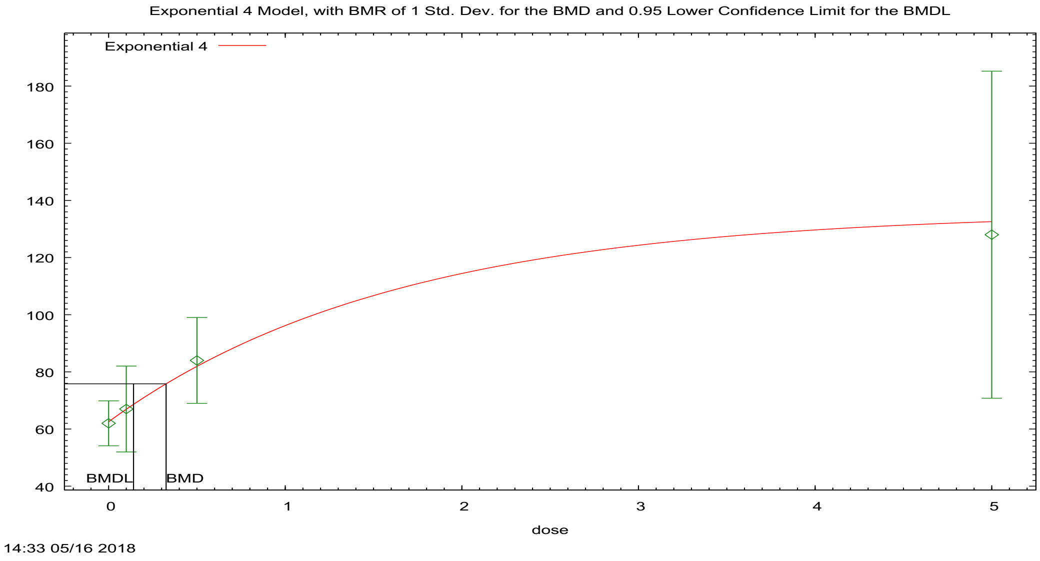

Figure 63. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.325386

BMDL at the 95% confidence level = 0.141103

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-13.715	-15.1386
rho	4.56656	4.89888
a	62.5469	58.9
b	0.61274	0.496936
c	2.17427	2.28183
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	62.55	11	13.28	-0.1303
0.1	10	67	66.91	21	15.49	0.01793
0.5	10	84	81.93	21	24.59	0.2664
5	10	128	132.6	80	73.78	-0.1956

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.3597	5	346.7194
A2	-146.5825	8	309.1649
A3	-147.6138	6	307.2276
R	-175.1698	2	354.3395
4	-148.293	5	306.586

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.17	6	<0.0001
Test 2	43.55	3	<0.0001

Test 3	2.063	2	0.3565
Test 6a	1.358	1	0.2438

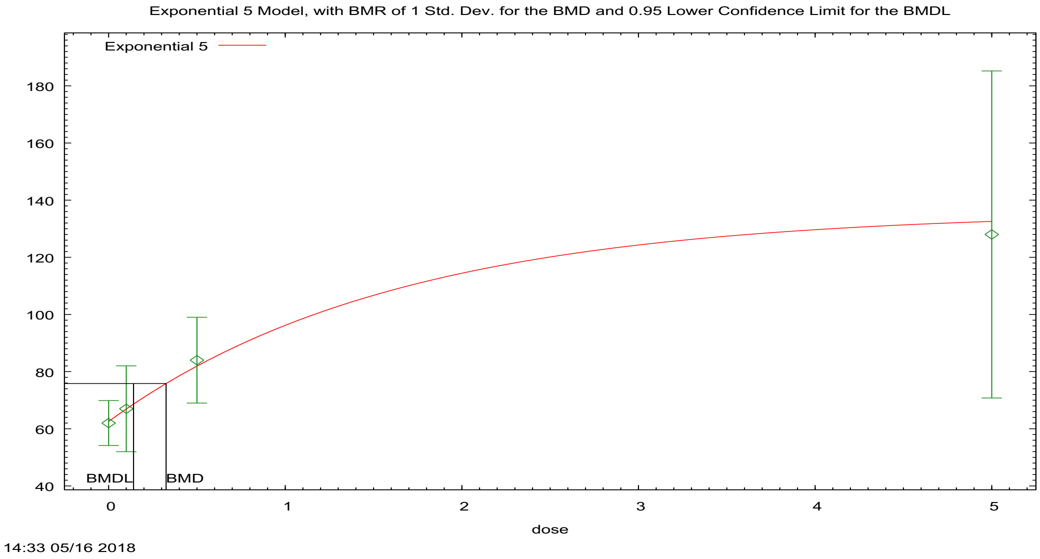

Figure 64. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.325386

BMDL at the 95% confidence level = 0.141103

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-13.7149	-15.1386

rho	4.56655	4.89888
a	62.5469	58.9
b	0.612739	0.496936
c	2.17427	2.28183
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	62.55	11	13.28	-0.1303
0.1	10	67	66.91	21	15.49	0.01793
0.5	10	84	81.93	21	24.59	0.2664
5	10	128	132.6	80	73.78	-0.1956

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.3597	5	346.7194
A2	-146.5825	8	309.1649
A3	-147.6138	6	307.2276
R	-175.1698	2	354.3395
5	-148.293	5	306.586

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.17	6	<0.0001
Test 2	43.55	3	<0.0001
Test 3	2.063	2	0.3565
Test 7a	1.358	1	0.2438

BMDS WIZARD OUTPUT REPORT

Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Sorbitol Dehydrogenase (U/L) in Females

1.18. BMDS Summary of Sorbitol Dehydrogenase in Females (28-Day Mice)

Table 18. Summary of BMD Modeling Results for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	**0.760**	**202.94**	**8.38**	**6.29**	**1.33**	**Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.**
Exponential (M3)	0.493	204.86	10.2	6.32	1.61	
Exponential (M4)	0.290	205.51	5.77	3.81	1.51	
Power	0.490	204.87	9.20	4.00	2.30	
Polynomial 3°	0.499	204.85	11.6	4.01	2.89	
Polynomial 2°	0.497	204.85	10.1	4.01	2.53	
Linear	0.571	203.51	5.77	3.81	1.51	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were -0.56, 0.75, -0.22, 0.03, respectively.

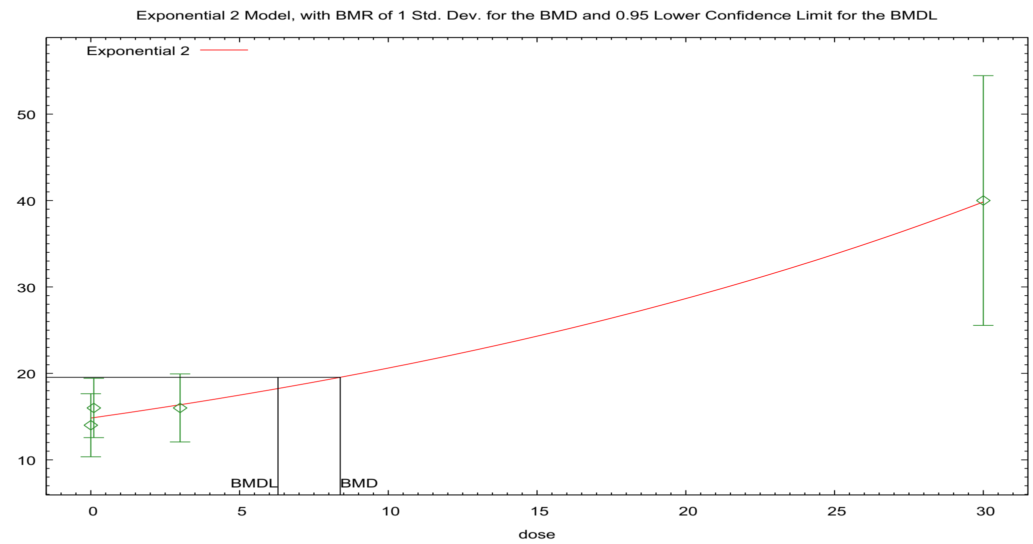

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Figure 65. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 8.38417

BMDL at the 95% confidence level = 6.29287

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.53233	-4.38245
rho	2.83099	2.80856
a	14.831	14.7983
b	0.0329331	0.0330832
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	14.83	5.1	4.72	-0.5572
0.1	10	16	14.88	4.8	4.74	0.7475
3	10	16	16.37	5.5	5.42	-0.2163
30	10	40	39.83	20.2	19.1	0.02755

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.9461	5	237.8923
A2	-96.97566	8	209.9513
A3	-97.19629	6	206.3926
R	-128.2687	2	260.5375

2	-97.47089	4	202.9418

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.59	6	<0.0001
Test 2	33.94	3	<0.0001
Test 3	0.4413	2	0.802
Test 4	0.5492	2	0.7599

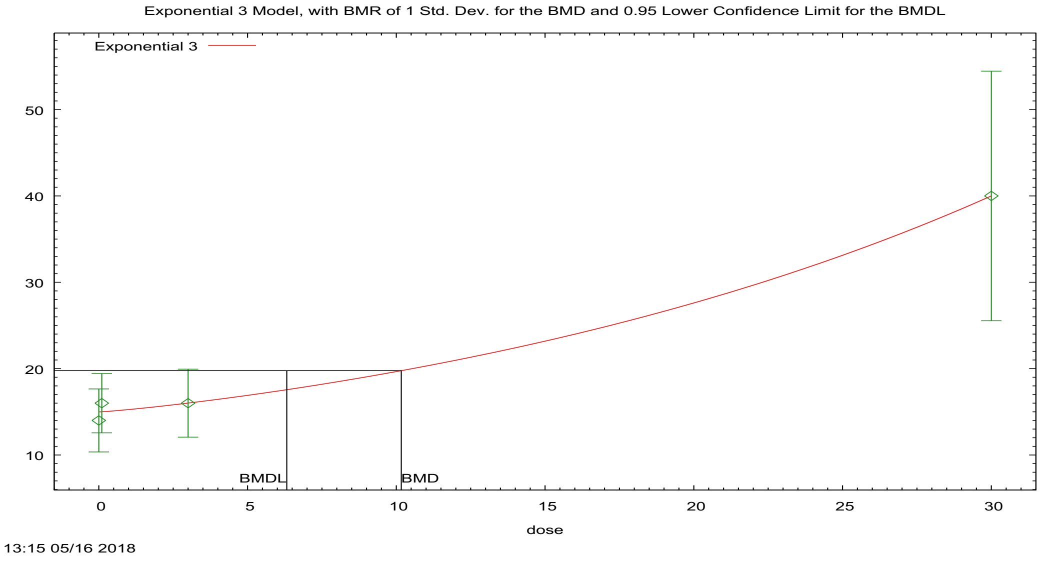

Figure 66. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 10.1665

BMDL at the 95% confidence level = 6.31813

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.51977	-4.38245
rho	2.82595	2.80856
a	14.9835	14.7983
b	0.0328197	0.0330832
c	n/a	0
d	1.16951	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	14.98	5.1	4.78	-0.6503
0.1	10	16	15	4.8	4.79	0.6587
3	10	16	16.01	5.5	5.25	-0.007944
30	10	40	40	20.2	19.15	-0.0004674

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.9461	5	237.8923
A2	-96.97566	8	209.9513
A3	-97.19629	6	206.3926
R	-128.2687	2	260.5375
3	-97.4308	5	204.8616

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.59	6	<0.0001
Test 2	33.94	3	<0.0001

Test 3	0.4413	2	0.802
Test 5a	0.469	1	0.4934

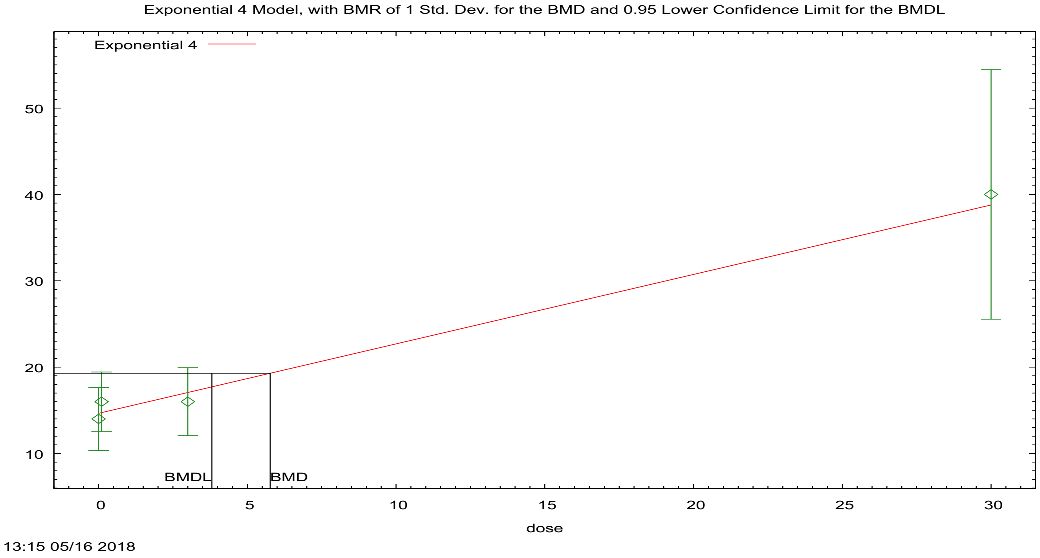

Figure 67. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 5.76843

BMDL at the 95% confidence level = 3.80958

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.70037	-4.38245

rho	2.89424	2.80856
a	14.6511	13.3
b	0.00000048235	0.000224083
c	113815	300.752
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	14.65	5.1	4.64	-0.4438
0.1	10	16	14.73	4.8	4.68	0.8577
3	10	16	17.06	5.5	5.78	-0.5817
30	10	40	38.78	20.2	18.98	0.2032

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.9461	5	237.8923
A2	-96.97566	8	209.9513
A3	-97.19629	6	206.3926
R	-128.2687	2	260.5375
4	-97.75732	5	205.5146

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.59	6	<0.0001
Test 2	33.94	3	<0.0001
Test 3	0.4413	2	0.802
Test 6a	1.122	1	0.2895

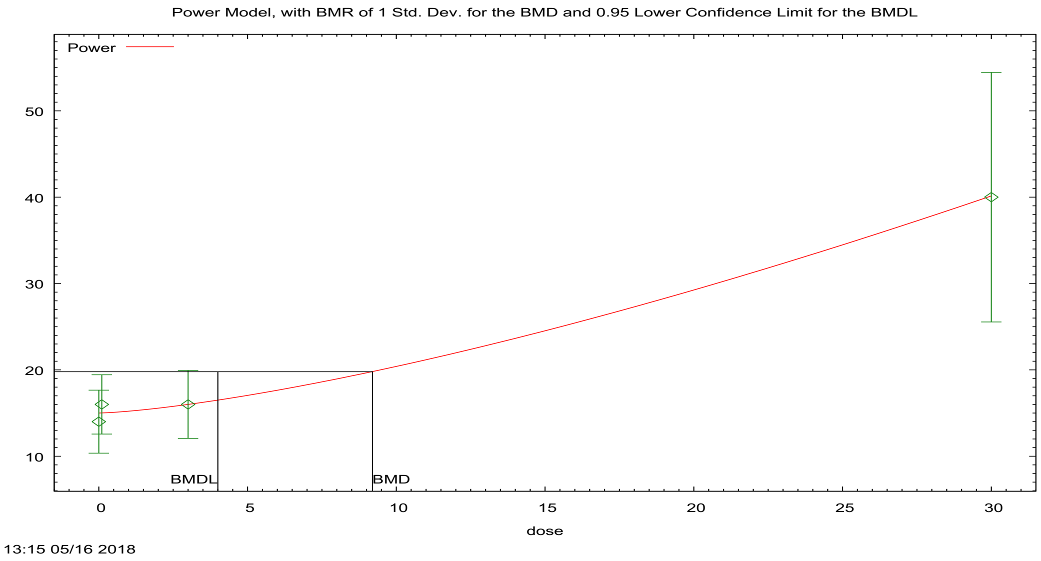

Figure 68. Plot of mean response by dose with fitted curve for Power model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 9.1984

BMDL at the 95% confidence level = 4.00238

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.52007	4.80267
rho	2.82611	0
control	14.9966	14
slope	0.215183	6.32358

power	1.39815	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	15	5.1	4.79	-0.658
0.1	10	16	15	4.8	4.79	0.656
3	10	16	16	5.5	5.25	0.0022
30	10	40	40	20.2	19.2	-0.000401

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.946143	5	237.892286
A2	-96.975661	8	209.951322
A3	-97.196287	6	206.392573
fitted	-97.434286	5	204.868572
R	-128.268737	2	260.537474

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.5862	6	<0.0001
Test 2	33.941	3	<0.0001
Test 3	0.441251	2	0.802
Test 4	0.475999	1	0.4902

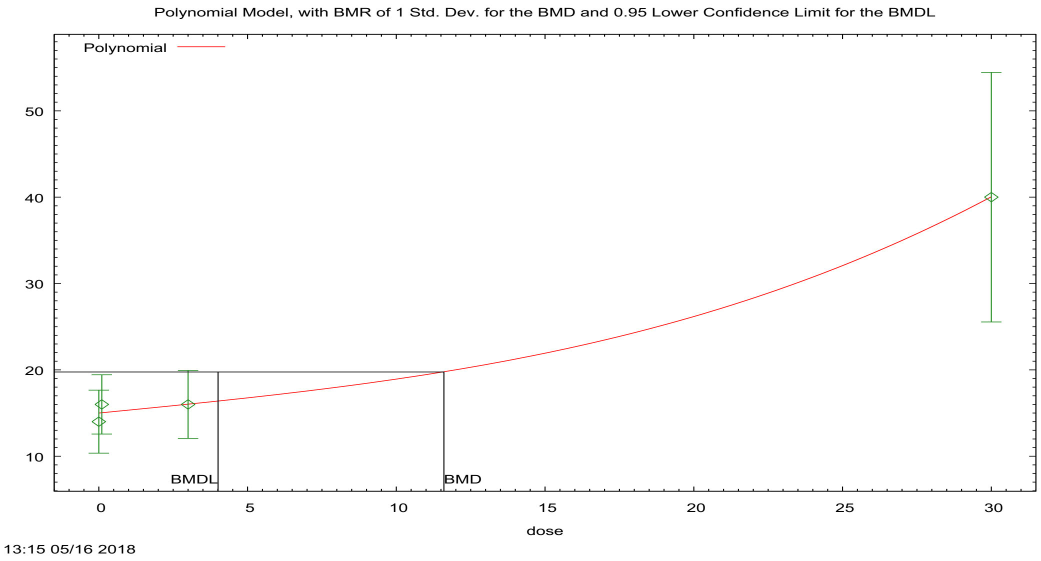

Figure 69. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 11.5999

BMDL at the 95% confidence level = 4.00852

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.51875	4.80267
rho	2.82552	0
beta_0	14.9776	14
beta_1	0.337764	20.7336

beta_2	0	0
beta_3	0.000551898	0.223213

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	15	5.1	4.78	-0.647
0.1	10	16	15	4.8	4.79	0.652
3	10	16	16	5.5	5.25	-0.00346
30	10	40	40	20.2	19.2	-0.00194

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.946143	5	237.892286
A2	-96.975661	8	209.951322
A3	-97.196287	6	206.392573
fitted	-97.425014	5	204.850029
R	-128.268737	2	260.537474

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.5862	6	<0.0001
Test 2	33.941	3	<0.0001
Test 3	0.441251	2	0.802
Test 4	0.457455	1	0.4988

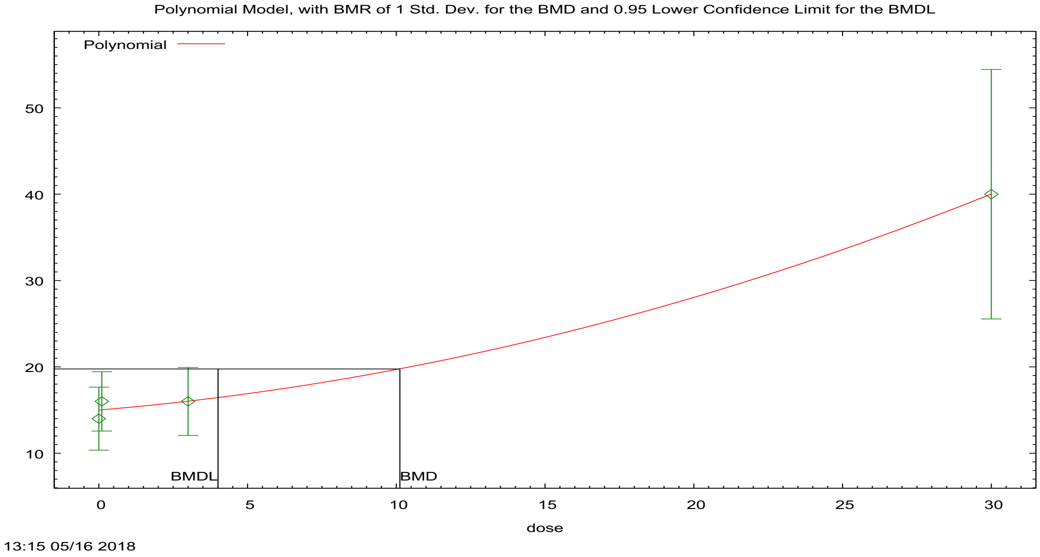

Figure 70. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 10.1185

BMDL at the 95% confidence level = 4.00732

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.51944	4.80267
rho	2.82578	0
beta_0	14.9795	14.9664
beta_1	0.288303	0.303817

beta_2	0.0181987	0.0176875

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	15	5.1	4.78	-0.648
0.1	10	16	15	4.8	4.79	0.654
3	10	16	16	5.5	5.25	-0.00494
30	10	40	40	20.2	19.2	-0.00122

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.946143	5	237.892286
A2	-96.975661	8	209.951322
A3	-97.196287	6	206.392573
fitted	-97.426827	5	204.853653
R	-128.268737	2	260.537474

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.5862	6	<0.0001
Test 2	33.941	3	<0.0001
Test 3	0.441251	2	0.802
Test 4	0.46108	1	0.4971

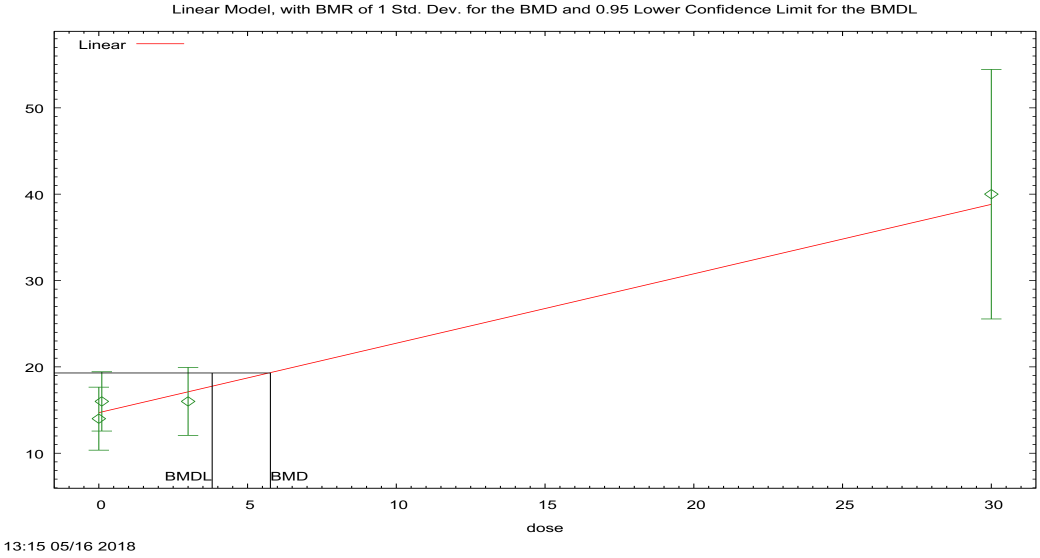

Figure 71. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 5.76847

BMDL at the 95% confidence level = 3.8096

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.70038	4.80267
rho	2.89425	0
beta_0	14.6511	14.4909
beta_1	0.804312	0.847022

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	14.7	5.1	4.64	-0.444
0.1	10	16	14.7	4.8	4.68	0.858
3	10	16	17.1	5.5	5.78	-0.582
30	10	40	38.8	20.2	19	0.203

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.946143	5	237.892286
A2	-96.975661	8	209.951322
A3	-97.196287	6	206.392573
fitted	-97.757311	4	203.514621
R	-128.268737	2	260.537474

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.5862	6	<0.0001
Test 2	33.941	3	<0.0001
Test 3	0.441251	2	0.802
Test 4	1.12205	2	0.5706

BMDS WIZARD OUTPUT REPORT

Summary of H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats – Sorbitol Dehydrogenase (U/L) at 12-month timepoint in Males

1.19. BMDS Summary of Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats)

Table 19. Summary of BMD Modeling Results for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	BMDL_{1SD} (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.738	206.75	17.6	11.6	1.52	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were not sufficiently close (> 3-fold difference), so the lowest BMDL was selected.
Exponential (M4)	**0.497**	**208.60**	**6.60**	**1.21**	**5.47**	
Power[c] Polynomial 3°[d] Polynomial 2°[e] Linear	0.761	206.68	13.0	6.95	1.87	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 1, and 50 mg/kg/day were -0.57, 0.16, 0.47, -0.07, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[d] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[e] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

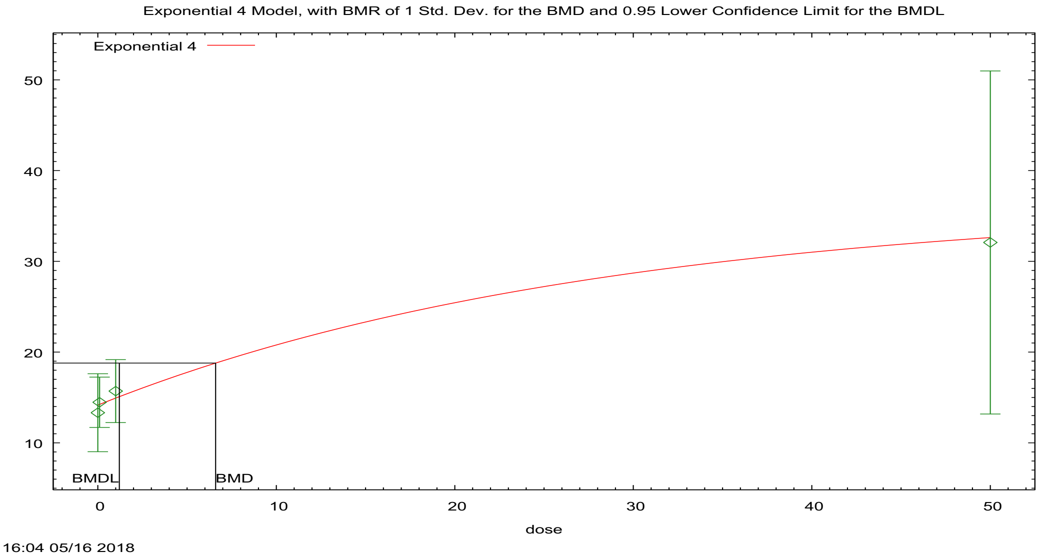

Figure 72. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 6.59887

BMDL at the 95% confidence level = 1.20614

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-7.62202	-7.70134
rho	4.03212	4.07591
a	14.1592	12.654
b	0.0353009	0.0515144
c	2.57315	2.66193
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.32	14.16	6.01	4.63	-0.5734
0.1	10	14.47	14.24	3.87	4.68	0.1569
1	10	15.7	14.93	4.85	5.15	0.4715
50	10	32.08	32.62	26.42	24.9	-0.06869

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC

A1	-123.1674	5	256.3348
A2	-97.88906	8	211.7781
A3	-99.06893	6	210.1379
R	-128.9829	2	261.9658
4	-99.29957	5	208.5991

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.19	6	<0.0001
Test 2	50.56	3	<0.0001
Test 3	2.36	2	0.3073
Test 6a	0.4613	1	0.497

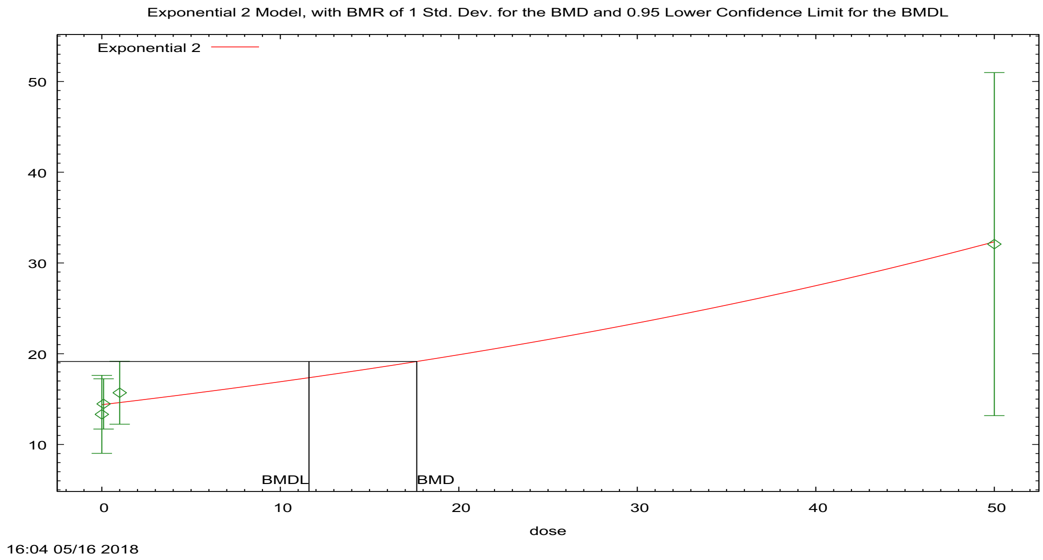

Figure 73. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 17.6448

BMDL at the 95% confidence level = 11.6067

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-7.81223	-7.70134
rho	4.10029	4.07591
a	14.386	14.372
b	0.0161975	0.0160881
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.32	14.39	6.01	4.76	-0.7083
0.1	10	14.47	14.41	3.87	4.78	0.04019
1	10	15.7	14.62	4.85	4.92	0.6936
50	10	32.08	32.33	26.42	25.04	-0.03211

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.1674	5	256.3348
A2	-97.88906	8	211.7781
A3	-99.06893	6	210.1379
R	-128.9829	2	261.9658
2	-99.37282	4	206.7456

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.19	6	<0.0001
Test 2	50.56	3	<0.0001
Test 3	2.36	2	0.3073
Test 4	0.6078	2	0.7379

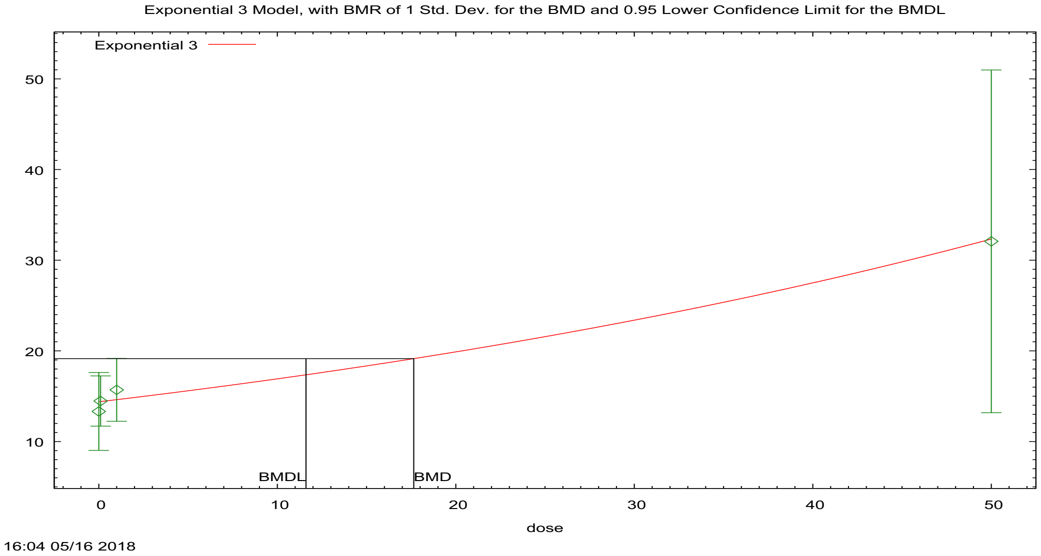

Figure 74. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 17.6448

BMDL at the 95% confidence level = 11.6067

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-7.81223	-7.70134
rho	4.10029	4.07591
a	14.386	14.372
b	0.0161975	0.0160881
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.32	14.39	6.01	4.76	-0.7083
0.1	10	14.47	14.41	3.87	4.78	0.04019
1	10	15.7	14.62	4.85	4.92	0.6936
50	10	32.08	32.33	26.42	25.04	-0.03211

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.1674	5	256.3348
A2	-97.88906	8	211.7781
A3	-99.06893	6	210.1379
R	-128.9829	2	261.9658
3	-99.37282	4	206.7456

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.19	6	<0.0001
Test 2	50.56	3	<0.0001
Test 3	2.36	2	0.3073
Test 5a	0.6078	2	0.7379

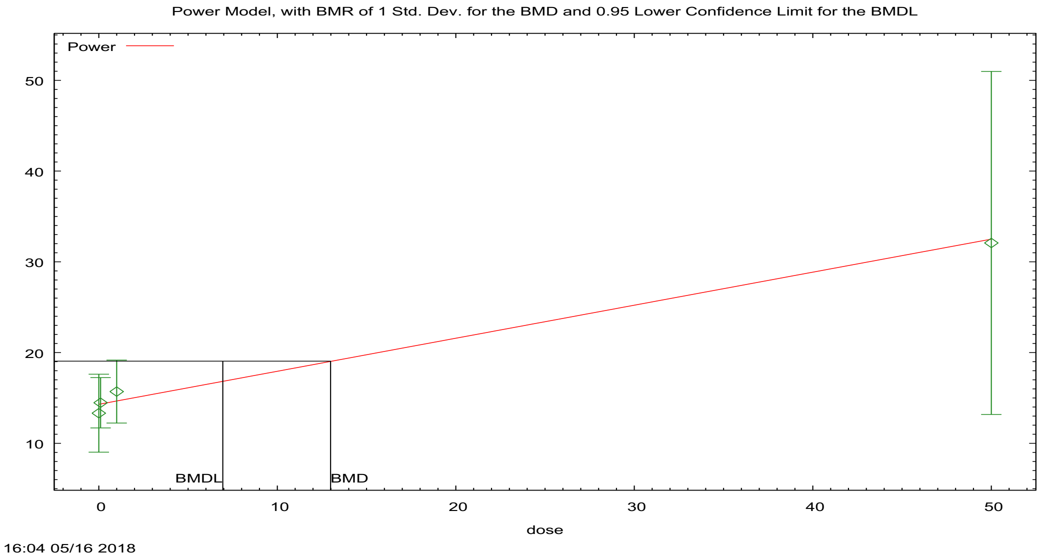

Figure 75. Plot of mean response by dose with fitted curve for Power model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 12.9849

BMDL at the 95% confidence level = 6.94645

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.71947	5.26373
rho	4.0664	0
control	14.3262	13.32
slope	0.36387	3.13168

power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.3	14.3	6.01	4.72	-0.673
0.1	10	14.5	14.4	3.87	4.75	0.0715
1	10	15.7	14.7	4.85	4.97	0.642
50	10	32.1	32.5	26.4	25	-0.0556

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.167387	5	256.334774
A2	-97.889063	8	211.778126
A3	-99.068928	6	210.137855
fitted	-99.341825	4	206.68365
R	-128.982884	2	261.965768

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.1876	6	<0.0001
Test 2	50.5566	3	<0.0001
Test 3	2.35973	2	0.3073
Test 4	0.545795	2	0.7612

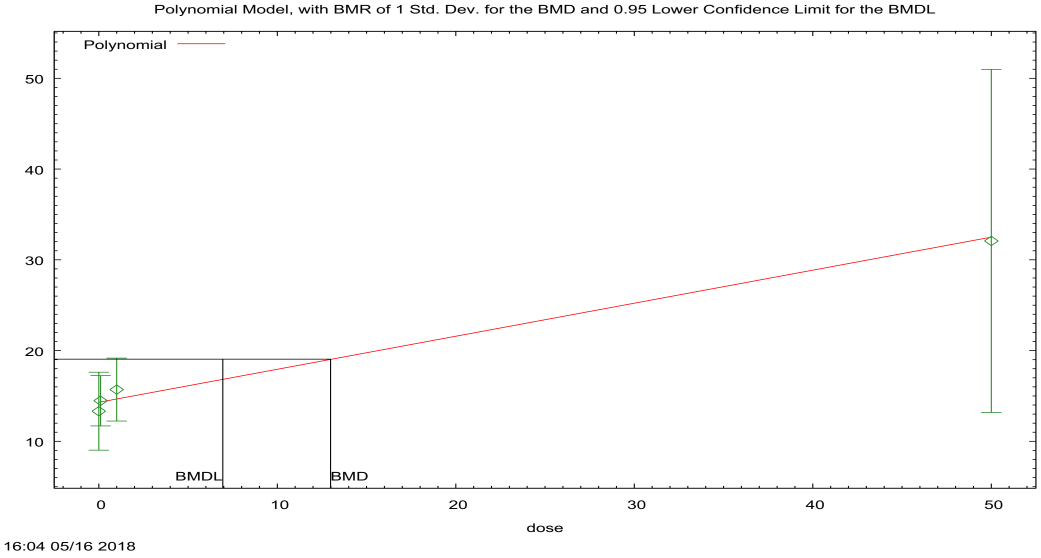

Figure 76. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 12.9849

BMDL at the 95% confidence level = 6.94645

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.71947	5.26373
rho	4.0664	0
beta_0	14.3262	13.32
beta_1	0.36387	12.5336

beta_2	7.95E-14	0
beta_3	1.59E-15	0.202253

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.3	14.3	6.01	4.72	-0.673
0.1	10	14.5	14.4	3.87	4.75	0.0715
1	10	15.7	14.7	4.85	4.97	0.642
50	10	32.1	32.5	26.4	25	-0.0556

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.167387	5	256.334774
A2	-97.889063	8	211.778126
A3	-99.068928	6	210.137855
fitted	-99.341825	4	206.68365
R	-128.982884	2	261.965768

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.1876	6	<0.0001
Test 2	50.5566	3	<0.0001
Test 3	2.35973	2	0.3073
Test 4	0.545795	2	0.7612

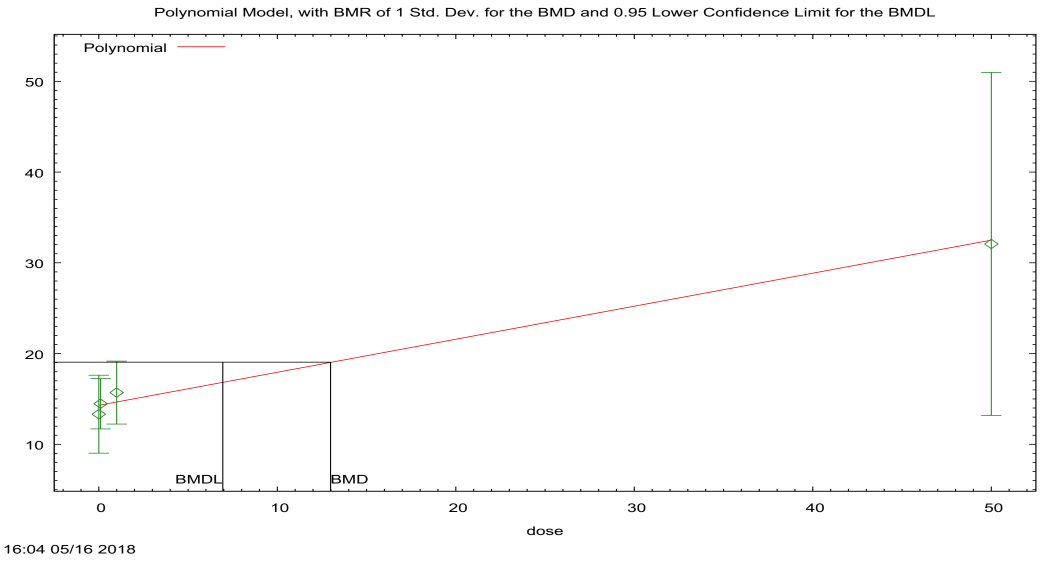

Figure 77. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 12.9849

BMDL at the 95% confidence level = 6.94645

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.71947	5.26373
rho	4.0664	0
beta_0	14.3262	13.769
beta_1	0.36387	2.0149

beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.3	14.3	6.01	4.72	-0.673
0.1	10	14.5	14.4	3.87	4.75	0.0715
1	10	15.7	14.7	4.85	4.97	0.642
50	10	32.1	32.5	26.4	25	-0.0556

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.167387	5	256.334774
A2	-97.889063	8	211.778126
A3	-99.068928	6	210.137855
fitted	-99.341825	4	206.68365
R	-128.982884	2	261.965768

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.1876	6	<0.0001
Test 2	50.5566	3	<0.0001
Test 3	2.35973	2	0.3073
Test 4	0.545795	2	0.7612

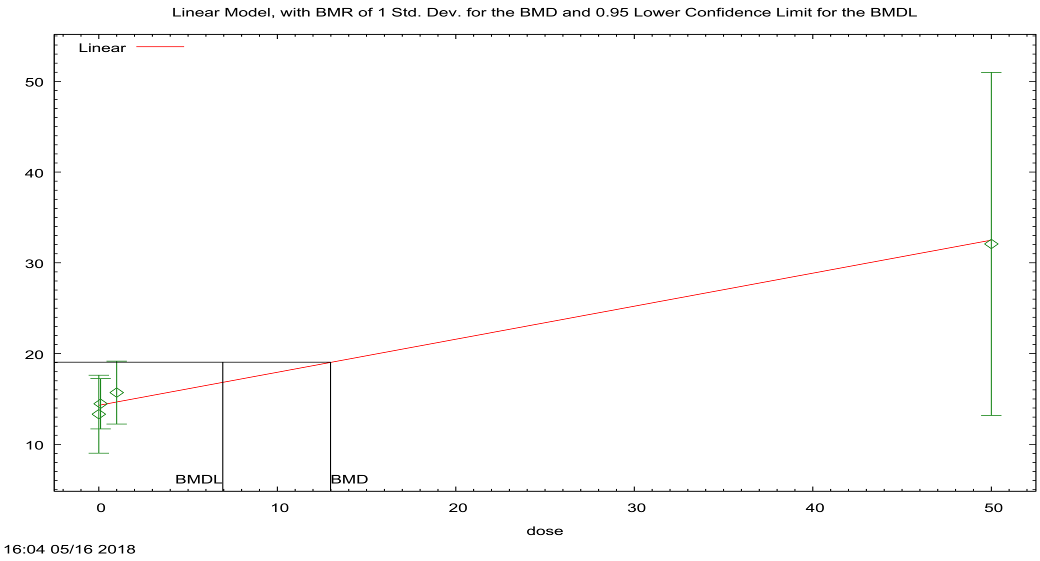

Figure 78. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 12.9849

BMDL at the 95% confidence level = 6.94645

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.71949	5.26373
rho	4.06641	0
beta_0	14.3262	14.36
beta_1	0.363869	0.354798

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.3	14.3	6.01	4.72	-0.673
0.1	10	14.5	14.4	3.87	4.75	0.0715
1	10	15.7	14.7	4.85	4.97	0.642
50	10	32.1	32.5	26.4	25	-0.0556

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.167387	5	256.334774
A2	-97.889063	8	211.778126
A3	-99.068928	6	210.137855
fitted	-99.341825	4	206.68365
R	-128.982884	2	261.965768

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.1876	6	<0.0001
Test 2	50.5566	3	<0.0001
Test 3	2.35973	2	0.3073
Test 4	0.545795	2	0.7612

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Single Cell Hepatocellular Necrosis in Males

1.20. BMDS Summary of Single Cell Hepatocellular Necrosis in Males (28-Day Mice)

Table 20. Summary of BMD Modeling Results for Single Cell Hepatocellular Necrosis in Males (28-Day Mice)

Model[a]	**Goodness of fit**		**BMD$_{10Pct}$ (mg/kg/day)**	**BMDL$_{10Pct}$ (mg/kg/day)**	**BMD/BMDL**	**Basis for model selection**
	***p*-value**	**AIC**				
Gamma	1.000	17.460	1.88	0.323	5.80	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were not sufficiently close (> 3-fold difference), so the lowest BMDL was selected.
Dichotomous-Hill[b]	1.000	17.460	2.42	0.343	7.06	
Logistic	1.000	17.460	2.72	1.16	2.34	
LogLogistic[c]	1.000	17.460	2.42	0.343	7.06	
Probit	1.000	17.460	2.45	1.04	2.37	
LogProbit	**1.000**	**17.460**	**2.01**	**0.299**	**6.72**	
Weibull	1.000	17.460	1.96	0.323	6.05	
Multistage 3°	0.998	17.469	1.45	0.323	4.48	
Multistage 2°	1.000	15.472	1.36	0.323	4.23	
Quantal-Linear	0.972	15.918	0.603	0.305	1.97	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were 0, 0, 0, 0, respectively.
[b] The Dichotomous-Hill model may appear equivalent to the LogLogistic model, however differences exist in digits not displayed in the table.
[c] The LogLogistic model may appear equivalent to the Dichotomous-Hill model, however differences exist in digits not displayed in the table.

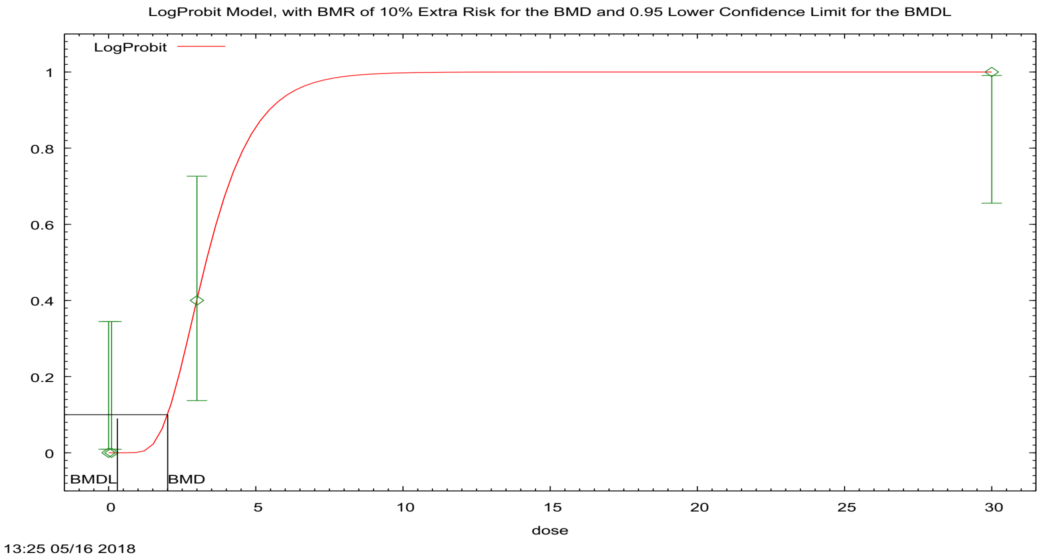

Figure 79. Plot of incidence rate by dose with fitted curve for LogProbit model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.0069

BMDL at the 95% confidence level = 0.298834

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-3.0632E+00	-5.0920E-01
slope	2.5576	0.579932

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.000000174299	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4602

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0 d.f = 2 P-value = 1

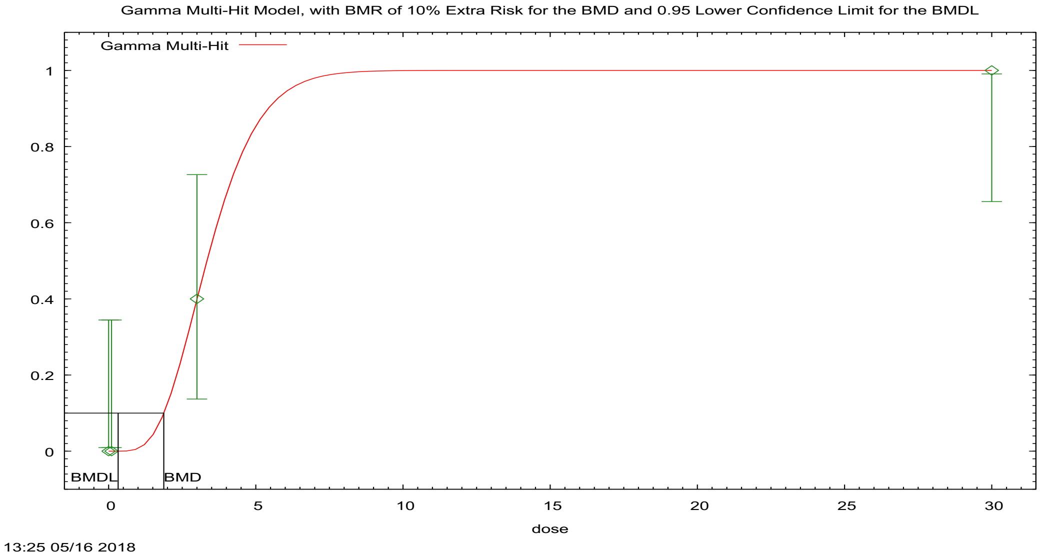

Figure 80. Plot of incidence rate by dose with fitted curve for Gamma model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Gamma Model. (Version: 2.17; Date: 6/22/2017)

The form of the probability function is: P[response]= background+(1-background)*CumGamma[slope*dose,power], where CumGamma(.) is the cumulative Gamma distribution function

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.87505

BMDL at the 95% confidence level = 0.323065

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	1.76301	0.117349
Power	6.20943	1.3

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.0000003739 96	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4602

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0 d.f = 2 P-value = 1

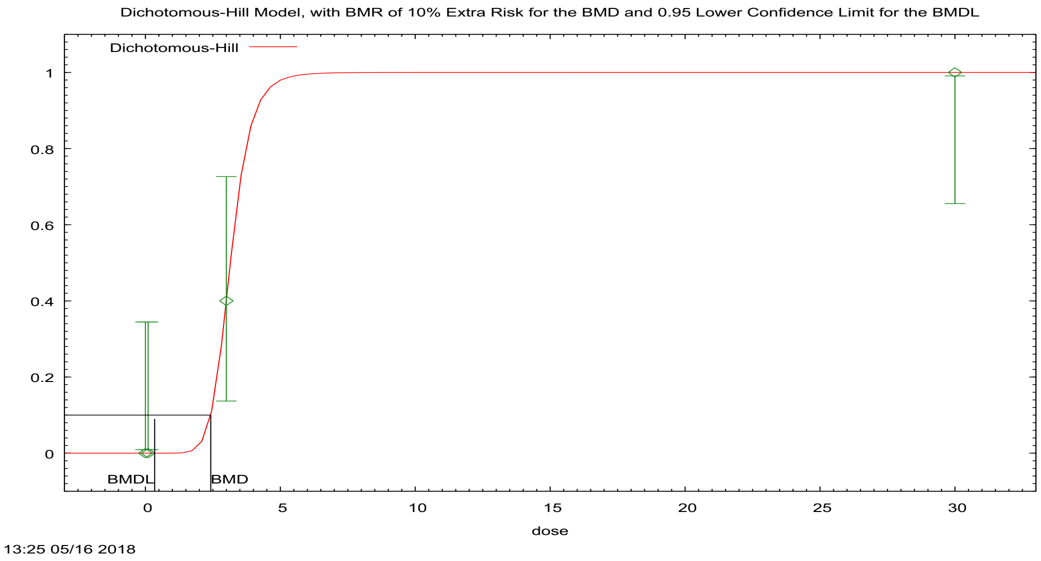

Figure 81. Plot of incidence rate by dose with fitted curve for Dichotomous-Hill model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Dichotomous Hill Model. (Version: 1.3; Date: 02/28/2013)

The form of the probability function is: P[response] = v*g +(v-v*g)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.42168

BMDL at the 95% confidence level = 0.343163

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
v	1	1

g	0	0
intercept	-9.5974E+00	-9.0088E-01
slope	8.36688	1.04549

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.000000128904	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4602

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0 d.f = 2 P-value = 1

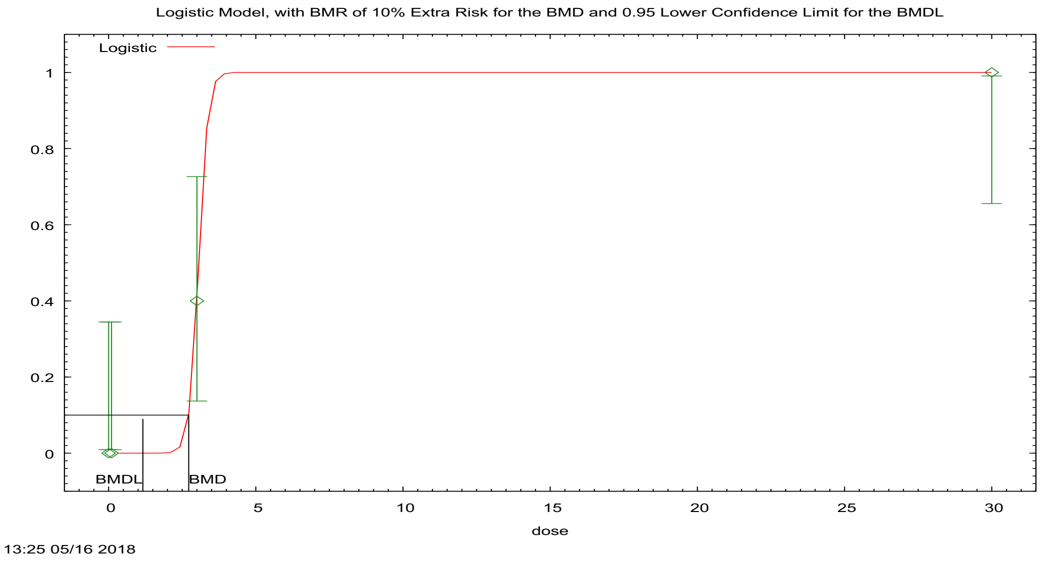

Figure 82. Plot of incidence rate by dose with fitted curve for Logistic model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = 1/[1+EXP(-intercept-slope*dose)]

Slope parameter is not restricted

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Warning: BMDU computation is at best imprecise for these data

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.72165

BMDL at the 95% confidence level = 1.16321

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0

intercept	-1.9717E+01	-2.3927E+00
slope	6.43701	0.186054

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.000000158926	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4602

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0   d.f = 2   P-value = 1

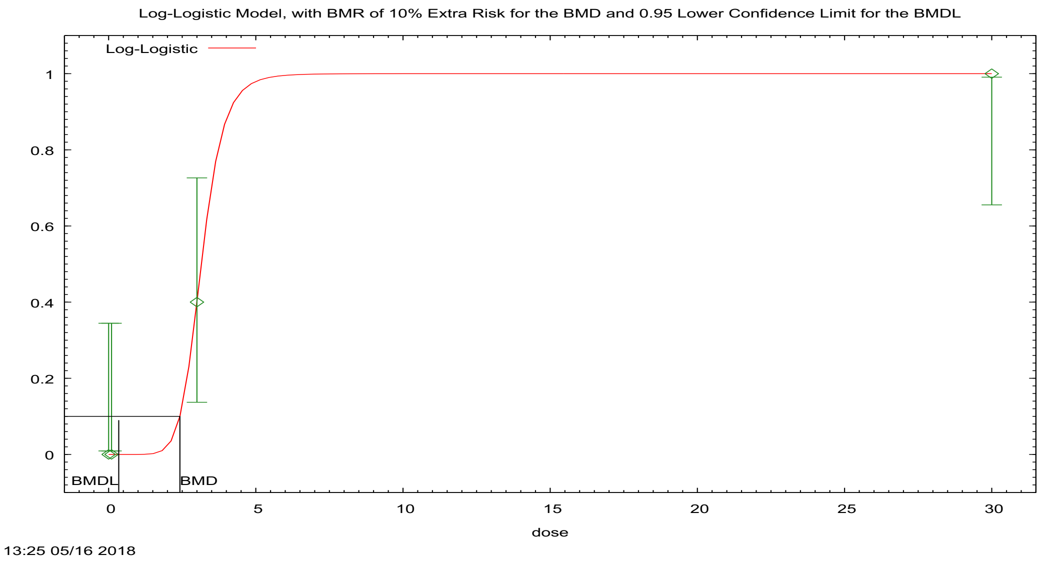

Figure 83. Plot of incidence rate by dose with fitted curve for LogLogistic model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.42169

BMDL at the 95% confidence level = 0.343163

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-9.5975E+00	-9.0088E-01
slope	8.36697	1.04549

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.000000128876	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4602

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0 d.f = 2 P-value = 1

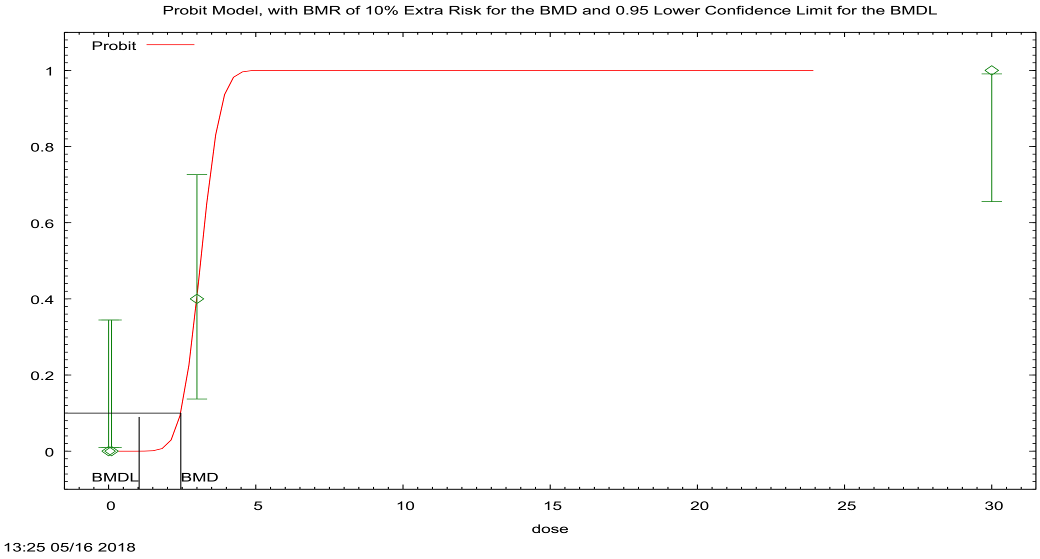

Figure 84. Plot of incidence rate by dose with fitted curve for Probit model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = CumNorm(Intercept+Slope*Dose), where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Warning: BMDU computation is at best imprecise for these data

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.45186

BMDL at the 95% confidence level = 1.03642

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-5.8808E+00	-1.6482E+00
slope	1.87582	0.123523

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.000000165492	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4602

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0   d.f = 2   P-value = 1

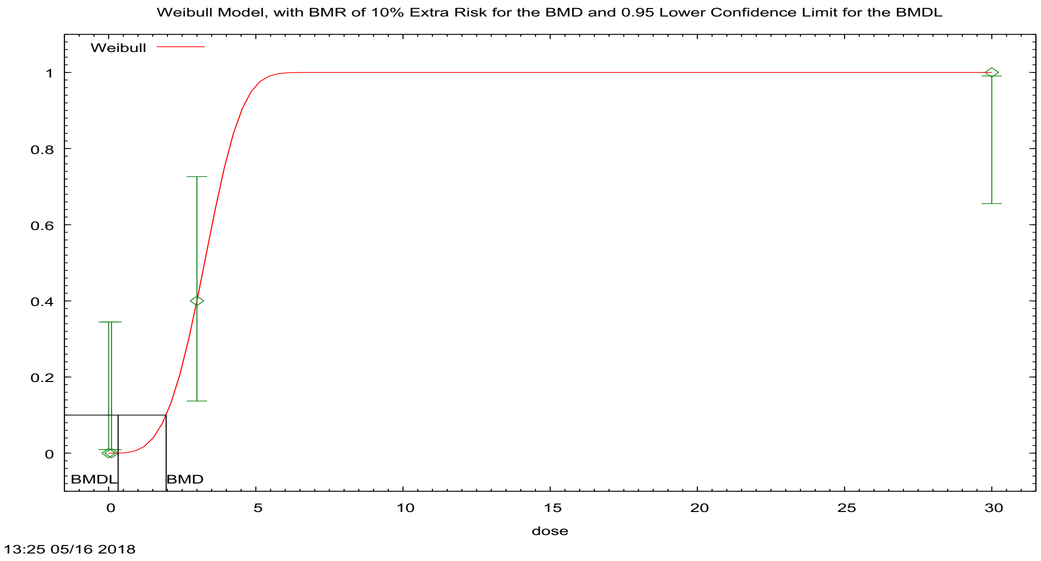

Figure 85. Plot of incidence rate by dose with fitted curve for Weibull model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Weibull Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]

Power parameter is restricted as power >=1

Warning: BMDU computation is at best imprecise for these data

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.95584

BMDL at the 95% confidence level = 0.323064

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333

Slope	0.0088635	0.0799298
Power	3.69018	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.0000361794	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4603

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0 d.f = 2 P-value = 1

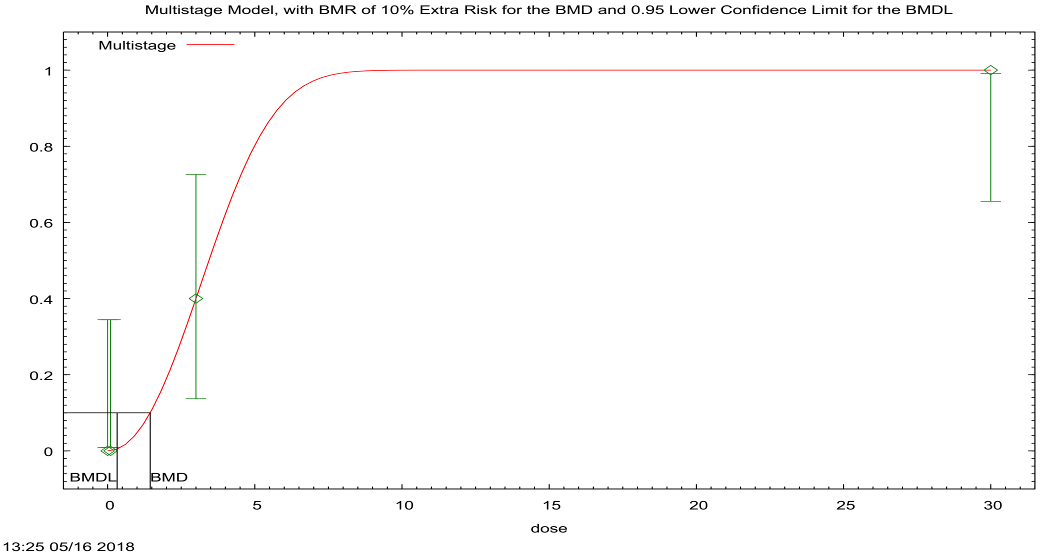

Figure 86. Plot of incidence rate by dose with fitted curve for Multistage 3° model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.44721

BMDL at the 95% confidence level = 0.322688

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0.0443672	0
Beta(3)	0.00410304	3.7049E+15

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.00896369	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4692

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0.0004	0.004	0	10	-0.07
3	0.3996	3.996	4	10	0
30	1	10	10	10	0

Chi^2 = 0 d.f = 2 P-value = 0.9978

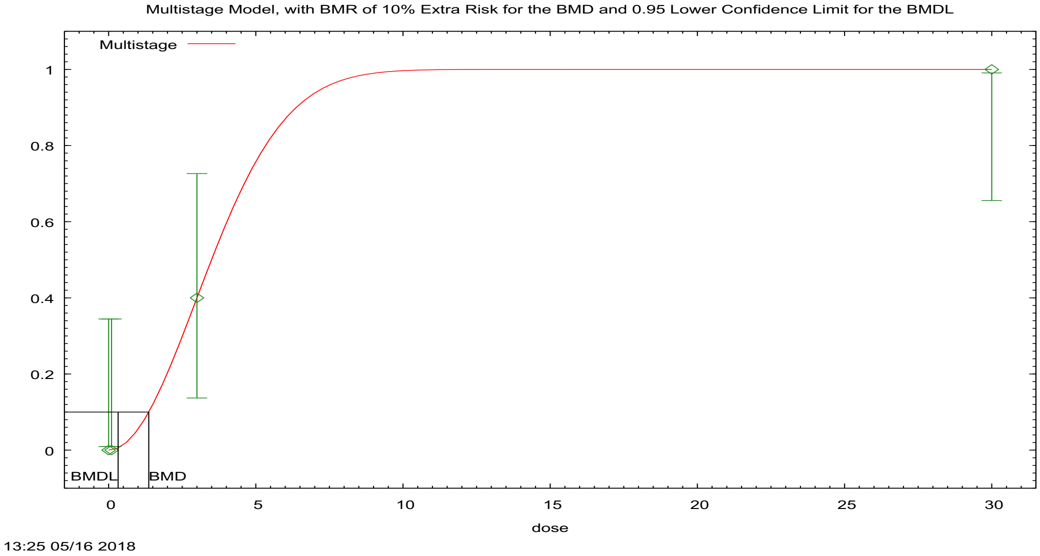

Figure 87. Plot of incidence rate by dose with fitted curve for Multistage 2° model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.36345

BMDL at the 95% confidence level = 0.322588

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0.0566762	1.1147E+17

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.74	1	0.0113435	3	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 15.4716

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0.0006	0.006	0	10	-0.08
3	0.3996	3.996	4	10	0
30	1	10	10	10	0

Chi^2 = 0.01 d.f = 3 P-value = 0.9999

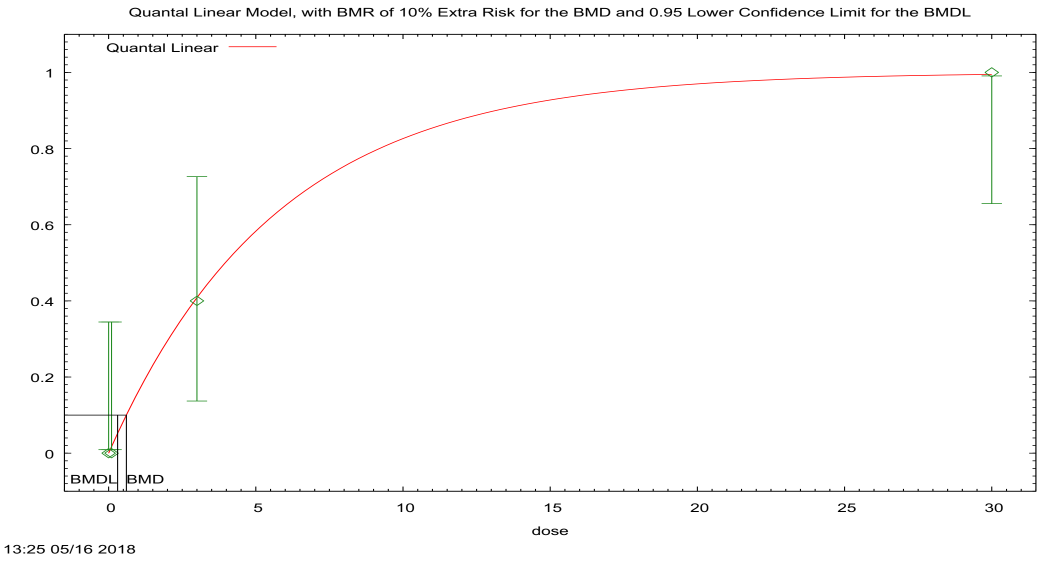

Figure 88. Plot of incidence rate by dose with fitted curve for Quantal-Linear model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Quantal Linear Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.602799

BMDL at the 95% confidence level = 0.305305

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	0.174785	0.0799298
Power	n/a	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.96	1	0.458177	3	0.93
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 15.9184

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0.0173	0.173	0	10	-0.42
3	0.4081	4.081	4	10	-0.05
30	0.9947	9.947	10	10	0.23

Chi^2 = 0.23 d.f = 3 P-value = 0.9722

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery – Hepatocellular Necrosis in Males

1.21. BMDS Summary of Hepatocellular Necrosis in Males (28-Day Rats)

Table 21. Summary of BMD Modeling Results for Hepatocellular Necrosis in Males (28-Day Rats)

Model[a]	**Goodness of fit**		**BMD_{10Pct} (mg/kg/day)**	**$BMDL_{10Pct}$ (mg/kg/day)**	**BMD/BMDL**	**Basis for model selection**
	***p*-value**	**AIC**				
Gamma	1.000	16.217	22.8	4.89	4.67	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were not sufficiently close (> 3-fold difference), so the lowest BMDL was selected.
Dichotomous-Hill	1.000	18.217	24.9	2.72	9.14	
Logistic	1.000	16.217	28.0	14.6	1.91	
LogLogistic	1.000	16.217	25.3	4.05	6.25	
Probit	1.000	16.217	26.1	13.1	1.99	
LogProbit	**1.000**	**16.217**	**21.5**	**2.70**	**7.98**	
Weibull	1.000	16.217	25.7	4.89	5.25	
Multistage 3°	1.000	14.224	20.0	4.89	4.09	
Multistage 2°	0.998	14.289	16.4	4.84	3.39	
Quantal-Linear	0.941	14.954	10.0	4.39	2.28	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.3, 3, and 30 mg/kg/day were 0, 0, 0, 0, respectively.

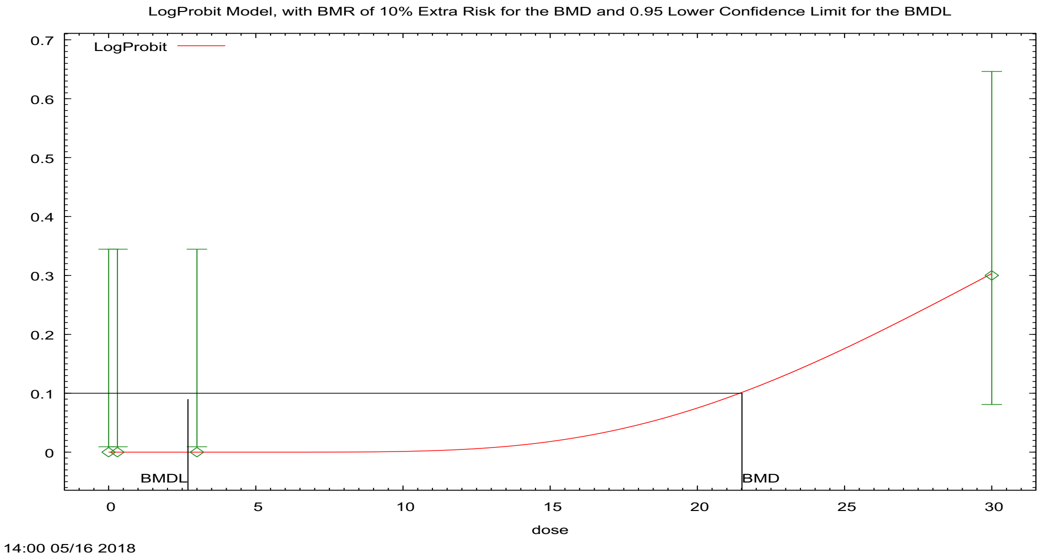

Figure 89. Plot of incidence rate by dose with fitted curve for LogProbit model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 21.5145

BMDL at the 95% confidence level = 2.69529

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-8.2701E+00	-1.5801E+00
slope	2.27735	0.253242

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	2	0.0000000801219	2	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 16.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0

0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0 d.f = 2 P-value = 1

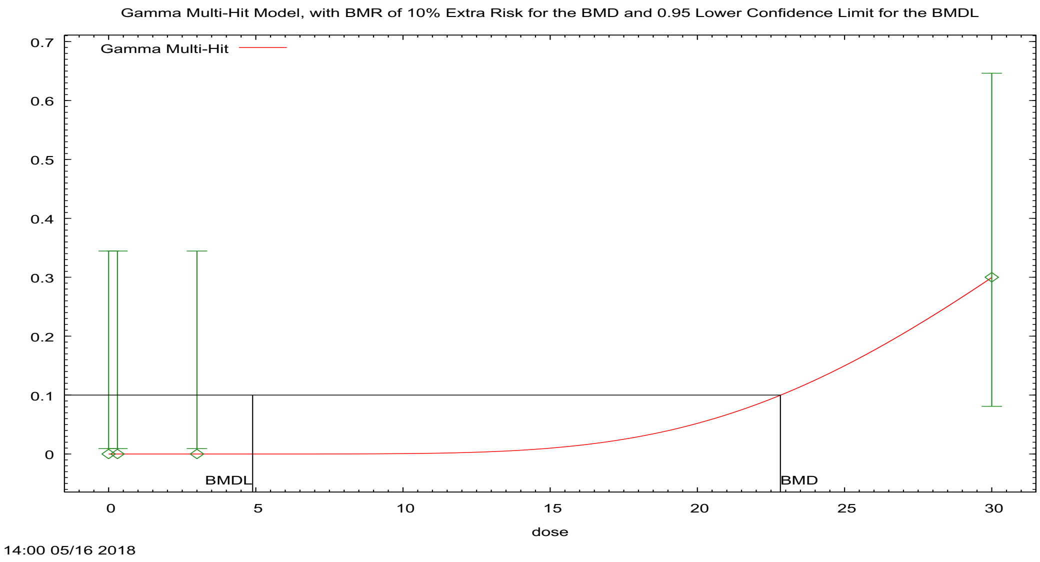

Figure 90. Plot of incidence rate by dose with fitted curve for Gamma model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Gamma Model. (Version: 2.17; Date: 6/22/2017)

The form of the probability function is: P[response]= background+(1-background)*CumGamma[slope*dose,power], where CumGamma(.) is the cumulative Gamma distribution function

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 22.8198

BMDL at the 95% confidence level = 4.89143

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	0.260092	0.0194895
Power	9.63903	1.40183

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	2	0.000000582716	2	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 16.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0   d.f = 2   P-value = 1

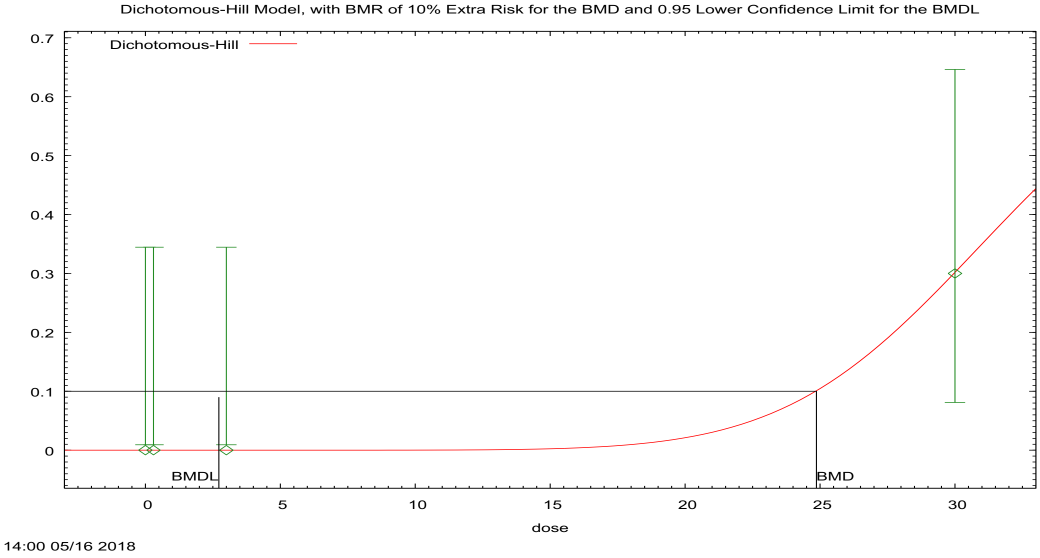

Figure 91. Plot of incidence rate by dose with fitted curve for Dichotomous-Hill model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Dichotomous Hill Model. (Version: 1.3; Date: 02/28/2013)

The form of the probability function is: P[response] = v*g +(v-v*g)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

Warning: BMDL computation is at best imprecise for these data

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 24.8662

BMDL at the 95% confidence level = 2.72083

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
v	0.789447	1
g	0	0

intercept	-2.6606E+01	-4.2523E+00
slope	7.67852	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	3	0.000000207435	1	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 18.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0   d.f = 1   P-value = 0.9997

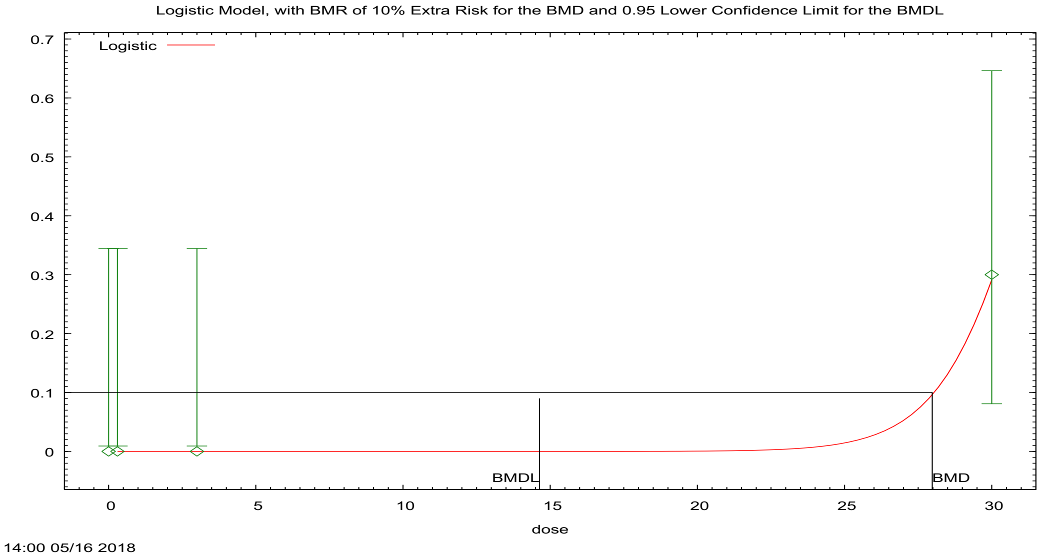

Figure 92. Plot of incidence rate by dose with fitted curve for Logistic model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = 1/[1+EXP(-intercept-slope*dose)]

Slope parameter is not restricted

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 27.9773

BMDL at the 95% confidence level = 14.6373

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-2.0869E+01	-3.1257E+00
slope	0.66738	0.0782927

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	2	0.000000166474	2	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 16.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0   d.f = 2   P-value = 1

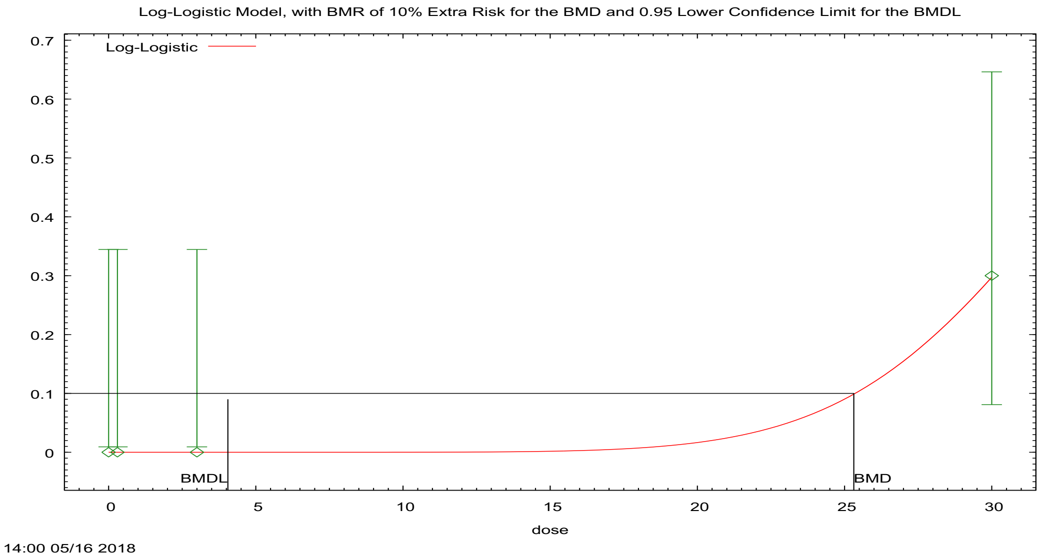

Figure 93. Plot of incidence rate by dose with fitted curve for LogLogistic model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 25.3124

BMDL at the 95% confidence level = 4.05137

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-2.7871E+01	-4.2523E+00
slope	7.94535	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	2	0.0000000972086	2	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 16.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0 d.f = 2 P-value = 1

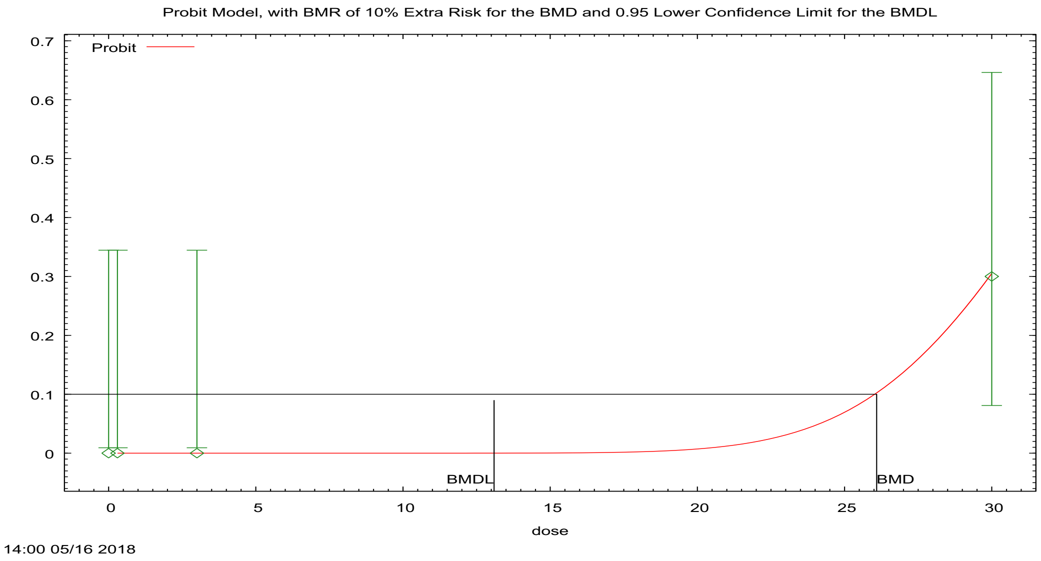

Figure 94. Plot of incidence rate by dose with fitted curve for Probit model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = CumNorm(Intercept+Slope*Dose), where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Warning: BMDU computation is at best imprecise for these data

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 26.0894

BMDL at the 95% confidence level = 13.0927

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values

background	n/a	0
intercept	-6.3329E+00	-2.1652E+00
slope	0.193616	0.0550069

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	2	0.0000000940851	2	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 16.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0   d.f = 2   P-value = 1

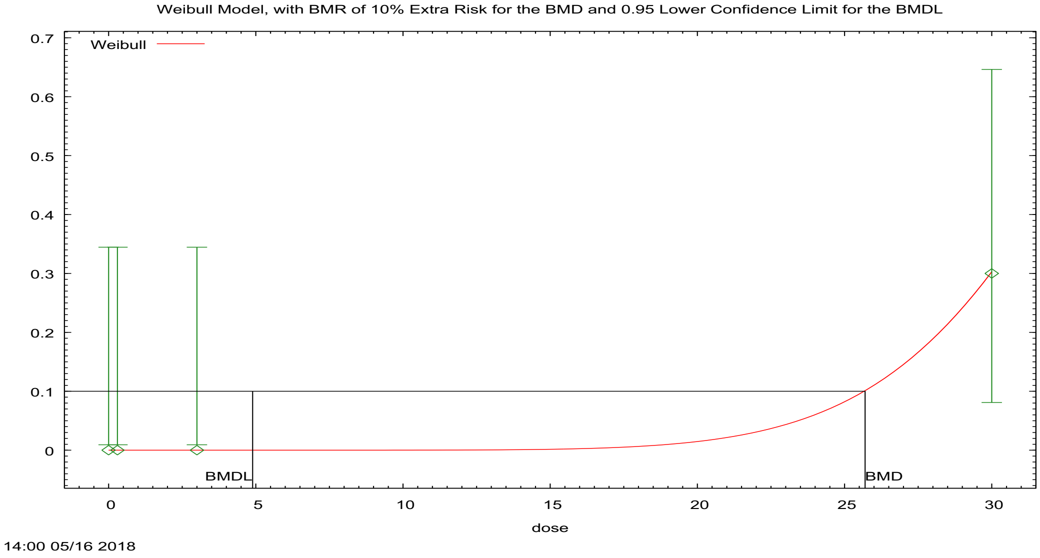

Figure 95. Plot of incidence rate by dose with fitted curve for Weibull model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Weibull Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]

Power parameter is restricted as power >=1

Warning: BMDU computation is at best imprecise for these data

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 25.6972

BMDL at the 95% confidence level = 4.89143

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333

Slope	8.2683E-13	0.00385791
Power	7.87671	1.29759

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	2	0.0000000947 531	2	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 16.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0 d.f = 2 P-value = 1

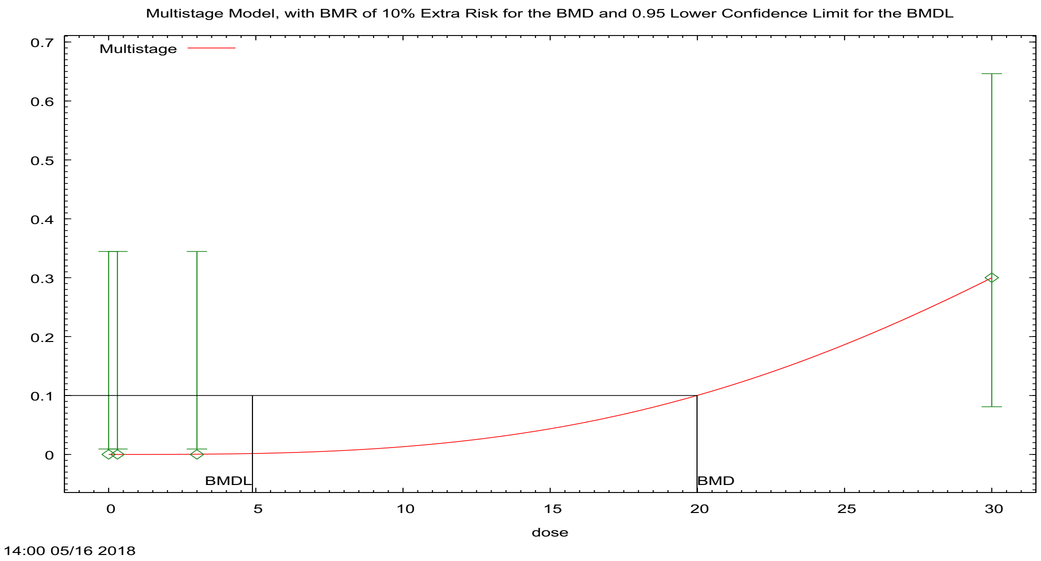

Figure 96. Plot of incidence rate by dose with fitted curve for Multistage 3° model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 19.9877

BMDL at the 95% confidence level = 4.88581

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0	0
Beta(3)	0.0000131943	0.0000132146

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	1	0.00713634	3	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 14.2244

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0.0004	0.004	0	10	-0.06
30	0.2997	2.997	3	10	0

Chi^2 = 0 d.f = 3 P-value = 0.9999

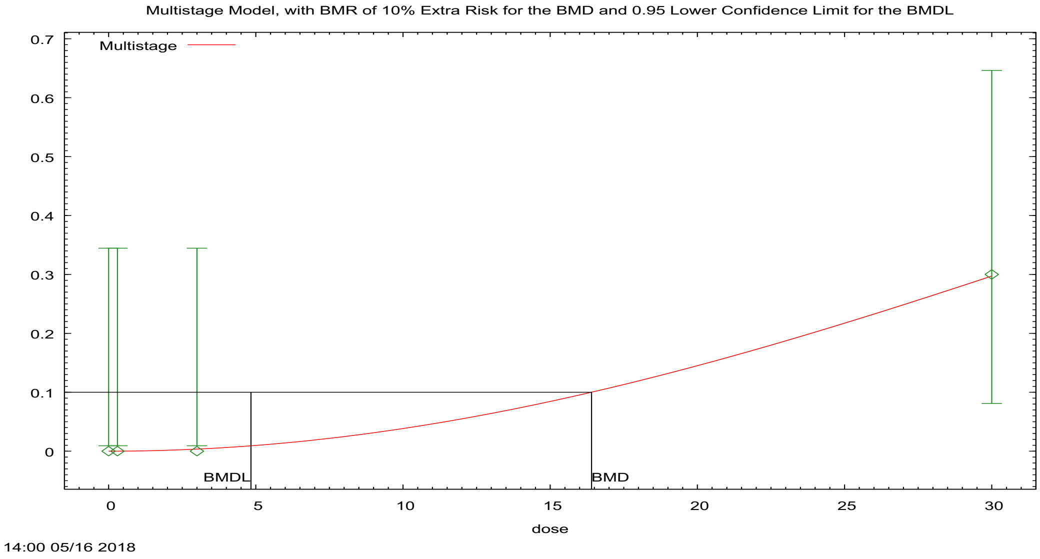

Figure 97. Plot of incidence rate by dose with fitted curve for Multistage 2° model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 16.4037

BMDL at the 95% confidence level = 4.83587

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0.000391555	0.000397609

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.14	1	0.0716147	3	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 14.2889

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	-0.02
3	0.0035	0.035	0	10	-0.19
30	0.297	2.97	3	10	0.02

Chi^2 = 0.04 d.f = 3 P-value = 0.9982

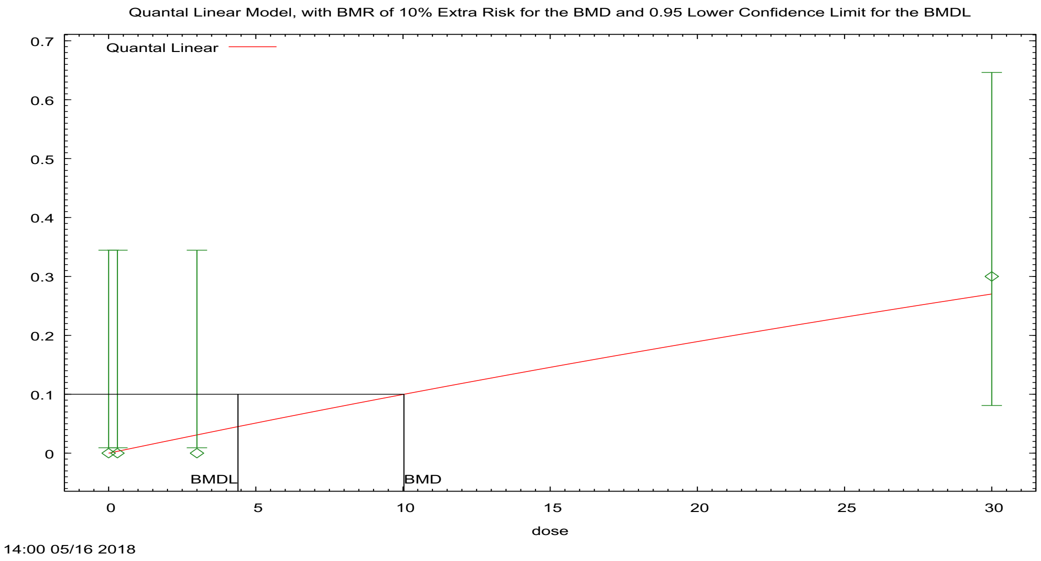

Figure 98. Plot of incidence rate by dose with fitted curve for Quantal-Linear model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Quantal Linear Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 10.0318

BMDL at the 95% confidence level = 4.39358

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	0.0105027	0.0106151
Power	n/a	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.48	1	0.737024	3	0.86
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 14.9543

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0.0031	0.031	0	10	-0.18
3	0.031	0.31	0	10	-0.57
30	0.2703	2.703	3	10	0.21

Chi^2 = 0.4 d.f = 3 P-value = 0.941

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Single Cell Hepatocellular Necrosis in Males

1.22. BMDS Summary of Single Cell Hepatocellular Necrosis in Males (90-Day Mice)

Table 22. Summary of BMD Modeling Results for Single Cell Hepatocellular Necrosis in Males (90-Day Mice)

Model[a]	**Goodness of fit**		**BMD_{10Pct} (mg/kg/day)**	**$BMDL_{10Pct}$ (mg/kg/day)**	**BMD/BMDL**	**Basis for model selection**
	***p*-value**	**AIC**				
Gamma	1.000	2.0001	1.39	0.452	3.08	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were not sufficiently close (> 3-fold difference), so the lowest BMDL was selected.
Dichotomous-Hill[b]	1.000	2.00	1.40	0.466	3.00	
Logistic	1.000	4.00	2.64	0.477	5.53	
LogLogistic[c]	1.000	2.00	1.40	0.466	3.00	
Probit	1.000	4.00	2.34	0.470	4.98	
LogProbit	1.000	4.00	1.00	0.464	2.16	
Weibull	1.000	2.00	3.61	0.449	8.04	
Multistage 3°	0.994	2.1593	1.24	0.437	2.84	Note: visual inspection of the selected model shows that the fitted curve does not fit the data well, and a different model may be more appropriate.
Multistage 2°	0.899	3.1588	0.759	0.349	2.17	
Quantal-Linear	**0.245**	**9.6272**	**0.236**	**0.126**	**1.87**	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were 0, -0.68, -1.58, 1.1, respectively.

[b] The Dichotomous-Hill model may appear equivalent to the LogLogistic model, however differences exist in digits not displayed in the table.

[c] The LogLogistic model may appear equivalent to the Dichotomous-Hill model, however differences exist in digits not displayed in the table.

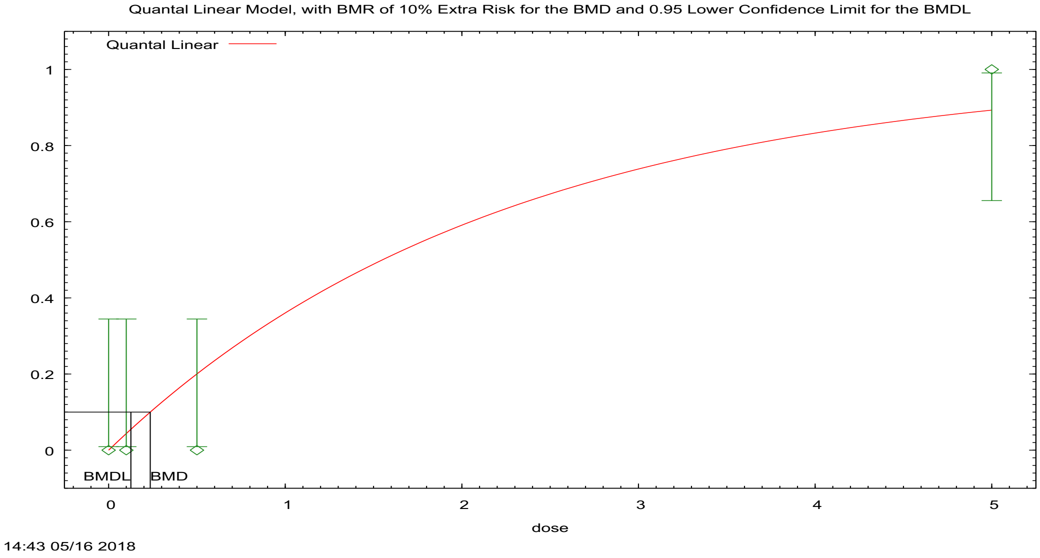

Figure 99. Plot of incidence rate by dose with fitted curve for Quantal-Linear model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Quantal Linear Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.235854

BMDL at the 95% confidence level = 0.126139

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	0.446718	0.479579
Power	n/a	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	-3.81	1	7.6272	3	0.05
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 9.6272

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0.0437	0.437	0	10	-0.68
0.5	0.2002	2.002	0	10	-1.58
5	0.8929	8.929	10	10	1.1

Chi^2 = 4.16 d.f = 3 P-value = 0.2447

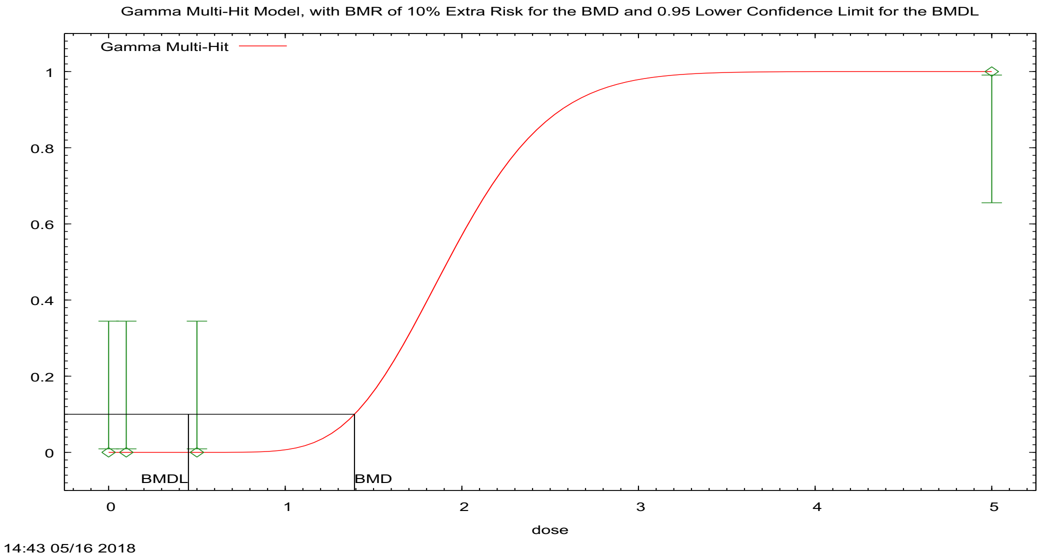

Figure 100. Plot of incidence rate by dose with fitted curve for Gamma model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Gamma Model. (Version: 2.17; Date: 6/22/2017)

The form of the probability function is: P[response]= background+(1-background)*CumGamma[slope*dose,power], where CumGamma(.) is the cumulative Gamma distribution function

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.39209

BMDL at the 95% confidence level = 0.45197

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	9.21034	1.6901
Power	18	5.22392

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	1	0.0000521053	3	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 2.00005

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0 d.f = 3 P-value = 1

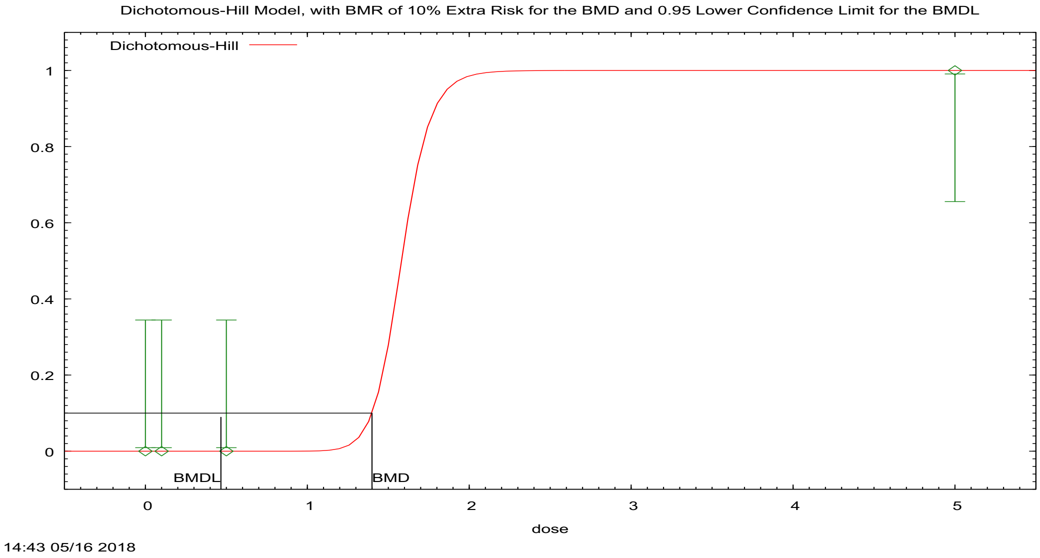

Figure 101. Plot of incidence rate by dose with fitted curve for Dichotomous-Hill model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Dichotomous Hill Model. (Version: 1.3; Date: 02/28/2013)

The form of the probability function is: P[response] = v*g +(v-v*g)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.39943

BMDL at the 95% confidence level = 0.466176

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
v	1	1
g	0	0
intercept	-8.2464E+00	-2.6100E-01
slope	18	1.63135

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	1	0.00000004	3	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 2

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0   d.f = 3   P-value = 1

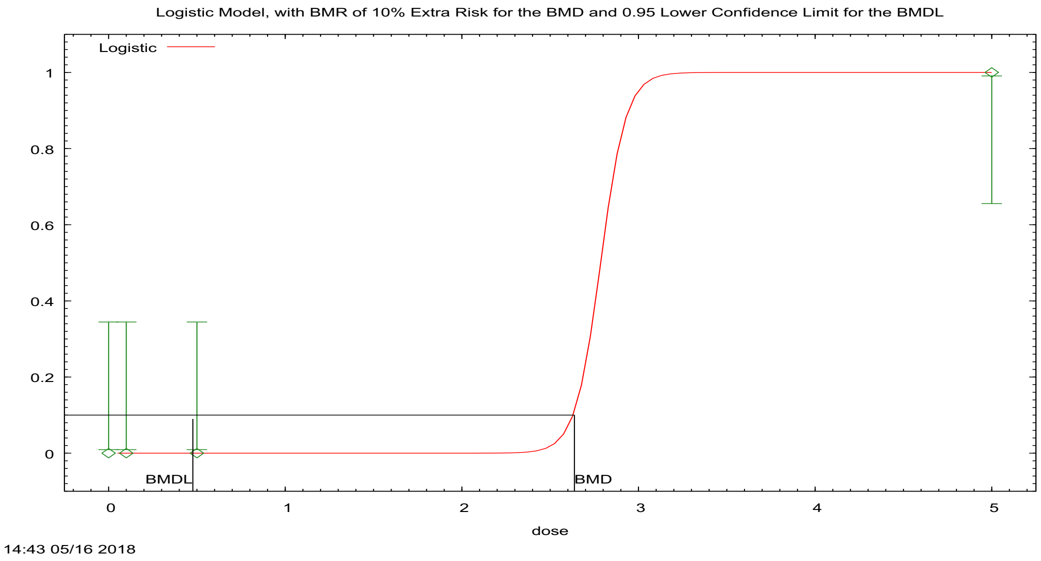

Figure 102. Plot of incidence rate by dose with fitted curve for Logistic model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = 1/[1+EXP(-intercept-slope*dose)]

Slope parameter is not restricted

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.63733

BMDL at the 95% confidence level = 0.476972

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-3.9049E+01	-3.2840E+00

slope	13.9732	1.25836

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	2	1.06359E-12	2	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 4

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0 d.f = 2 P-value = 1

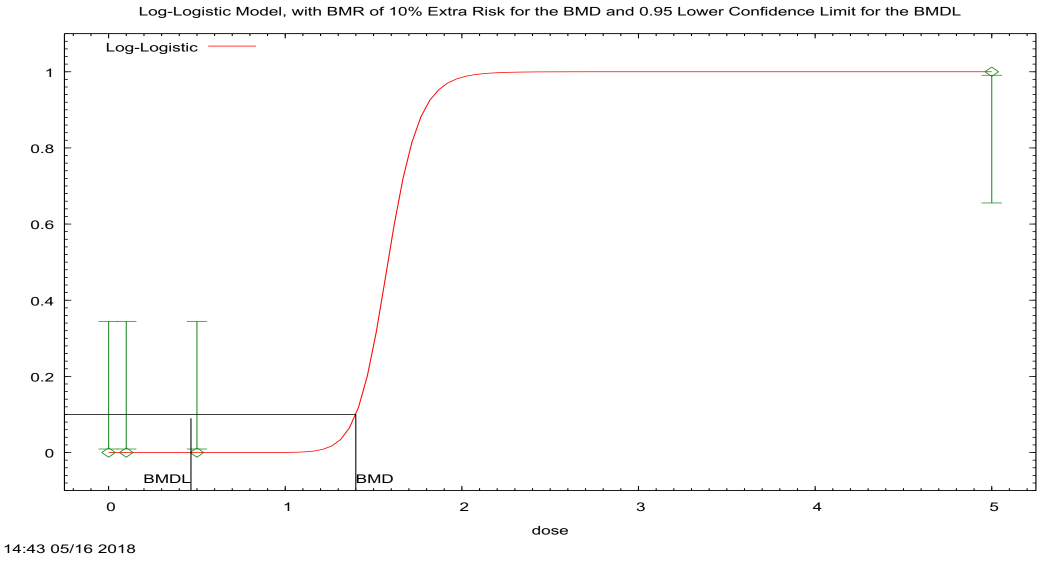

Figure 103. Plot of incidence rate by dose with fitted curve for LogLogistic model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.39944

BMDL at the 95% confidence level = 0.466176

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-8.2466E+00	-2.6100E-01
slope	18	1.63135

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	1	0.00000004	3	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 2

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid

0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0   d.f = 3   P-value = 1

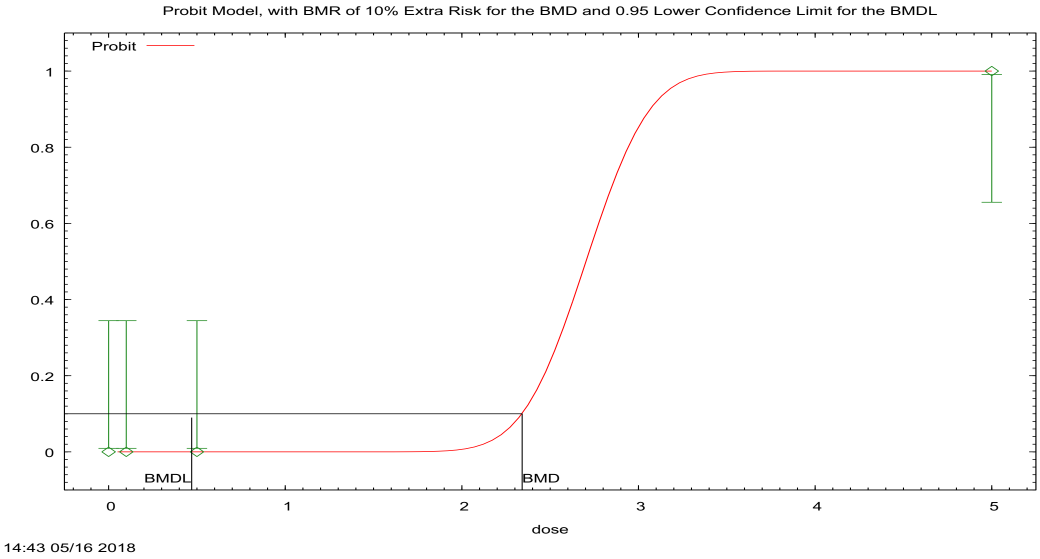

Figure 104. Plot of incidence rate by dose with fitted curve for Probit model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = CumNorm(Intercept+Slope*Dose), where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.34148

BMDL at the 95% confidence level = 0.470268

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-9.5416E+00	-2.2679E+00
slope	3.52773	0.839812

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	2	7.99361E-14	2	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 4

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0   d.f = 2   P-value = 1

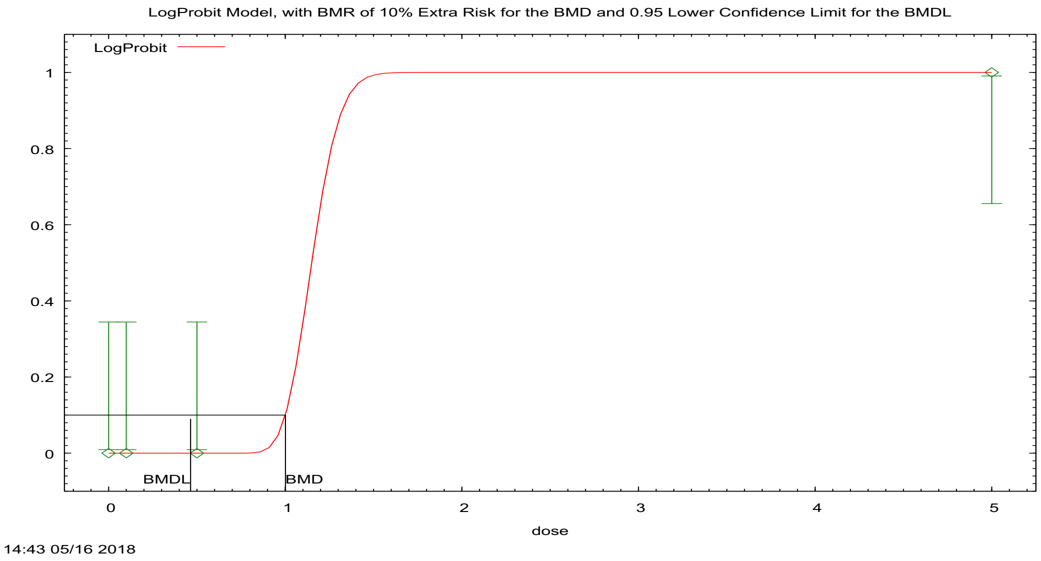

Figure 105. Plot of incidence rate by dose with fitted curve for LogProbit model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.00134

BMDL at the 95% confidence level = 0.464193

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-1.2939E+00	-1.4493E-01

slope	9.24923	0.905889

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	2	1.31006E-13	2	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 4

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0 d.f = 2 P-value = 1

Weibull Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL

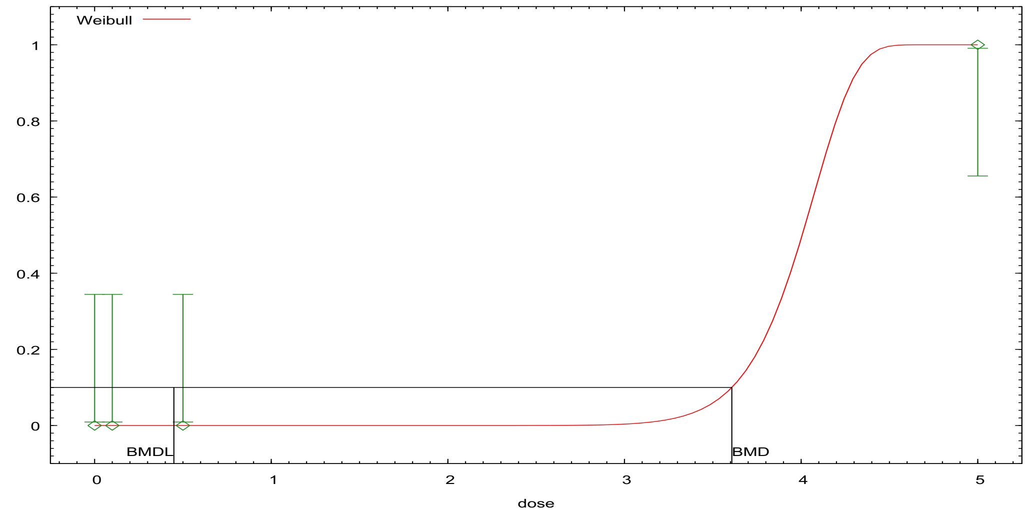

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Figure 106. Plot of incidence rate by dose with fitted curve for Weibull model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Weibull Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 3.60768

BMDL at the 95% confidence level = 0.448866

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	9.8305E-12	0.0591487
Power	18	2.30036

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	1	0	3	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 2

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid

0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0   d.f = 3   P-value = 1

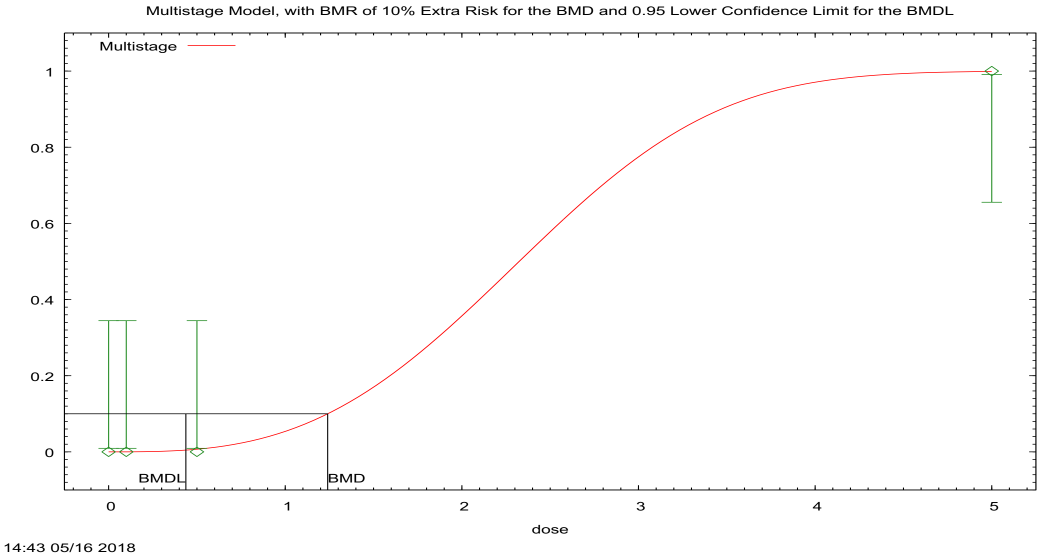

Figure 107. Plot of incidence rate by dose with fitted curve for Multistage 3° model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.24024

BMDL at the 95% confidence level = 0.437315

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0	0
Beta(3)	0.0552283	8.0027E+17

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	-0.08	1	0.15927	3	0.98
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 2.15927

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0.0001	0.001	0	10	-0.02
0.5	0.0069	0.069	0	10	-0.26
5	0.999	9.99	10	10	0.1

Chi^2 = 0.08 d.f = 3 P-value = 0.9941

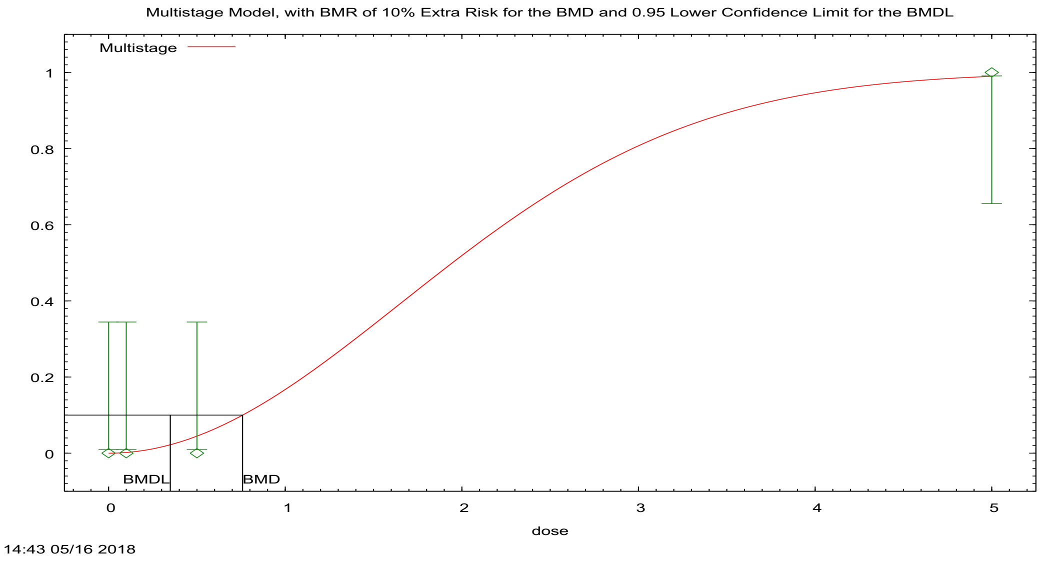

Figure 108. Plot of incidence rate by dose with fitted curve for Multistage 2° model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.758655

BMDL at the 95% confidence level = 0.349241

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0.183058	4.0136E+18

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	-0.58	1	1.1588	3	0.76
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 3.1588

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0.0018	0.018	0	10	-0.14
0.5	0.0447	0.447	0	10	-0.68
5	0.9897	9.897	10	10	0.32

Chi^2 = 0.59 d.f = 3 P-value = 0.8986

BMDS WIZARD OUTPUT REPORT

BMDS Summary for Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice – Single Cell Hepatocellular Necrosis in Males

1.23. BMDS Summary of Single Cell Hepatocellular Necrosis in Males (Reproductive Mice)

Table 23. Summary of BMD Modeling Results for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice)

Model[a]	Goodness of fit		BMD_{10Pct} (mg/kg/day)	$BMDL_{10Pct}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Gamma	0.992	47.275	0.399	0.172	2.32	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Dichotomous-Hill LogLogistic	0.977	47.275	0.464	0.253	1.83	
Logistic	0.969	45.337	0.362	0.253	1.43	
Probit	0.960	45.358	0.349	0.236	1.48	
LogProbit	0.977	47.275	0.443	0.248	1.79	
Weibull	1.000	47.275	0.407	0.166	2.45	
Multistage 3°	1.000	47.275	0.408	0.145	2.81	
Multistage 2°	**0.995**	**45.285**	**0.368**	**0.151**	**2.43**	
Quantal-Linear	0.261	48.991	0.162	0.106	1.53	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were 0.07, -0.08, 0.01, 0, respectively.

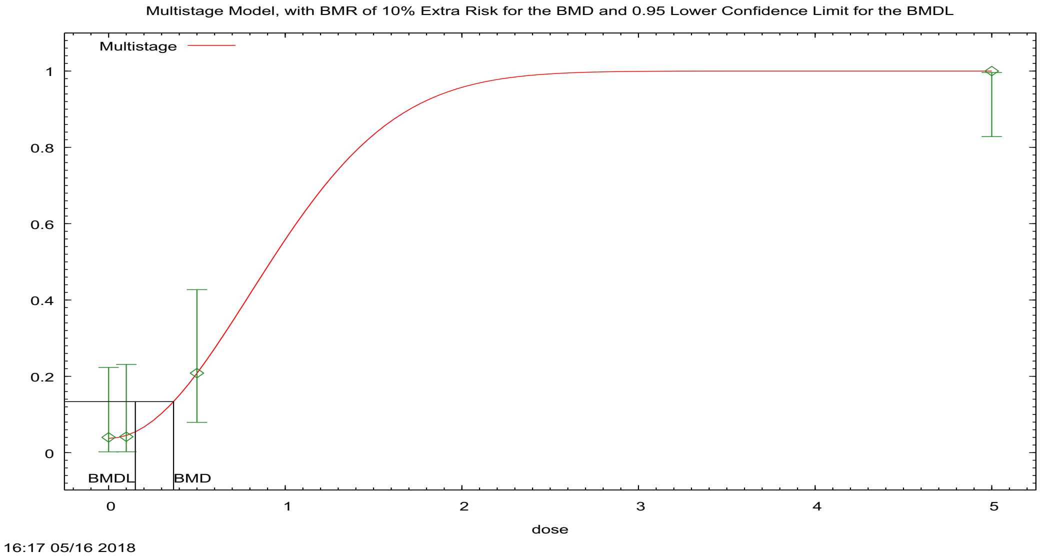

Figure 109. Plot of incidence rate by dose with fitted curve for Multistage 2° model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.36786

BMDL at the 95% confidence level = 0.151378

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0374803	0
Beta(1)	0	0
Beta(2)	0.778596	4.0136E+18

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	2	0.0105166	2	0.99
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 45.2851

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid

0	0.0375	0.937	1	25	0.07
0.1	0.0449	1.079	1	24	-0.08
0.5	0.2077	4.985	5	24	0.01
5	1	24	24	24	0

Chi^2 = 0.01 d.f = 2 P-value = 0.9948

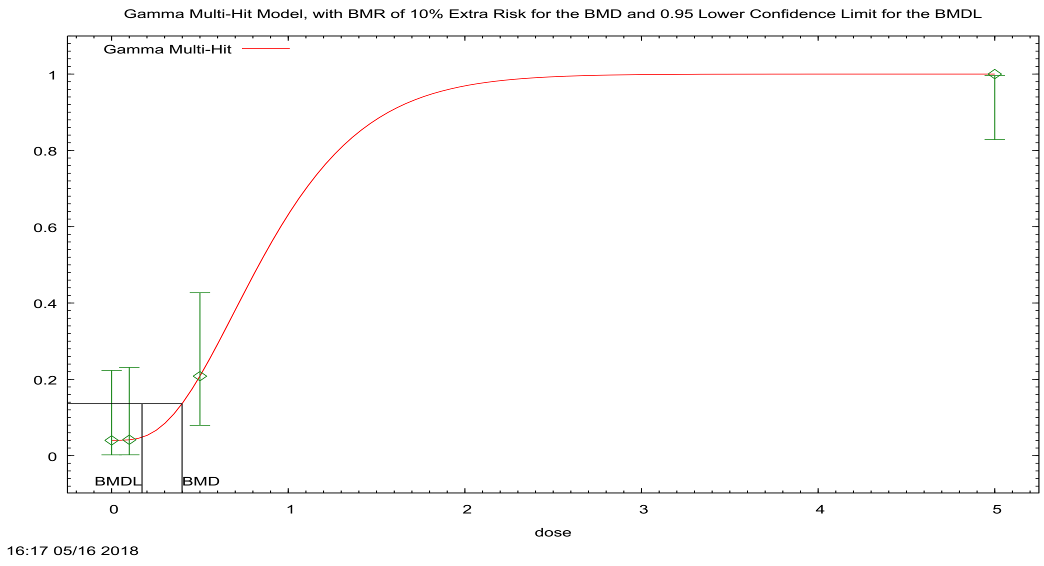

Figure 110. Plot of incidence rate by dose with fitted curve for Gamma model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Gamma Model. (Version: 2.17; Date: 6/22/2017)

The form of the probability function is: P[response]= background+(1-background)*CumGamma[slope*dose,power], where CumGamma(.) is the cumulative Gamma distribution function

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.398912

BMDL at the 95% confidence level = 0.172112

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0402031	0.0740741
Slope	4.06483	1.66473
Power	3.81438	4.20395

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	3	0.000137835	1	0.99
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 47.2747

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0402	1.005	1	25	0
0.1	0.0414	0.995	1	24	0.01
0.5	0.2084	5	5	24	0
5	1	24	24	24	0.01

Chi^2 = 0   d.f = 1   P-value = 0.9921

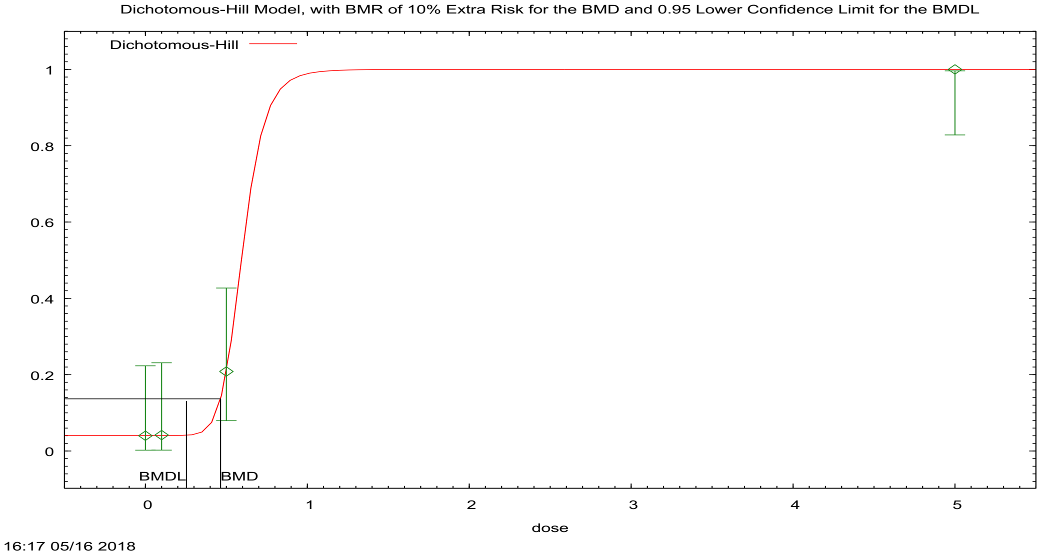

Figure 111. Plot of incidence rate by dose with fitted curve for Dichotomous-Hill model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Dichotomous Hill Model. (Version: 1.3; Date: 02/28/2013)

The form of the probability function is: P[response] = v*g +(v-v*g)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.464183

BMDL at the 95% confidence level = 0.253434

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
v	1	1
g	0.0408163	0.04
intercept	4.45404	-1.3477E-01

slope	8.66641	2.6015

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	3	0.000868905	1	0.98
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 47.2754

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0408	1.02	1	25	-0.02
0.1	0.0408	0.98	1	24	0.02
0.5	0.2083	5	5	24	0
5	1	24	24	24	0

Chi^2 = 0 d.f = 1 P-value = 0.9765

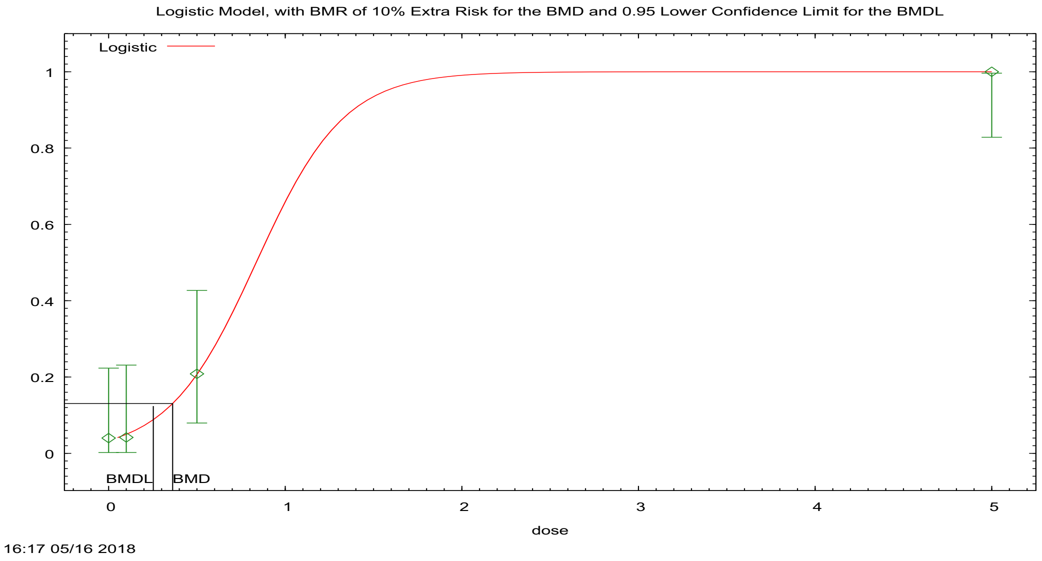

Figure 112. Plot of incidence rate by dose with fitted curve for Logistic model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = 1/[1+EXP(-intercept-slope*dose)]

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.362437

BMDL at the 95% confidence level = 0.253091

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-3.3521E+00	-2.5489E+00
slope	4.01471	1.29949

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.67	2	0.062635	2	0.97
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 45.3372

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0338	0.846	1	25	0.17

0.1	0.0497	1.193	1	24	-0.18
0.5	0.2067	4.961	5	24	0.02
5	1	24	24	24	0

Chi^2 = 0.06   d.f = 2   P-value = 0.9693

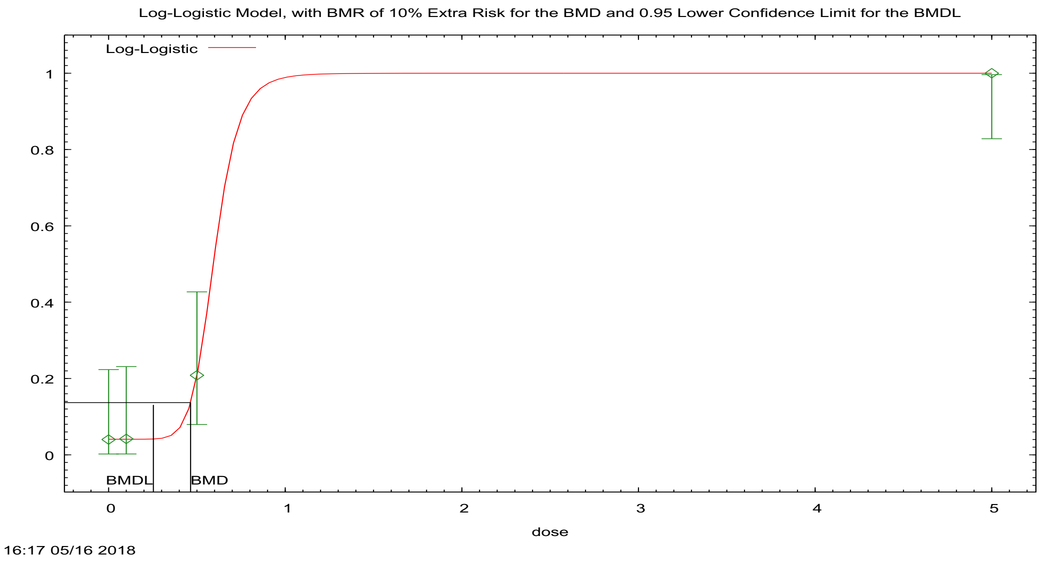

Figure 113. Plot of incidence rate by dose with fitted curve for LogLogistic model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.464183

BMDL at the 95% confidence level = 0.253434

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0.0408163	0.04
intercept	4.45403	-1.3477E-01
slope	8.66639	2.6015

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	3	0.000868905	1	0.98
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 47.2754

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0408	1.02	1	25	-0.02
0.1	0.0408	0.98	1	24	0.02
0.5	0.2083	5	5	24	0
5	1	24	24	24	0

Chi^2 = 0   d.f = 1   P-value = 0.9765

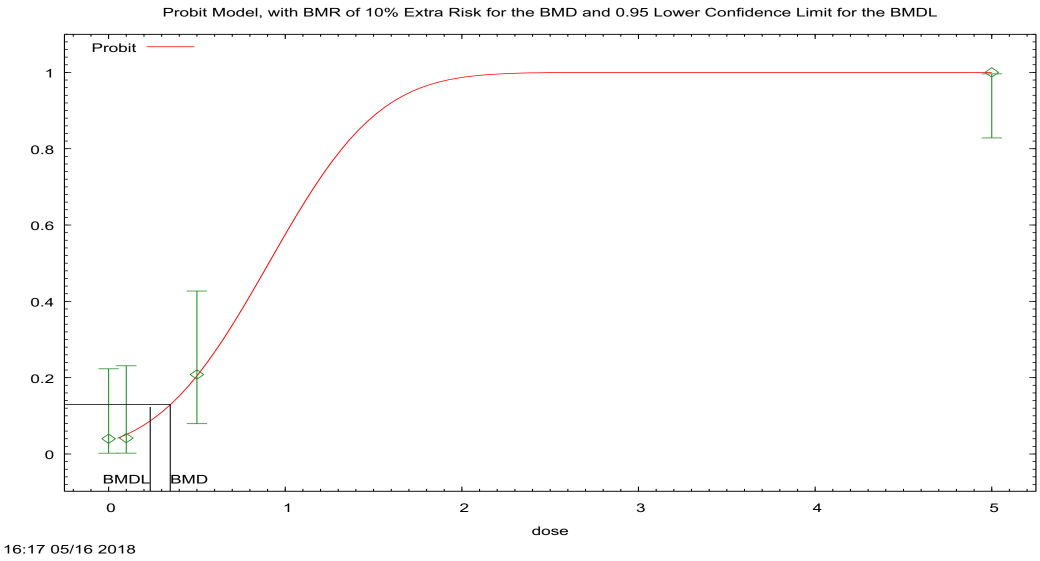

Figure 114. Plot of incidence rate by dose with fitted curve for Probit model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = CumNorm(Intercept+Slope*Dose), where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.34906

BMDL at the 95% confidence level = 0.235626

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-1.8366E+00	-1.5650E+00
slope	2.03222	0.78084

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.68	2	0.0831399	2	0.96
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 45.3577

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0331	0.828	1	25	0.19
0.1	0.0512	1.229	1	24	-0.21
0.5	0.206	4.943	5	24	0.03
5	1	24	24	24	0

Chi^2 = 0.08 d.f = 2 P-value = 0.9596

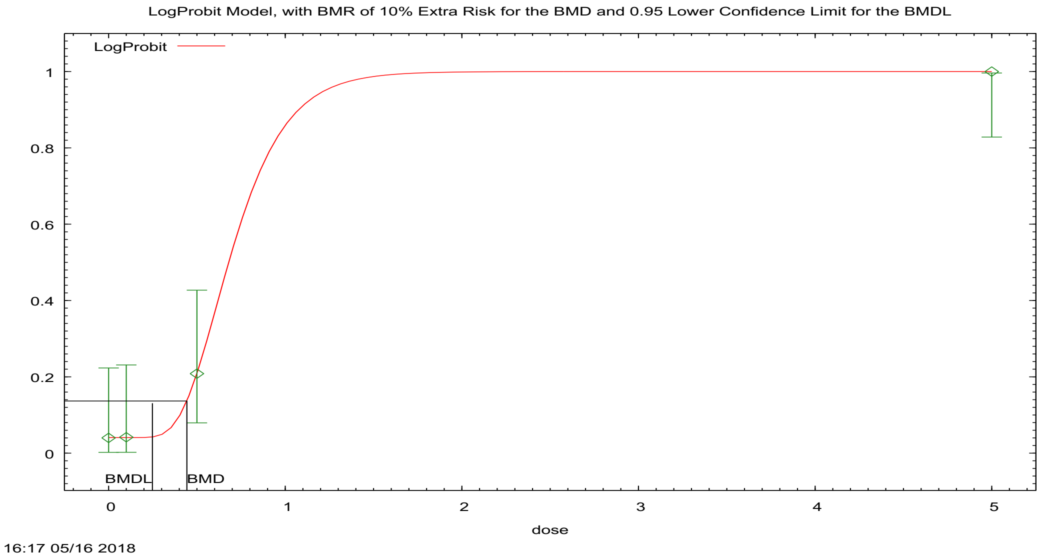

Figure 115. Plot of incidence rate by dose with fitted curve for LogProbit model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.44311

BMDL at the 95% confidence level = 0.248138

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0.0408136	0.04
intercept	1.04702	-1.2059E-02
slope	2.86087	1.27378

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	3	0.000868989	1	0.98
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 47.2754

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0408	1.02	1	25	-0.02
0.1	0.0408	0.98	1	24	0.02
0.5	0.2083	5	5	24	0
5	1	24	24	24	0

Chi^2 = 0   d.f = 1   P-value = 0.9765

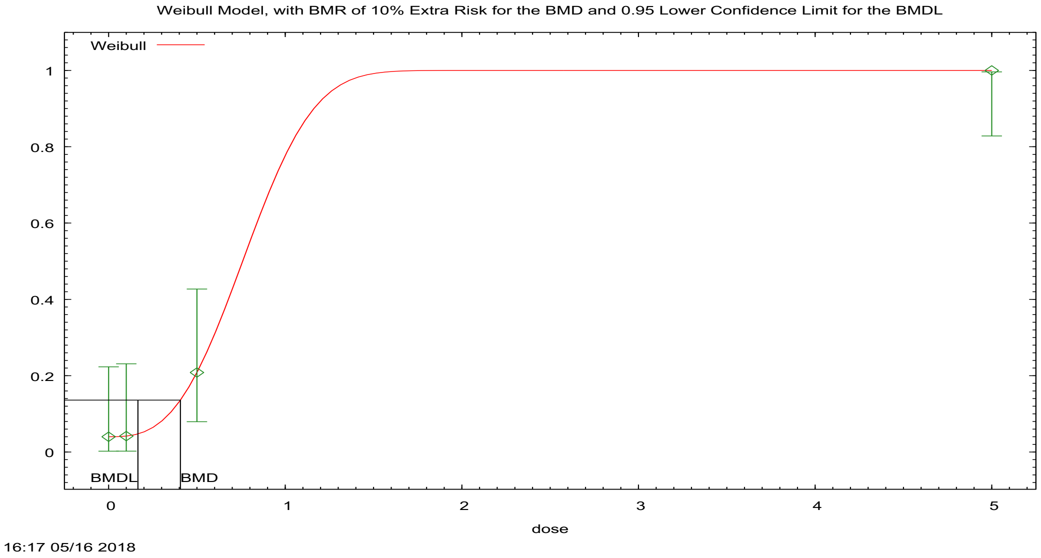

Figure 116. Plot of incidence rate by dose with fitted curve for Weibull model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Weibull Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.406554

BMDL at the 95% confidence level = 0.166046

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0399917	0.0740741
Slope	1.45834	0.126527
Power	2.9195	2.00352

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	3	0.0000003108 24	1	1
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 47.2746

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.04	1	1	25	0
0.1	0.0417	1	1	24	0
0.5	0.2083	4.999	5	24	0
5	1	24	24	24	0

Chi^2 = 0 d.f = 1 P-value = 0.9996

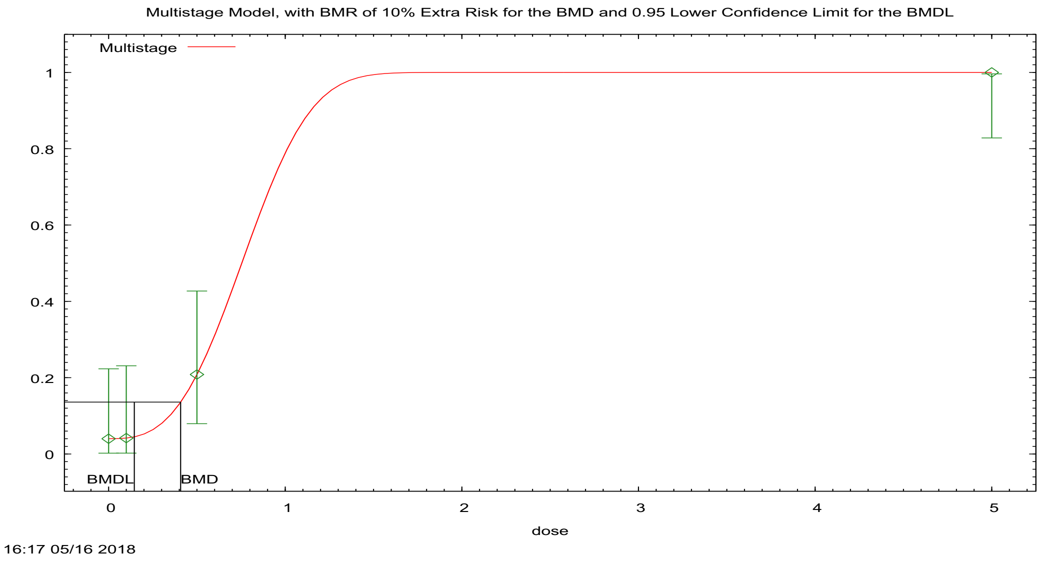

Figure 117. Plot of incidence rate by dose with fitted curve for Multistage 3° model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.407818

BMDL at the 95% confidence level = 0.14537

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.04	0
Beta(1)	0	0

Beta(2)	0.0244097	0
Beta(3)	1.49352	8.0027E+17

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	3	1.42109E-14	1	1
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 47.2746

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.04	1	1	25	0
0.1	0.0417	1	1	24	0
0.5	0.2083	5	5	24	0
5	1	24	24	24	0

Chi^2 = 0 d.f = 1 P-value = 1

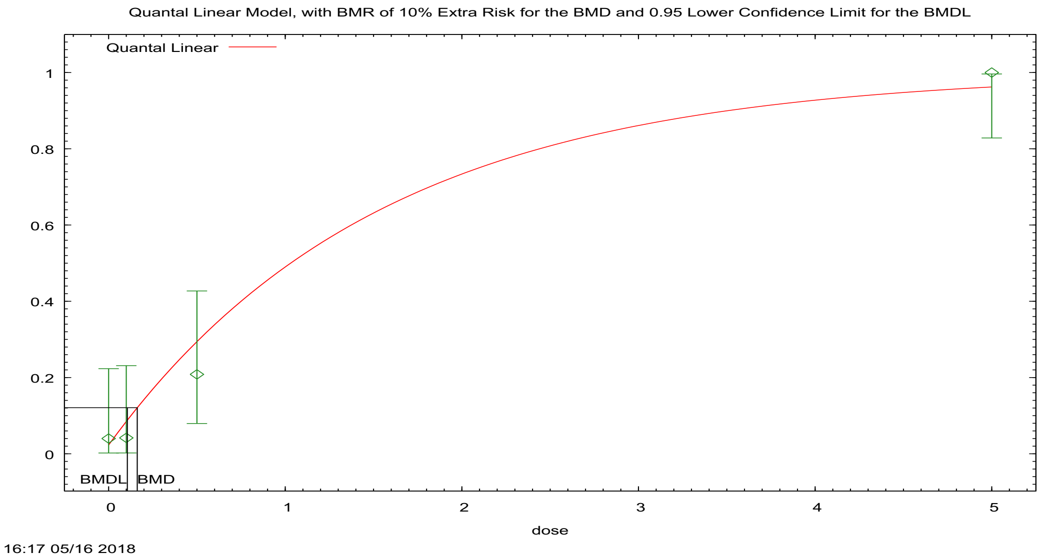

Figure 118. Plot of incidence rate by dose with fitted curve for Quantal-Linear model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Quantal Linear Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.162062

BMDL at the 95% confidence level = 0.106106

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0231249	0.0740741
Slope	0.650123	0.636227
Power	n/a	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-22.5	2	3.71609	2	0.16
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 48.9907

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0231	0.578	1	25	0.56
0.1	0.0846	2.031	1	24	-0.76
0.5	0.2942	7.061	5	24	-0.92
5	0.9621	23.091	24	24	0.97

Chi^2 = 2.68 d.f = 2 P-value = 0.2614

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Liver Weight to Brain Weight (g/100g) in Males

1.24. BMDS Summary of Liver Weight to Brain Weight in Males (28-Day Mice)

Table 24. Summary of BMD Modeling Results for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	**Goodness of fit**		**BMD_{1SD} (mg/kg/day)**	**$BMDL_{1SD}$ (mg/kg/day)**	**BMD/BMDL**	**Basis for model selection**
	***p*-value**	**AIC**				
Exponential (M4) **Exponential (M5)[b]**	**0.726**	**392.82**	**0.296**	**0.194**	**1.53**	**Only one model met inclusion criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)).**

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were -0.21, 0.31, -0.31, 0.23, respectively.

[b] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

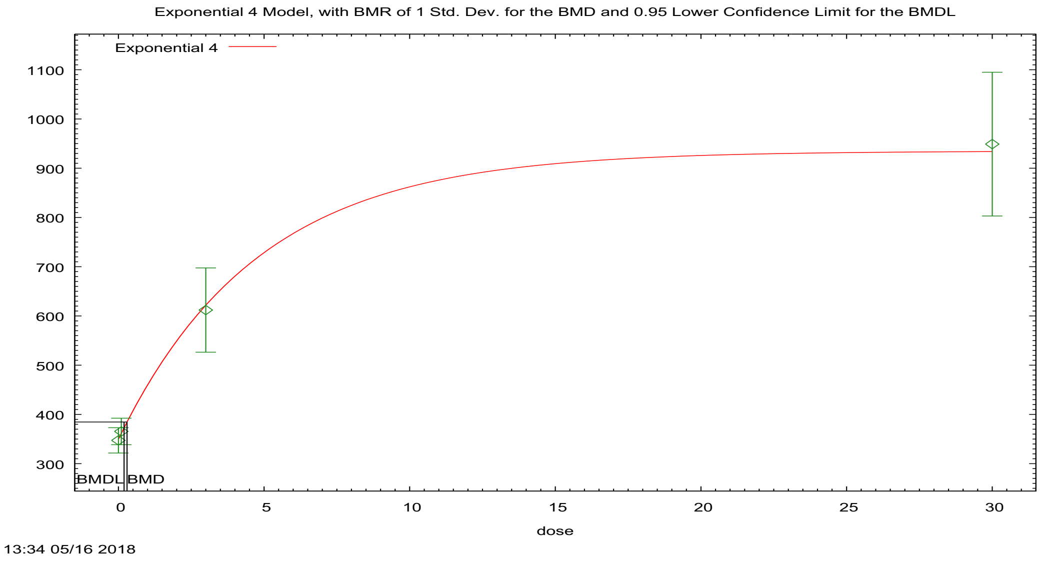

Figure 119. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.295612

BMDL at the 95% confidence level = 0.193746

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-14.3917	-13.9147
rho	3.67106	3.60787
a	349.675	329.948
b	0.208529	0.0890268
c	2.67347	3.01988
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347.3	349.7	35.93	34.98	-0.2134
0.1	10	365.4	361.8	37.57	37.23	0.3138
3	10	612	621.8	119.7	100.6	-0.3098
30	10	949	933.7	204.1	212.2	0.227

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.757	5	429.5139
A2	-191.0033	8	398.0066
A3	-191.3498	6	394.6996
R	-243.798	2	491.596

4	-191.4114	5	392.8228

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.6	6	<0.0001
Test 2	37.51	3	<0.0001
Test 3	0.693	2	0.7072
Test 6a	0.1232	1	0.7256

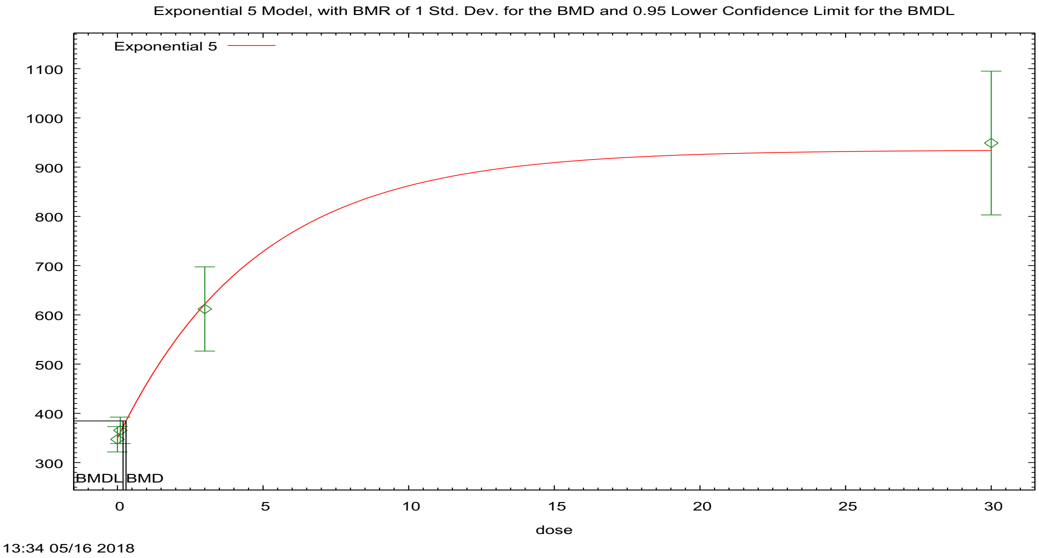

Figure 120. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.295612

BMDL at the 95% confidence level = 0.193746

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-14.3917	-13.9147
rho	3.67106	3.60787
a	349.675	329.948
b	0.208529	0.0890268
c	2.67347	3.01988
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347.3	349.7	35.93	34.98	-0.2134
0.1	10	365.4	361.8	37.57	37.23	0.3138
3	10	612	621.8	119.7	100.6	-0.3098
30	10	949	933.7	204.1	212.2	0.227

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.757	5	429.5139
A2	-191.0033	8	398.0066
A3	-191.3498	6	394.6996
R	-243.798	2	491.596
5	-191.4114	5	392.8228

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.6	6	<0.0001
Test 2	37.51	3	<0.0001

Test 3	0.693	2	0.7072
Test 7a	0.1232	1	0.7256

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Liver Weight to Brain Weight (g/100g brain) in Females

1.25. BMDS Summary of Liver Weight to Brain Weight in Females (28-Day Mice)

Table 25. Summary of BMD Modeling Results for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	**Goodness of fit**		**BMD$_{1SD}$ (mg/kg/day)**	**BMDL$_{1SD}$ (mg/kg/day)**	**BMD/BMDL**	**Basis for model selection**
	***p*-value**	**AIC**				
Exponential (M4) **Exponential (M5)**[b]	**0.381**	**340.54**	**1.14**	**0.751**	**1.52**	**Only one model met inclusion criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)).**

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.035), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were -0.64, 0.66, -0.02, 0, respectively.

[b] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

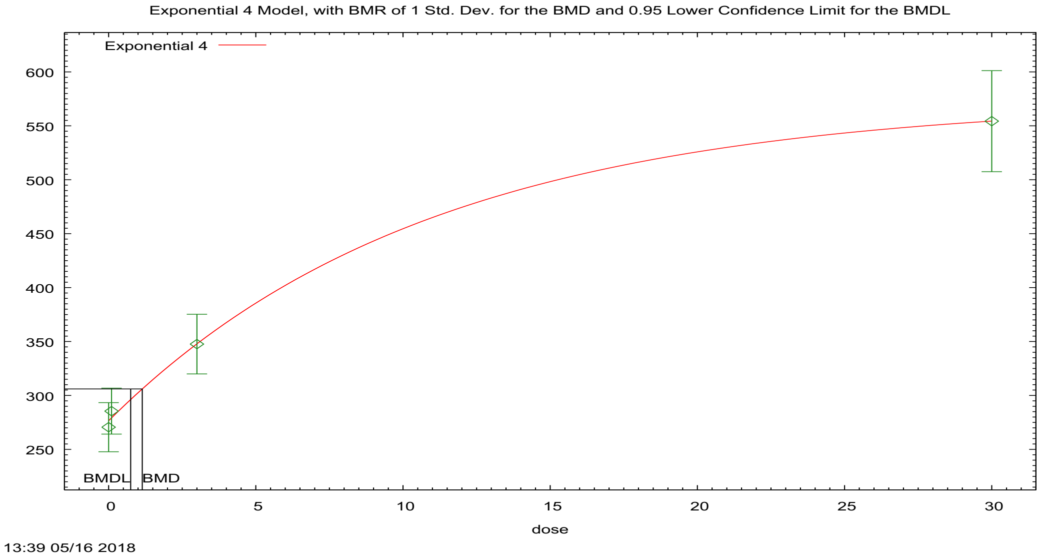

Figure 121. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.14268

BMDL at the 95% confidence level = 0.75065

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.14733	-5.34291
rho	2.11933	2.16682
a	276.535	257.053
b	0.0915598	0.0823334
c	2.07363	2.26425
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	270.6	276.5	31.83	29.49	-0.6383
0.1	10	285.5	279.2	29.77	29.8	0.6611
3	10	347.6	347.8	38.68	37.61	-0.01903
30	10	554.3	554.4	65.5	61.63	-0.003785

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.1109	5	348.2218
A2	-164.8074	8	345.6148
A3	-164.886	6	341.772
R	-211.7408	2	427.4817

4	-165.2698	5	340.5397

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.87	6	<0.0001
Test 2	8.607	3	0.035
Test 3	0.1572	2	0.9244
Test 6a	0.7677	1	0.3809

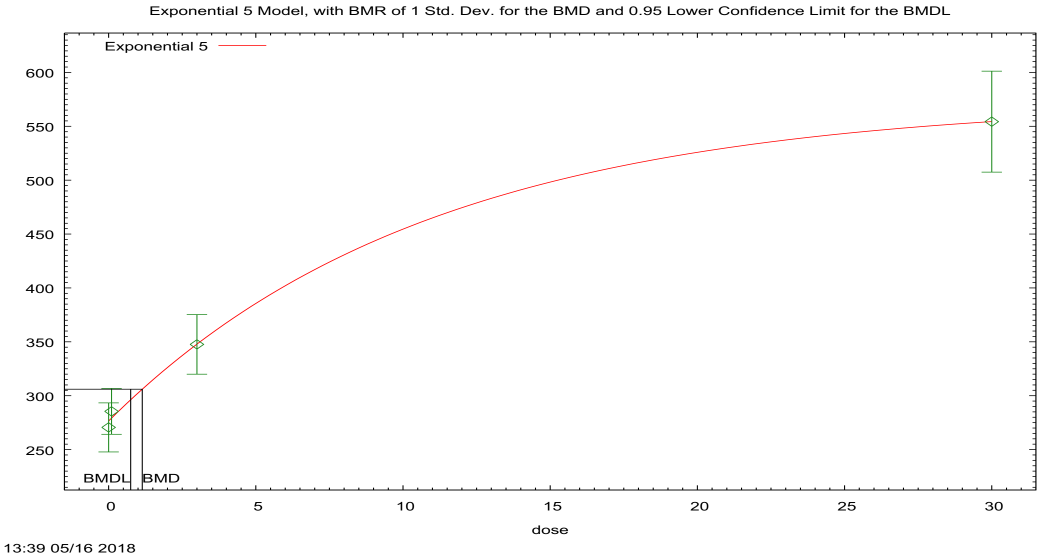

Figure 122. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.14268

BMDL at the 95% confidence level = 0.75065

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.14729	-5.34291
rho	2.11933	2.16682
a	276.535	257.053
b	0.0915596	0.0823334
c	2.07363	2.26425
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	270.6	276.5	31.83	29.49	-0.6383
0.1	10	285.5	279.2	29.77	29.8	0.6611
3	10	347.6	347.8	38.68	37.61	-0.01902
30	10	554.3	554.4	65.5	61.63	-0.003788

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.1109	5	348.2218
A2	-164.8074	8	345.6148
A3	-164.886	6	341.772
R	-211.7408	2	427.4817
5	-165.2698	5	340.5397

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.87	6	<0.0001
Test 2	8.607	3	0.035

Test 3	0.1572	2	0.9244
Test 7a	0.7677	1	0.3809

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery – Liver Weight to Brain Weight (g/100g brain) in Males

1.26. BMDS Summary of Liver Weight to Brain Weight in Males (28-Day Rats)

Table 26. Summary of BMD Modeling Results for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M4)	**0.762**	**389.53**	**1.01**	**0.611**	**1.65**	**Only one model met inclusion criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)).**

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0263), selected model in bold; scaled residuals for selected model for doses 0, 0.3, 3, and 30 mg/kg/day were 0.05, -0.1, 0.1, -0.04, respectively.

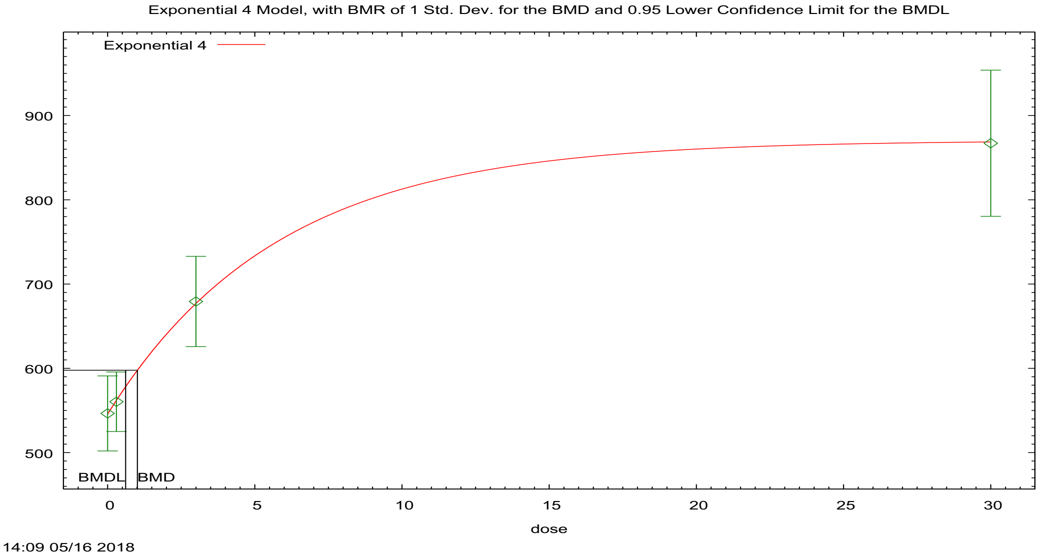

Figure 123. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.01078

BMDL at the 95% confidence level = 0.610799

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-12.9002	-13.4573
rho	3.30092	3.39985
a	545.71	519.162
b	0.172629	0.074374
c	1.59511	1.75365
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	546.5	545.7	62.27	52	0.04719
0.3	10	560.3	562.1	49.37	54.6	-0.1024
3	10	679.3	677	74.89	74.22	0.09887
30	10	867.1	868.6	121.2	112	-0.04414

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.9575	5	397.915
A2	-189.3381	8	394.6761
A3	-189.7208	6	391.4416
R	-220.4231	2	444.8461

4	-189.7667	5	389.5334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.17	6	<0.0001
Test 2	9.239	3	0.02628
Test 3	0.7655	2	0.682
Test 6a	0.09174	1	0.762

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Liver Weight to Brain Weight (%) in Males

1.27. BMDS Summary of Liver Weight to Brain Weight in Males (90-Day Mice)

Table 27. Summary of BMD Modeling Results for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.619	373.81	0.630	0.496	1.27	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M4)[c]	0.747	374.96	0.395	0.210	1.88	
Exponential (M5)[d]	0.747	374.96	0.395	0.210	1.88	
Power[e] **Polynomial 3°[f]** **Polynomial 2°[g]** **Linear**	**0.949**	**372.96**	**0.400**	**0.300**	**1.34**	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.19, 0.5, -0.36, 0.06, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] The Exponential (M4) model may appear equivalent to the Exponential (M5) model, however differences exist in digits not displayed in the table.

[d] The Exponential (M5) model may appear equivalent to the Exponential (M4) model, however differences exist in digits not displayed in the table.

[e] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[g] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

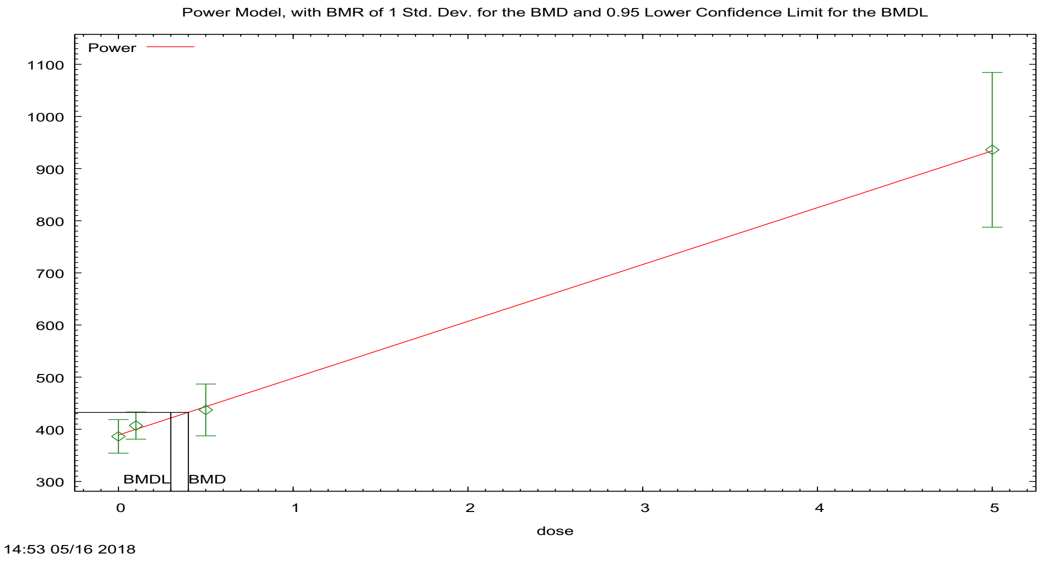

Figure 124. Plot of mean response by dose with fitted curve for Power model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.400252

BMDL at the 95% confidence level = 0.299666

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-12.4949	9.2714
rho	3.3602	0
control	389.017	386.366
slope	108.602	139.636
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386	389	45	43.5	-0.193
0.1	10	407	400	36.4	45.5	0.502
0.5	10	437	443	69.4	54.1	-0.363
5	9	936	932	193	189	0.0626

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.182127	5	406.364254
A2	-181.17551	8	378.351021
A3	-182.426362	6	376.852725
fitted	-182.47882	4	372.957641
R	-233.69519	2	471.39038

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.039	6	<0.0001
Test 2	34.0132	3	<0.0001
Test 3	2.5017	2	0.2863
Test 4	0.104916	2	0.9489

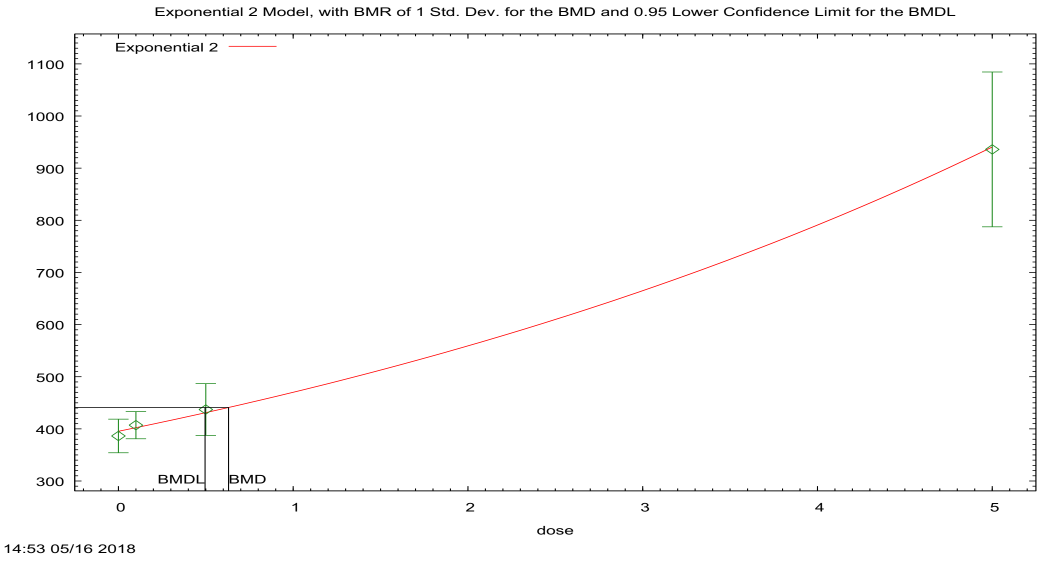

Figure 125. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.630028

BMDL at the 95% confidence level = 0.495699

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-11.8538	-12.7752
rho	3.26009	3.41177
a	395.343	395.553
b	0.173345	0.172612
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386.4	395.3	45.01	45.62	-0.6223
0.1	10	407.1	402.3	36.41	46.93	0.3265
0.5	10	437.1	431.1	69.39	52.55	0.3588
5	9	936	940.6	193.2	187.4	-0.07359

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.1821	5	406.3643
A2	-181.1755	8	378.351
A3	-182.4264	6	376.8527
R	-233.6952	2	471.3904
2	-182.9059	4	373.8117

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105	6	<0.0001
Test 2	34.01	3	<0.0001
Test 3	2.502	2	0.2863

Test 4	0.959	2	0.6191

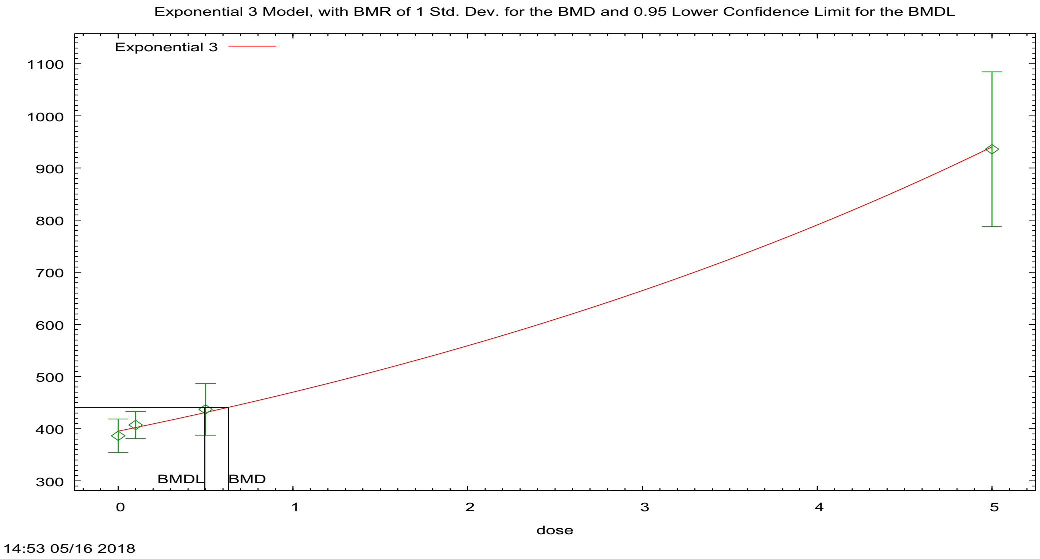

Figure 126. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.630028

BMDL at the 95% confidence level = 0.495699

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-11.8538	-12.7752
rho	3.26009	3.41177

a	395.343	395.553
b	0.173345	0.172612
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386.4	395.3	45.01	45.62	-0.6223
0.1	10	407.1	402.3	36.41	46.93	0.3265
0.5	10	437.1	431.1	69.39	52.55	0.3588
5	9	936	940.6	193.2	187.4	-0.07359

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.1821	5	406.3643
A2	-181.1755	8	378.351
A3	-182.4264	6	376.8527
R	-233.6952	2	471.3904
3	-182.9059	4	373.8117

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105	6	<0.0001
Test 2	34.01	3	<0.0001
Test 3	2.502	2	0.2863
Test 5a	0.959	2	0.6191

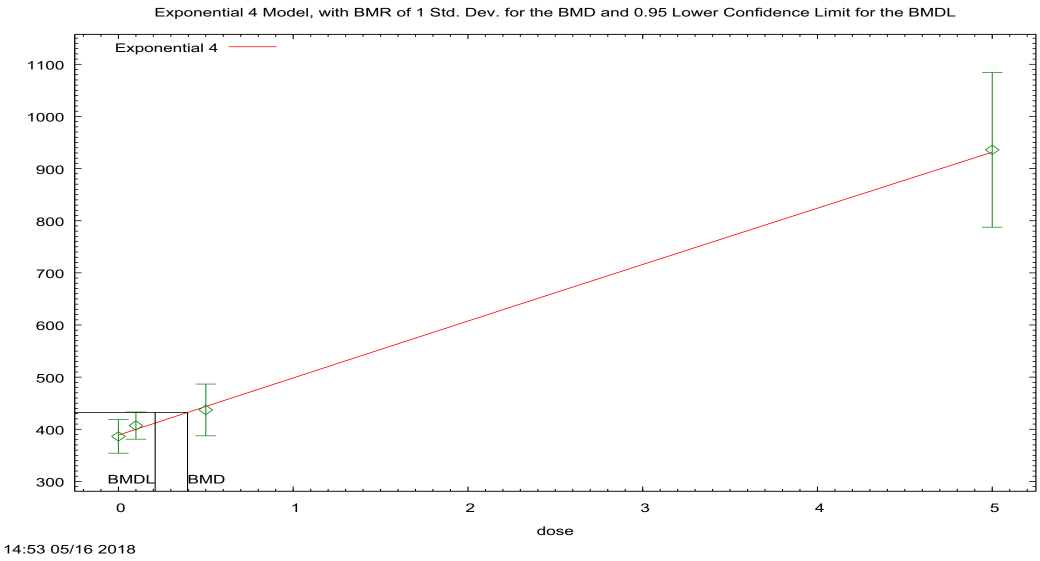

Figure 127. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.395422

BMDL at the 95% confidence level = 0.210227

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-12.5182	-12.7752
rho	3.36398	3.41177
a	388.84	367.048
b	0.00509897	0.0950512

c	56.4368	5.09997
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386.4	388.8	45.01	43.42	-0.1802
0.1	10	407.1	399.8	36.41	45.5	0.5054
0.5	10	437.1	443.7	69.39	54.22	-0.3865
5	9	936	931.5	193.2	188.7	0.07162

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.1821	5	406.3643
A2	-181.1755	8	378.351
A3	-182.4264	6	376.8527
R	-233.6952	2	471.3904
4	-182.4784	5	374.9568

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105	6	<0.0001
Test 2	34.01	3	<0.0001
Test 3	2.502	2	0.2863
Test 6a	0.1041	1	0.747

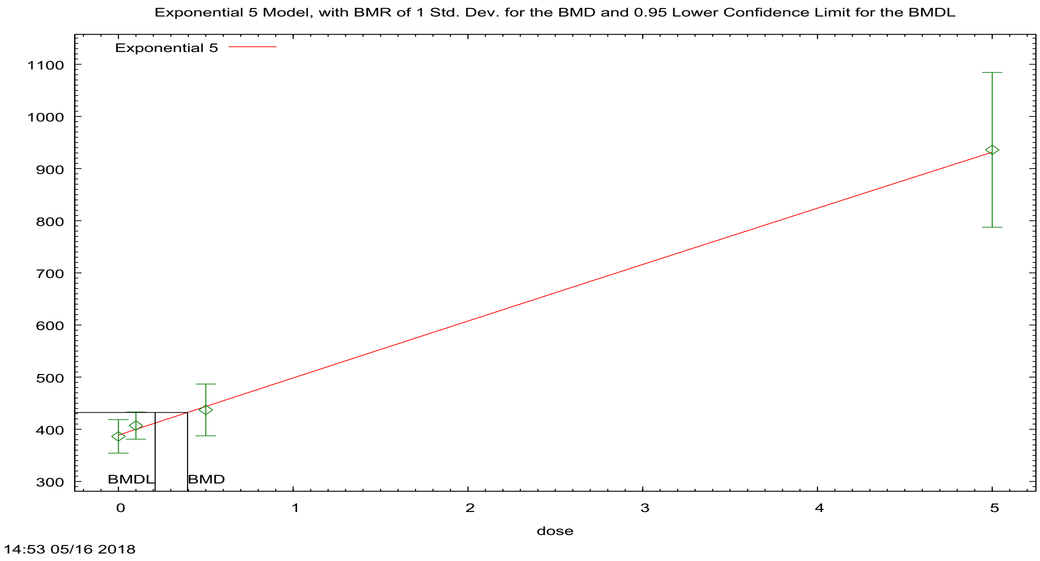

Figure 128. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.395425

BMDL at the 95% confidence level = 0.210227

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-12.5182	-12.7752
rho	3.36397	3.41177
a	388.84	367.048
b	0.00509556	0.0950512

c	56.4734	5.09997
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386.4	388.8	45.01	43.42	-0.1802
0.1	10	407.1	399.8	36.41	45.5	0.5054
0.5	10	437.1	443.7	69.39	54.22	-0.3865
5	9	936	931.5	193.2	188.7	0.07161

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.1821	5	406.3643
A2	-181.1755	8	378.351
A3	-182.4264	6	376.8527
R	-233.6952	2	471.3904
5	-182.4784	5	374.9568

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105	6	<0.0001
Test 2	34.01	3	<0.0001
Test 3	2.502	2	0.2863
Test 7a	0.1041	1	0.747

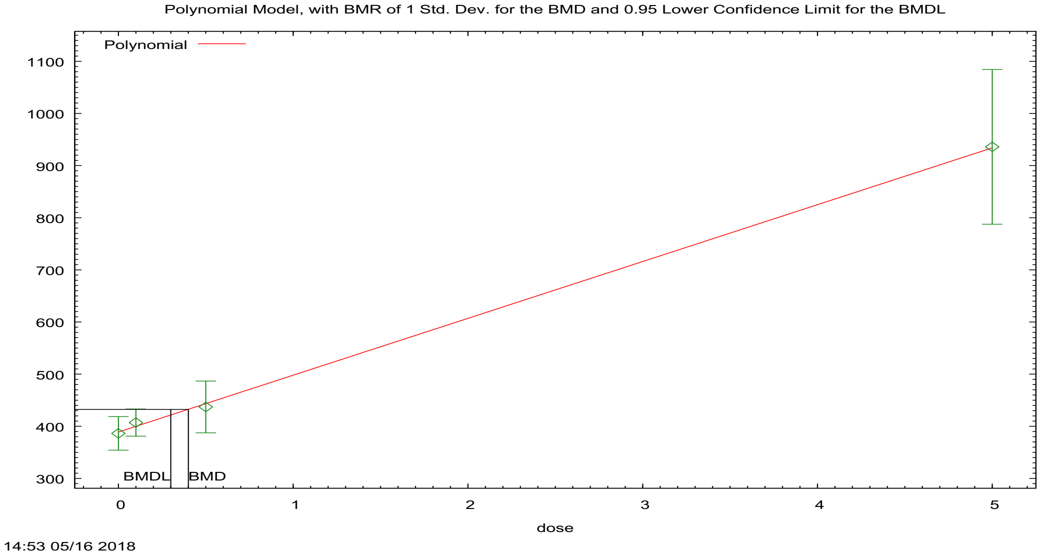

Figure 129. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.400252

BMDL at the 95% confidence level = 0.299666

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-12.4949	9.2714
rho	3.3602	0
beta_0	389.017	386.366
beta_1	108.602	236.541

beta_2	0	0
beta_3	2.57962E-84	54.4047

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386	389	45	43.5	-0.193
0.1	10	407	400	36.4	45.5	0.502
0.5	10	437	443	69.4	54.1	-0.363
5	9	936	932	193	189	0.0626

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.182127	5	406.364254
A2	-181.17551	8	378.351021
A3	-182.426362	6	376.852725
fitted	-182.47882	4	372.957641
R	-233.69519	2	471.39038

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.039	6	<0.0001
Test 2	34.0132	3	<0.0001
Test 3	2.5017	2	0.2863
Test 4	0.104916	2	0.9489

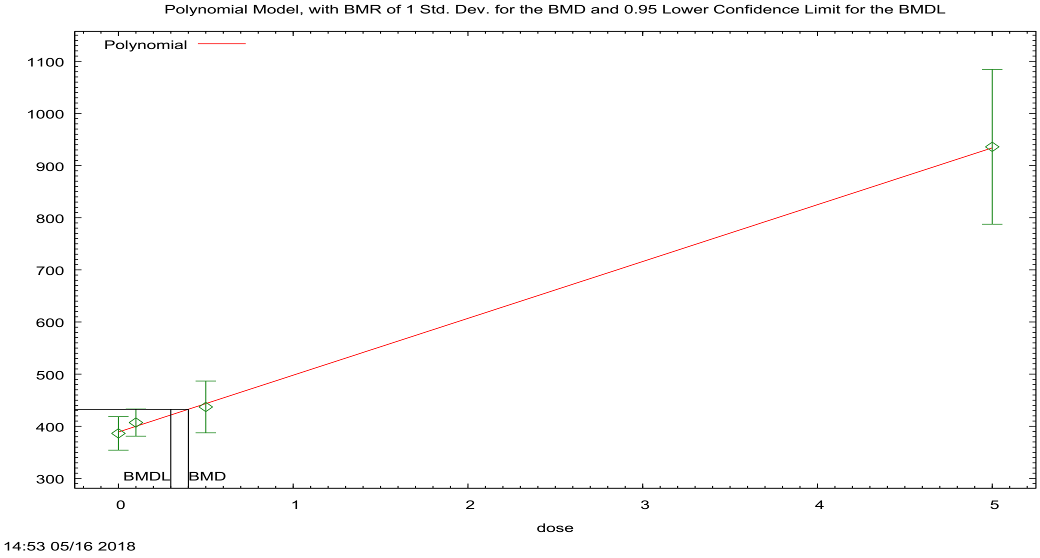

Figure 130. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.400252

BMDL at the 95% confidence level = 0.299666

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-12.4949	9.2714
rho	3.3602	0
beta_0	389.017	391.396
beta_1	108.602	92.5683

beta_2	0	3.26869

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386	389	45	43.5	-0.193
0.1	10	407	400	36.4	45.5	0.502
0.5	10	437	443	69.4	54.1	-0.363
5	9	936	932	193	189	0.0626

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.182127	5	406.364254
A2	-181.17551	8	378.351021
A3	-182.426362	6	376.852725
fitted	-182.47882	4	372.957641
R	-233.69519	2	471.39038

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.039	6	<0.0001
Test 2	34.0132	3	<0.0001
Test 3	2.5017	2	0.2863
Test 4	0.104916	2	0.9489

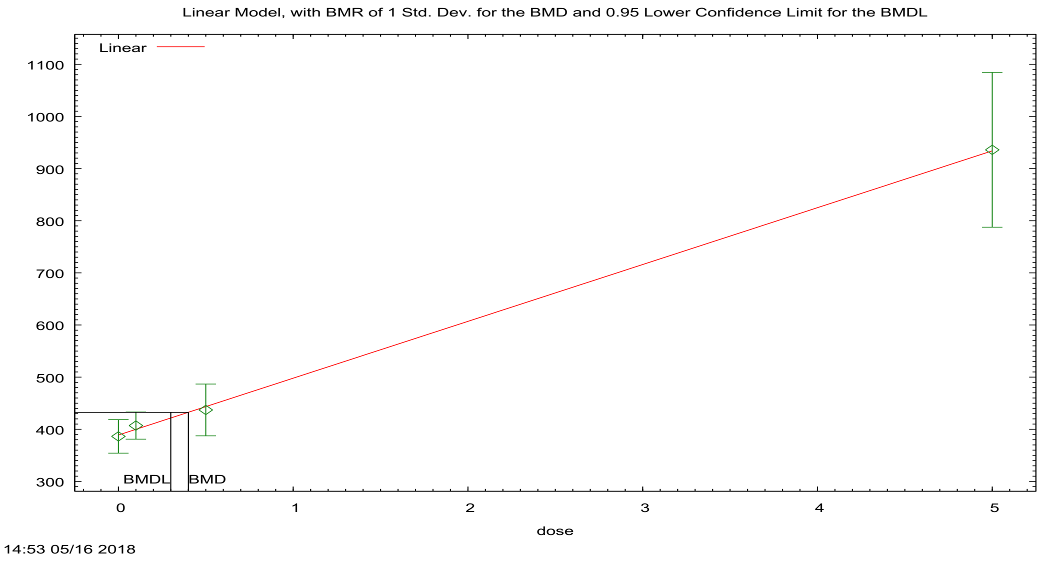

Figure 131. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.400252

BMDL at the 95% confidence level = 0.299666

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-12.4949	9.2714
rho	3.3602	0
beta_0	389.017	388.458
beta_1	108.602	109.411

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386	389	45	43.5	-0.193
0.1	10	407	400	36.4	45.5	0.502
0.5	10	437	443	69.4	54.1	-0.363
5	9	936	932	193	189	0.0626

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.182127	5	406.364254
A2	-181.17551	8	378.351021
A3	-182.426362	6	376.852725
fitted	-182.47882	4	372.957641
R	-233.69519	2	471.39038

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.039	6	<0.0001
Test 2	34.0132	3	<0.0001
Test 3	2.5017	2	0.2863
Test 4	0.104916	2	0.9489

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Liver Weight to Brain Weight (%) in Females

1.28. BMDS Summary of Liver Weight to Brain Weight in Females (90-Day Mice)

Table 28. Summary of BMD Modeling Results for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	**0.520**	**368.12**	**1.34**	**0.929**	**1.44**	**Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.**
Exponential (M3)	0.268	370.04	1.59	0.933	1.70	
Exponential (M4)	0.227	370.28	1.10	0.449	2.45	
Power	0.275	370.01	1.47	0.714	2.05	
Polynomial 3°[b] Polynomial 2°	0.261	370.08	1.57	0.709	2.21	
Linear	0.483	368.27	1.10	0.699	1.57	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were 0.05, -0.08, 0.03, 0, respectively.

[b] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model.

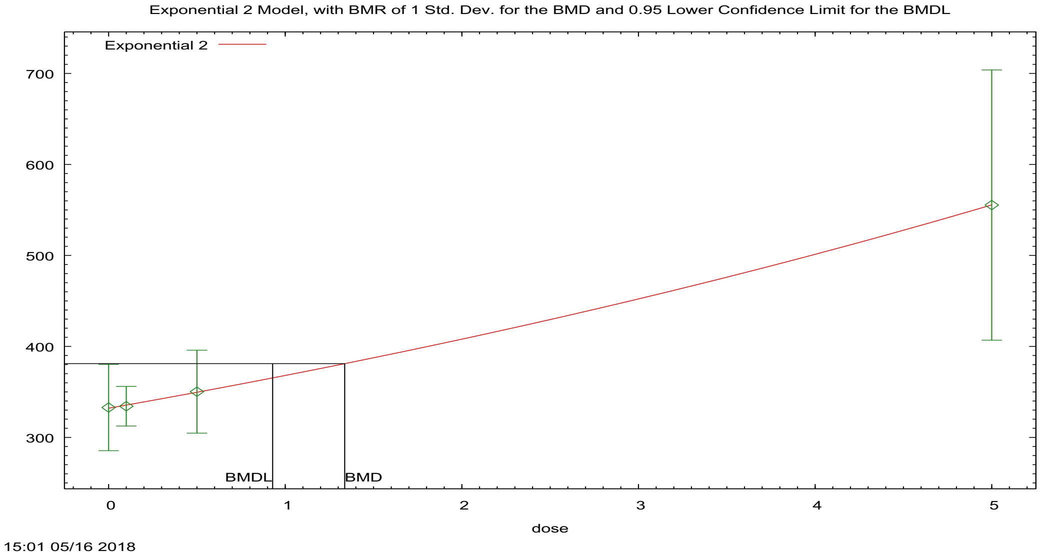

Figure 132. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.33655

BMDL at the 95% confidence level = 0.928594

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-21.701	-24.6464
rho	5.07868	5.5678
a	332.061	332.075
b	0.102919	0.102859
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	332.8	332.1	66.34	48.97	0.04942
0.1	10	334.2	335.5	30.44	50.26	-0.07851
0.5	9	350.2	349.6	59.32	55.8	0.03335
5	9	555.3	555.5	193.2	180.9	-0.003207

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.7363	5	397.4727
A2	-177.1145	8	370.229
A3	-179.4087	6	370.8173
R	-205.5727	2	415.1453
2	-180.062	4	368.124

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.92	6	<0.0001
Test 2	33.24	3	<0.0001
Test 3	4.588	2	0.1008
Test 4	1.307	2	0.5203

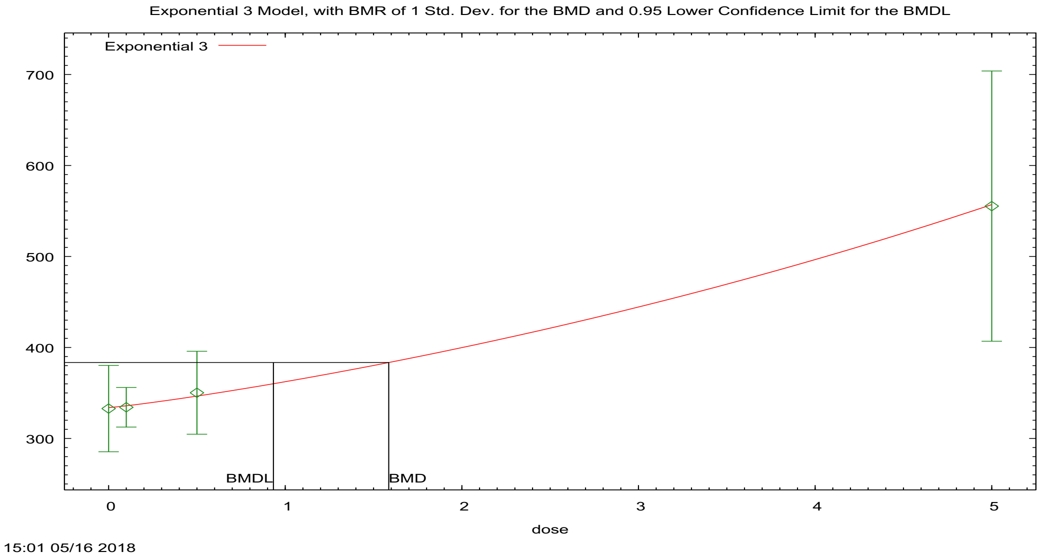

Figure 133. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.58582

BMDL at the 95% confidence level = 0.933248

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-21.7049	-24.6464
rho	5.07872	5.5678
a	333.889	332.075
b	0.111062	0.102859
c	n/a	0
d	1.13876	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	332.8	333.9	66.34	49.57	-0.06782
0.1	10	334.2	335.9	30.44	50.32	-0.1026
0.5	9	350.2	346.5	59.32	54.47	0.2026
5	9	555.3	557	193.2	181.8	-0.02782

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.7363	5	397.4727
A2	-177.1145	8	370.229
A3	-179.4087	6	370.8173
R	-205.5727	2	415.1453
3	-180.0222	5	370.0445

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.92	6	<0.0001
Test 2	33.24	3	<0.0001
Test 3	4.588	2	0.1008

Test 5a	1.227	1	0.268

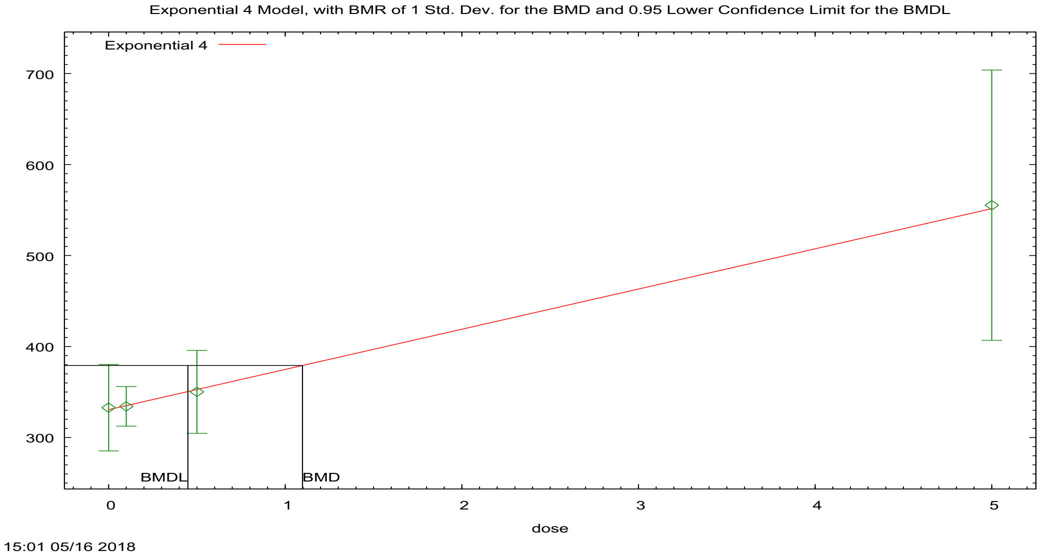

Figure 134. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.09769

BMDL at the 95% confidence level = 0.448825

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-21.9721	-24.6464
rho	5.1258	5.5678

a	330.674	316.185
b	0.0000741586	0.0718443
c	1803.04	3.51269
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	332.8	330.7	66.34	48.51	0.1403
0.1	10	334.2	335.1	30.44	50.18	-0.05327
0.5	9	350.2	352.8	59.32	57.25	-0.1338
5	9	555.3	551.6	193.2	180	0.06242

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.7363	5	397.4727
A2	-177.1145	8	370.229
A3	-179.4087	6	370.8173
R	-205.5727	2	415.1453
4	-180.1376	5	370.2751

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.92	6	<0.0001
Test 2	33.24	3	<0.0001
Test 3	4.588	2	0.1008
Test 6a	1.458	1	0.2273

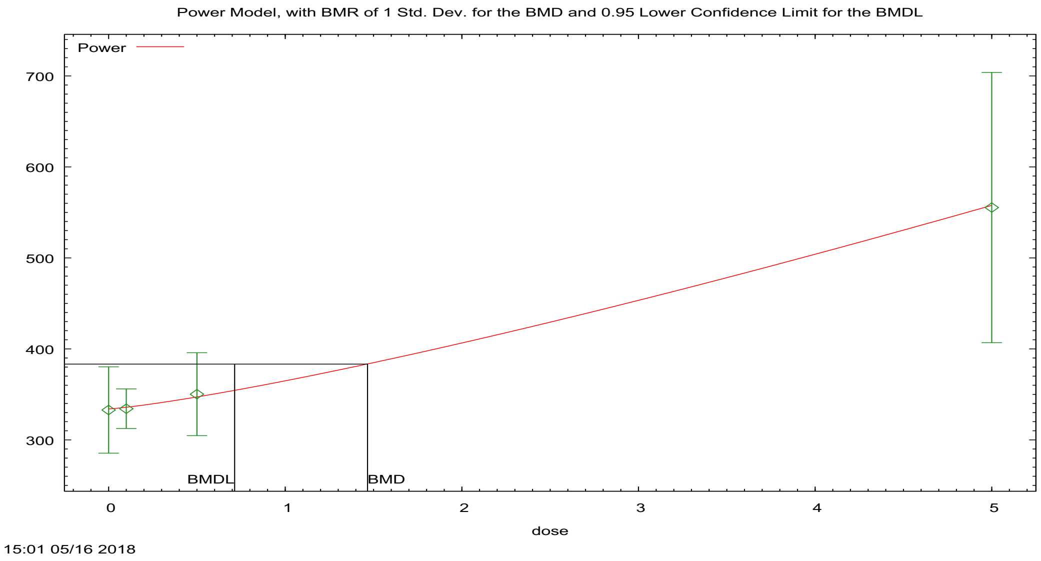

Figure 135. Plot of mean response by dose with fitted curve for Power model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.46578

BMDL at the 95% confidence level = 0.713574

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-21.717	9.30788
rho	5.08057	0
control	333.778	332.826
slope	30.9436	28.4057

power	1.22806	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	333	334	66.3	49.5	-0.0608
0.1	10	334	336	30.4	50.2	-0.0857
0.5	9	350	347	59.3	54.6	0.177
5	9	555	557	193	182	-0.0293

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.736349	5	397.472698
A2	-177.114505	8	370.229011
A3	-179.408666	6	370.817331
fitted	-180.005253	5	370.010505
R	-205.572651	2	415.145302

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.9163	6	<0.0001
Test 2	33.2437	3	<0.0001
Test 3	4.58832	2	0.1008
Test 4	1.19317	1	0.2747

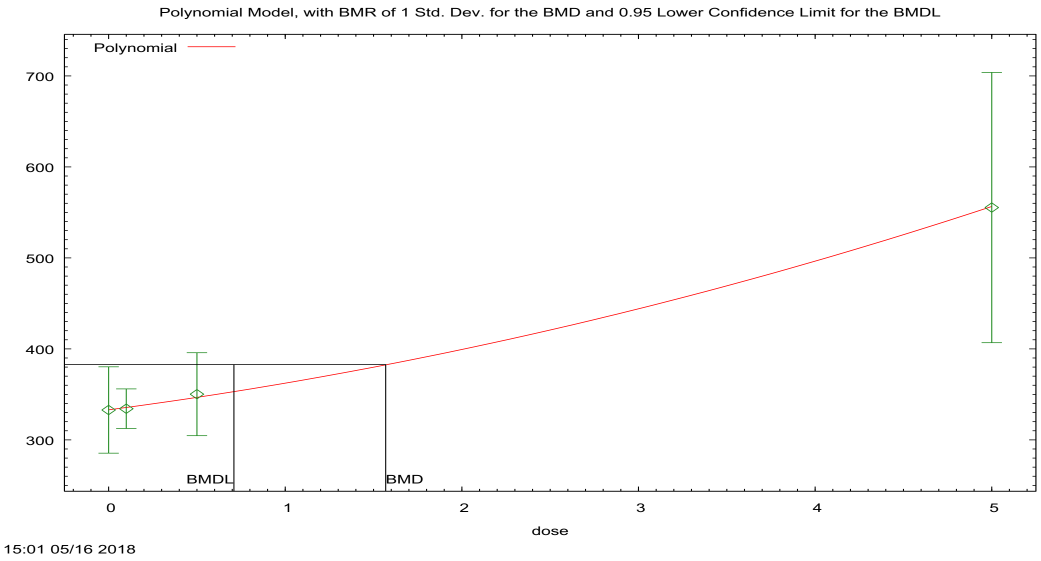

Figure 136. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.56853

BMDL at the 95% confidence level = 0.709326

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-21.6616	9.30788
rho	5.07164	0
beta_0	333.382	332.826
beta_1	25.4879	8.57755

beta_2	3.84048	57.4294
beta_3	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	333	333	66.3	49.4	-0.0356
0.1	10	334	336	30.4	50.4	-0.108
0.5	9	350	347	59.3	54.7	0.172
5	9	555	557	193	182	-0.0248

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.736349	5	397.472698
A2	-177.114505	8	370.229011
A3	-179.408666	6	370.817331
fitted	-180.041834	5	370.083668
R	-205.572651	2	415.145302

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.9163	6	<0.0001
Test 2	33.2437	3	<0.0001
Test 3	4.58832	2	0.1008
Test 4	1.26634	1	0.2605

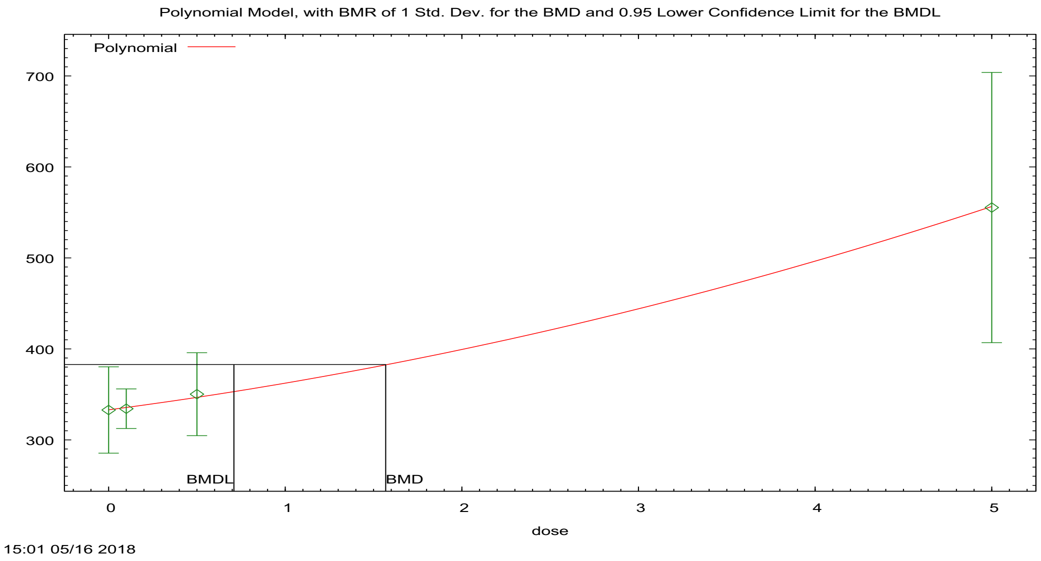

Figure 137. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.56853

BMDL at the 95% confidence level = 0.709326

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-21.6616	9.30788
rho	5.07164	0
beta_0	333.382	331.897
beta_1	25.4879	35.1703

beta_2	3.84048	1.90335

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	333	333	66.3	49.4	-0.0356
0.1	10	334	336	30.4	50.4	-0.108
0.5	9	350	347	59.3	54.7	0.172
5	9	555	557	193	182	-0.0248

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.736349	5	397.472698
A2	-177.114505	8	370.229011
A3	-179.408666	6	370.817331
fitted	-180.041834	5	370.083668
R	-205.572651	2	415.145302

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.9163	6	<0.0001
Test 2	33.2437	3	<0.0001
Test 3	4.58832	2	0.1008
Test 4	1.26634	1	0.2605

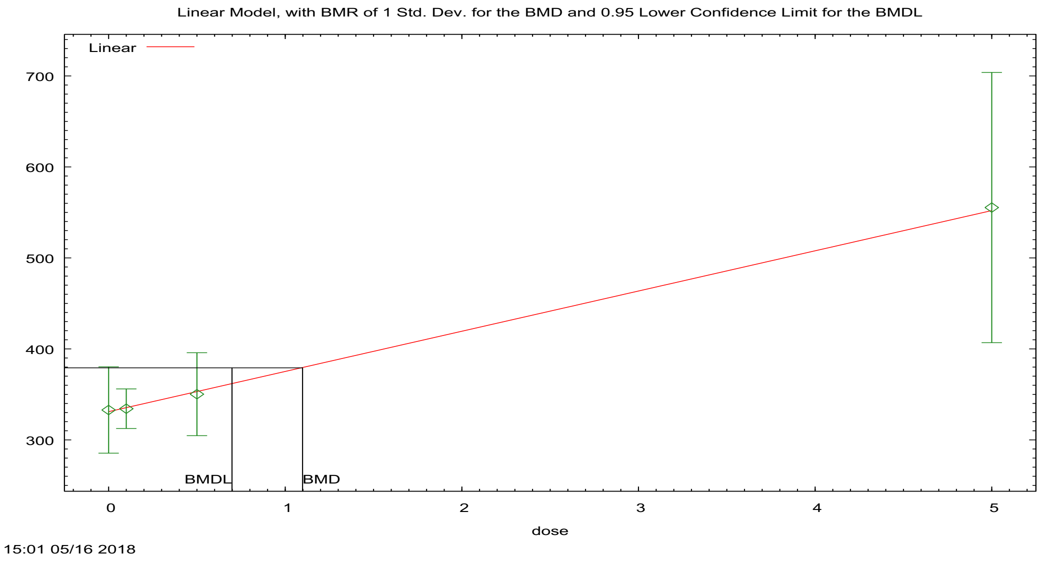

Figure 138. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.09783

BMDL at the 95% confidence level = 0.698635

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-21.9718	9.30788
rho	5.12574	0
beta_0	330.675	330.186
beta_1	44.1828	44.9779

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	333	331	66.3	48.5	0.14
0.1	10	334	335	30.4	50.2	-0.0533
0.5	9	350	353	59.3	57.2	-0.134
5	9	555	552	193	180	0.0623

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.736349	5	397.472698
A2	-177.114505	8	370.229011
A3	-179.408666	6	370.817331
fitted	-180.137486	4	368.274971
R	-205.572651	2	415.145302

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.9163	6	<0.0001
Test 2	33.2437	3	<0.0001
Test 3	4.58832	2	0.1008
Test 4	1.45764	2	0.4825

BMDS WIZARD OUTPUT REPORT

BMDS Summary of Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice – Liver Weight to Brain Weight (g/100g brain) in Males

1.29. BMDS Summary of Liver Weight to Brain Weight in Males (Reproductive Mice)

Table 29. Summary of BMD Modeling Results for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean

Model[a]	**Goodness of fit**		**BMD_{1SD} (mg/kg/day)**	**$BMDL_{1SD}$ (mg/kg/day)**	**BMD/BMDL**	**Basis for model selection**
	***p*-value**	**AIC**				
Exponential (M4) Exponential (M5)[b]	**0.570**	**927.48**	**0.232**	**0.165**	**1.40**	**Only one model met inclusion criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)).**

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.15, 0.27, -0.13, 0.02, respectively.

[b] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

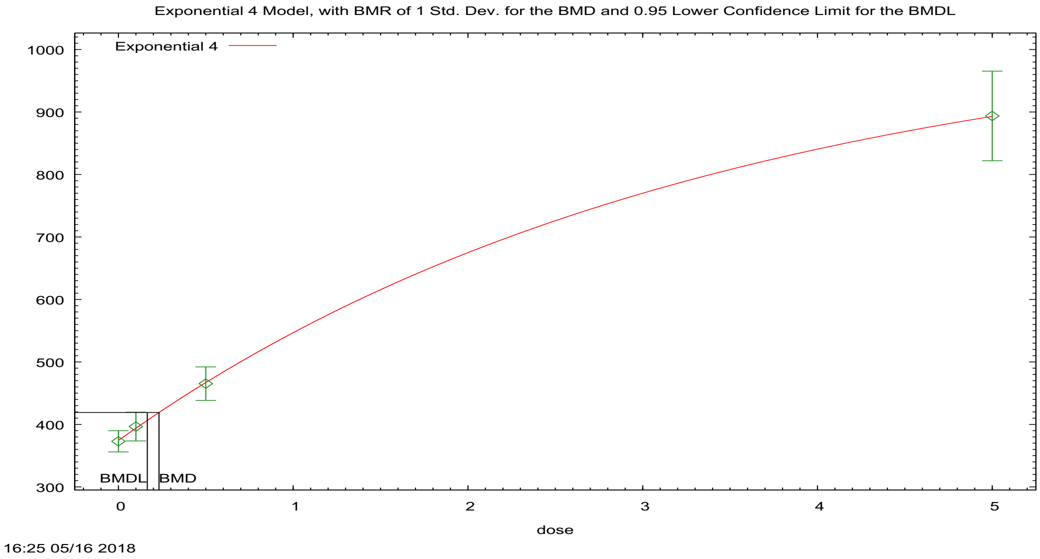

Figure 139. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.23223

BMDL at the 95% confidence level = 0.16532

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-10.3467	-10.4607
rho	3.02939	3.05296
a	374.308	354.287
b	0.297892	0.513265
c	2.78911	2.64868
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	372.9	374.3	41.08	44.76	-0.1535
0.1	24	396.6	394	54.49	48.37	0.2689
0.5	24	465.3	467	63.57	62.58	-0.1333
5	24	893.7	893	169.8	167.1	0.02143

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.6261	5	989.2522
A2	-458.1745	8	932.349
A3	-458.5804	6	929.1608
R	-576.4866	2	1156.973

4	-458.7417	5	927.4834

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.6	6	<0.0001
Test 2	62.9	3	<0.0001
Test 3	0.8118	2	0.6664
Test 6a	0.3226	1	0.5701

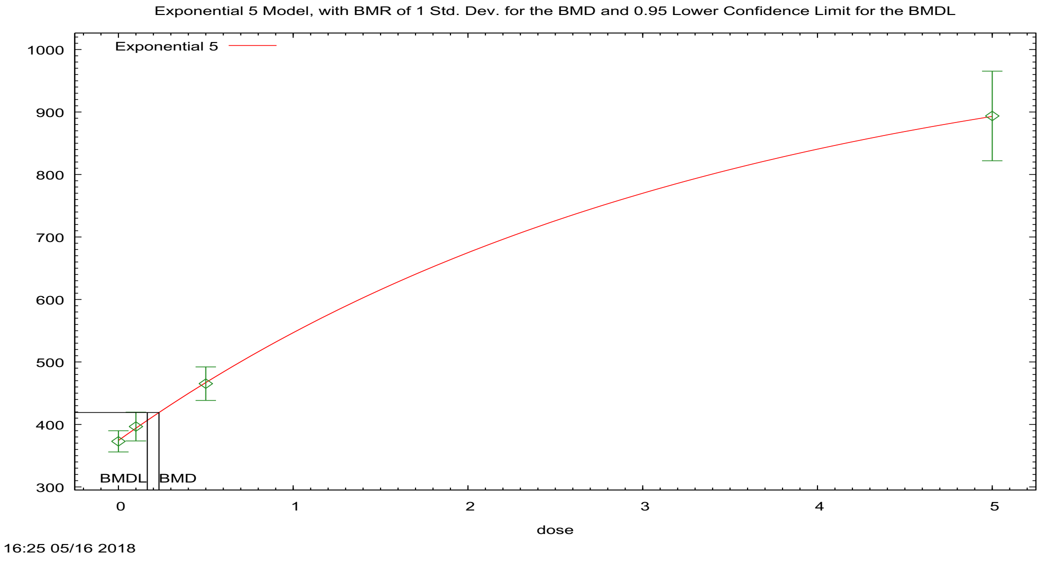

Figure 140. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.23223

BMDL at the 95% confidence level = 0.16532

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-10.3467	-10.4607
rho	3.02939	3.05296
a	374.308	354.287
b	0.297893	0.513265
c	2.78911	2.64868
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	372.9	374.3	41.08	44.76	-0.1535
0.1	24	396.6	394	54.49	48.37	0.2689
0.5	24	465.3	467	63.57	62.58	-0.1333
5	24	893.7	893	169.8	167.1	0.02143

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.6261	5	989.2522
A2	-458.1745	8	932.349
A3	-458.5804	6	929.1608
R	-576.4866	2	1156.973
5	-458.7417	5	927.4834

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.6	6	<0.0001
Test 2	62.9	3	<0.0001

Test 3	0.8118	2	0.6664
Test 7a	0.3226	1	0.5701

BMDS WIZARD OUTPUT REPORT

BMDS Summary of Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice – Offspring Weight (g) at Postnatal Day 21 in Males

1.30. BMDS Summary of Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice)

Table 30. Summary of BMD Modeling Results for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.268	152.90	2.12	1.66	1.27	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.416	152.92	4.52	1.86	2.43	
Exponential (M4)	0.268	152.90	2.12	1.25	1.70	
Power	0.416	152.92	4.57	1.99	2.30	
Polynomial 3°	**0.715**	**150.93**	**3.87**	**3.06**	**1.26**	
Polynomial 2°	0.681	151.03	3.40	3.06	1.11	
Linear	0.312	152.59	2.28	1.84	1.24	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.233), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.64, 0.16, 0.48, 0, respectively.

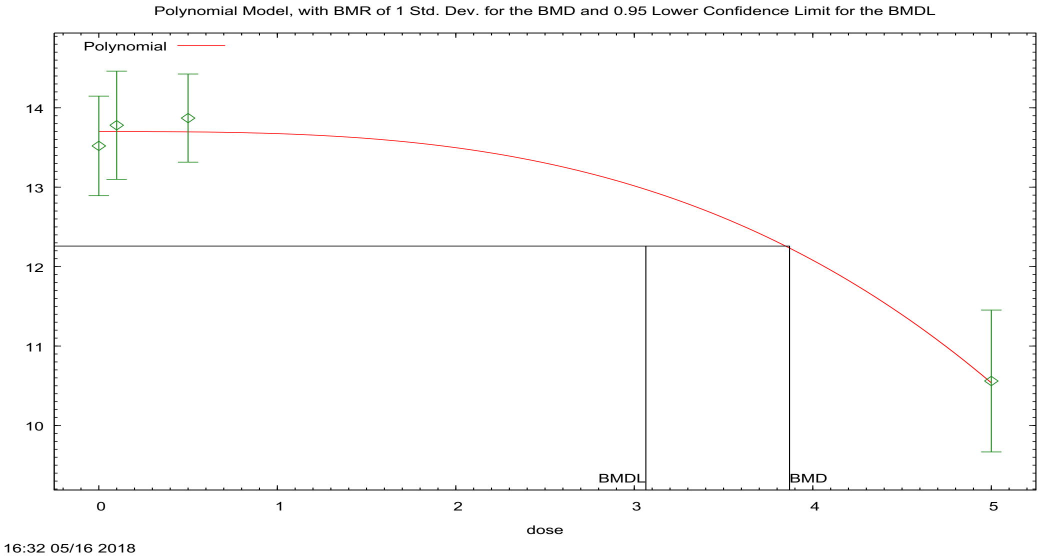

Figure 141. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.86966

BMDL at the 95% confidence level = 3.06466

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.15434	2.24633
rho	n/a	0
beta_0	13.7264	13.52
beta_1	-7.86983E-23	0
beta_2	0	-5.29648
beta_3	-0.0253302	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.5	13.7	1.38	1.47	-0.645
0.1	18	13.8	13.7	1.37	1.47	0.155
0.5	23	13.9	13.7	1.28	1.47	0.479
5	20	10.6	10.6	1.91	1.47	-0.000515

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.130858	5	154.261716
A2	-69.989194	8	155.978389
A3	-72.130858	5	154.261716
fitted	-72.46686	3	150.933721

R	-97.85625	2	199.712499

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.7341	6	<0.0001
Test 2	4.28333	3	0.2325
Test 3	4.28333	3	0.2325
Test 4	0.672005	2	0.7146

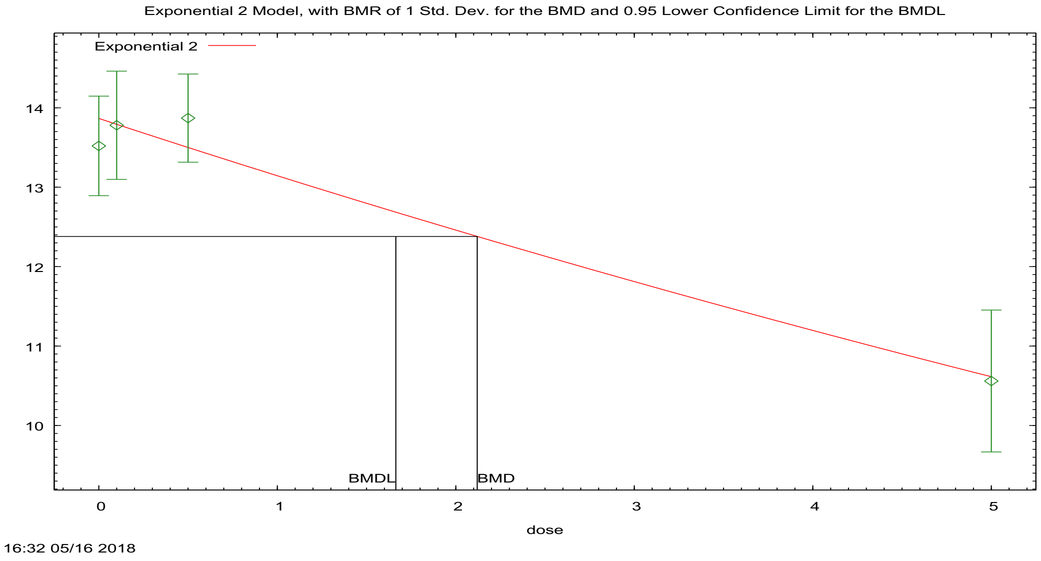

Figure 142. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.12008

BMDL at the 95% confidence level = 1.66414

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.791404	0.759289
rho	n/a	0
a	13.8655	11.9502
b	0.0534487	0.0539212
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.52	13.87	1.38	1.48	-1.066
0.1	18	13.78	13.79	1.37	1.48	-0.03315
0.5	23	13.87	13.5	1.28	1.48	1.195
5	20	10.56	10.61	1.91	1.48	-0.1622

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.13086	5	154.2617
A2	-69.98919	8	155.9784
A3	-72.13086	5	154.2617
R	-97.85625	2	199.7125
2	-73.44756	3	152.8951

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.73	6	<0.0001
Test 2	4.283	3	0.2325

Test 3	4.283	3	0.2325
Test 4	2.633	2	0.268

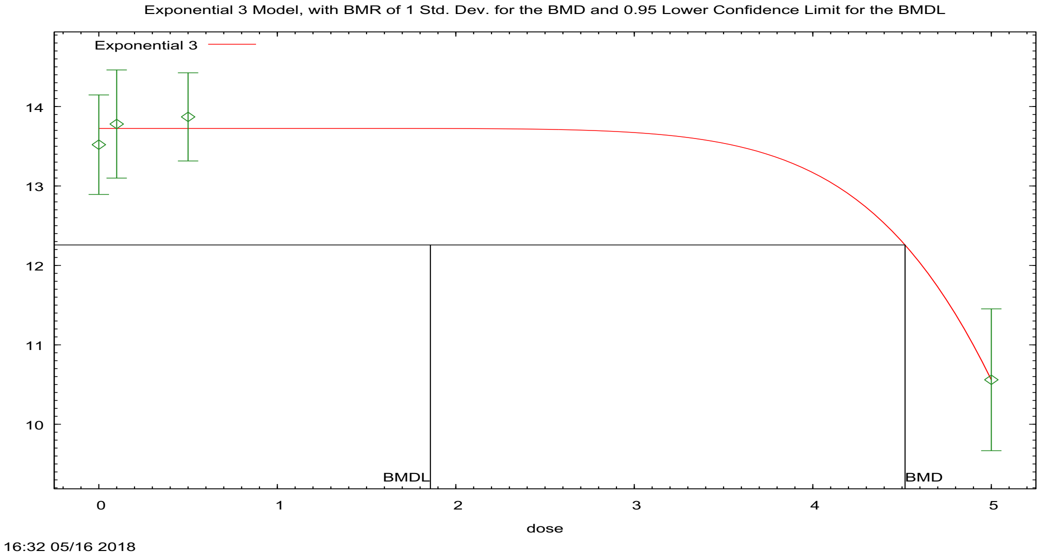

Figure 143. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.51681

BMDL at the 95% confidence level = 1.85773

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values

lnalpha	0.767364	0.759289
rho	n/a	0
a	13.7253	11.9502
b	0.170118	0.0539212
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.52	13.73	1.38	1.47	-0.6411
0.1	18	13.78	13.73	1.37	1.47	0.1581
0.5	23	13.87	13.73	1.28	1.47	0.4728
5	20	10.56	10.56	1.91	1.47	-0.000000008943

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.13086	5	154.2617
A2	-69.98919	8	155.9784
A3	-72.13086	5	154.2617
R	-97.85625	2	199.7125
3	-72.46192	4	152.9238

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.73	6	<0.0001
Test 2	4.283	3	0.2325
Test 3	4.283	3	0.2325
Test 5a	0.6621	1	0.4158

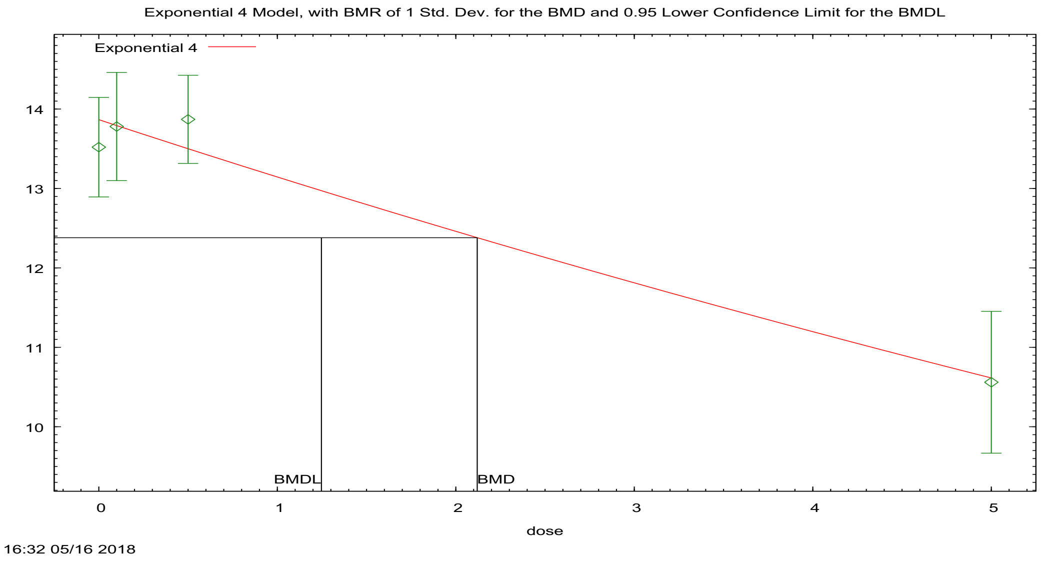

Figure 144. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.12008

BMDL at the 95% confidence level = 1.24698

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.791404	0.759289
rho	n/a	0
a	13.8655	14.5635

b	0.0534487	0.438137
c	0	0.690572
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.52	13.87	1.38	1.48	-1.066
0.1	18	13.78	13.79	1.37	1.48	-0.03315
0.5	23	13.87	13.5	1.28	1.48	1.195
5	20	10.56	10.61	1.91	1.48	-0.1622

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.13086	5	154.2617
A2	-69.98919	8	155.9784
A3	-72.13086	5	154.2617
R	-97.85625	2	199.7125
4	-73.44756	3	152.8951

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.73	6	<0.0001
Test 2	4.283	3	0.2325
Test 3	4.283	3	0.2325
Test 6a	2.633	2	0.268

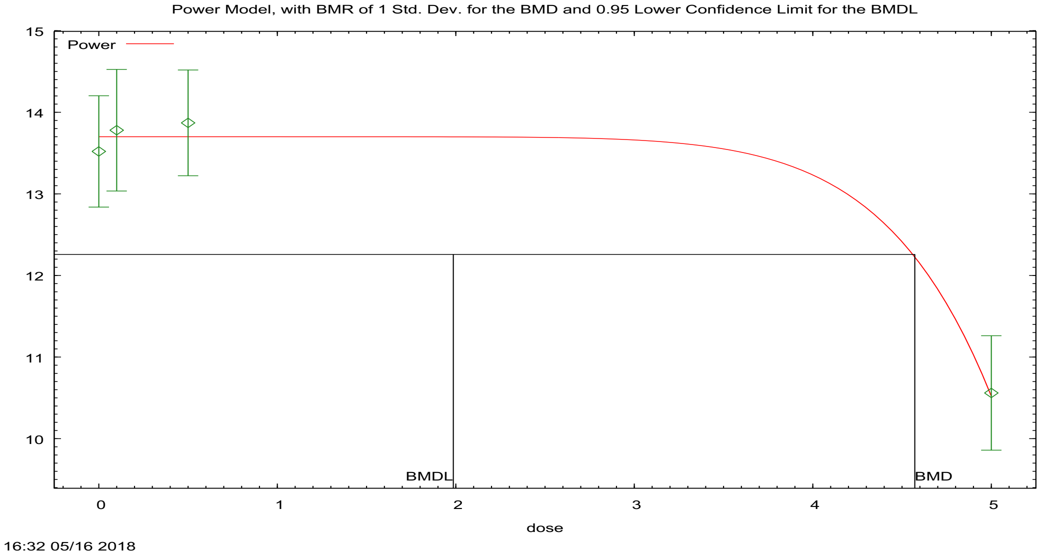

Figure 145. Plot of mean response by dose with fitted curve for Power model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.57146

BMDL at the 95% confidence level = 1.98598

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.15408	2.24633
rho	n/a	0

control	13.7253	10.56
slope	-0.00000319984	3.34953
power	8.57732	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.5	13.7	1.38	1.47	-0.641
0.1	18	13.8	13.7	1.37	1.47	0.158
0.5	23	13.9	13.7	1.28	1.47	0.473
5	20	10.6	10.6	1.91	1.47	0.0000000353

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.130858	5	154.261716
A2	-69.989194	8	155.978389
A3	-72.130858	5	154.261716
fitted	-72.461924	4	152.923849
R	-97.85625	2	199.712499

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.7341	6	<0.0001
Test 2	4.28333	3	0.2325
Test 3	4.28333	3	0.2325
Test 4	0.662132	1	0.4158

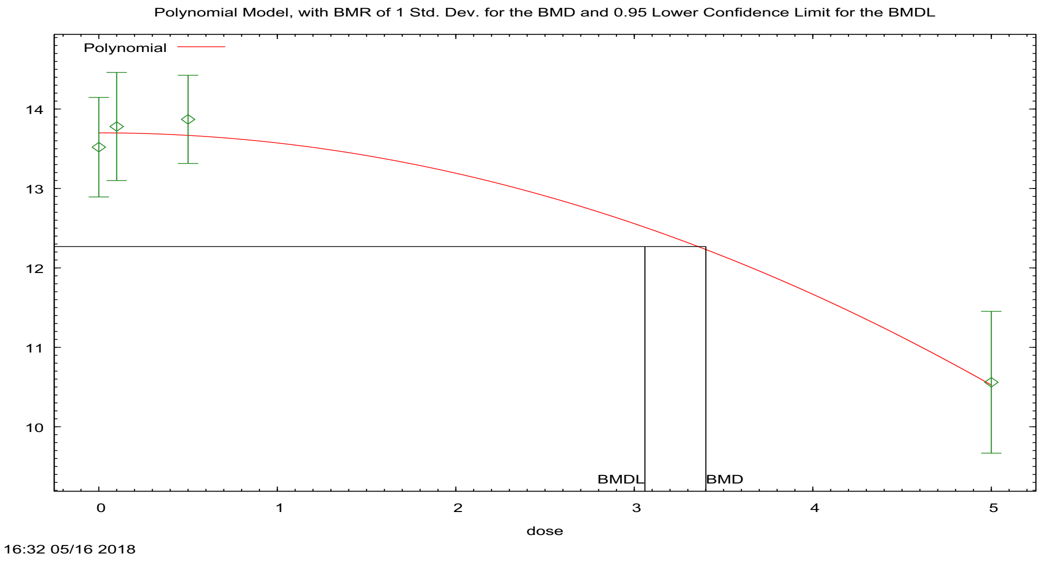

Figure 146. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.40062

BMDL at the 95% confidence level = 3.05942

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.15686	2.24633
rho	n/a	0
beta_0	13.7369	13.6042

beta_1	-2.69168E-23	0
beta_2	-0.126998	-0.263833

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.5	13.7	1.38	1.47	-0.677
0.1	18	13.8	13.7	1.37	1.47	0.128
0.5	23	13.9	13.7	1.28	1.47	0.538
5	20	10.6	10.6	1.91	1.47	-0.00582

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.130858	5	154.261716
A2	-69.989194	8	155.978389
A3	-72.130858	5	154.261716
fitted	-72.514804	3	151.029608
R	-97.85625	2	199.712499

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.7341	6	<0.0001
Test 2	4.28333	3	0.2325
Test 3	4.28333	3	0.2325
Test 4	0.767891	2	0.6812

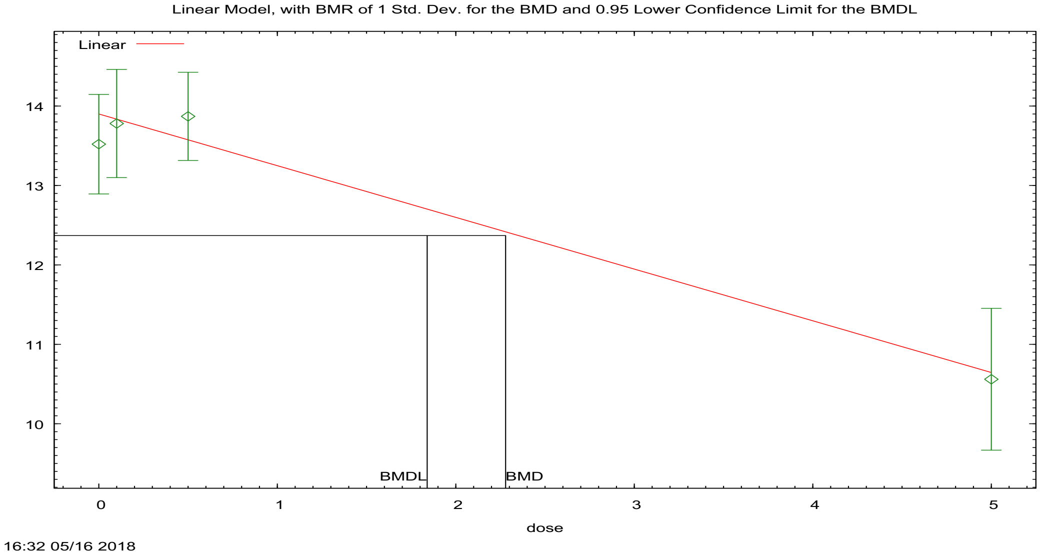

Figure 147. Plot of mean response by dose with fitted curve for Linear model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.27908

BMDL at the 95% confidence level = 1.83952

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.19842	2.24633
rho	n/a	0
beta_0	13.8522	13.8414

beta_1	-0.650574	-0.649196

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.5	13.9	1.38	1.48	-1.03
0.1	18	13.8	13.8	1.37	1.48	-0.0204
0.5	23	13.9	13.5	1.28	1.48	1.11
5	20	10.6	10.6	1.91	1.48	-0.119

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.130858	5	154.261716
A2	-69.989194	8	155.978389
A3	-72.130858	5	154.261716
fitted	-73.297359	3	152.594717
R	-97.85625	2	199.712499

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.7341	6	<0.0001
Test 2	4.28333	3	0.2325
Test 3	4.28333	3	0.2325
Test 4	2.333	2	0.3115

BMDS WIZARD OUTPUT REPORT

BMDS Summary of Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice – Offspring Weight (g) at Postnatal Day 21 in Females

1.31. BMDS Summary of Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice)

Table 31. Summary of BMD Modeling Results for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.169	123.03	2.33	1.80	1.29	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.270	122.69	4.56	2.10	2.17	
Exponential (M4)	0.169	123.03	2.33	1.41	1.65	
Power	0.270	122.69	4.67	2.18	2.14	
Polynomial 3°	**0.541**	**120.71**	**3.95**	**3.66**	**1.08**	
Polynomial 2°	0.503	120.85	3.51	2.15	1.63	
Linear	0.193	122.76	2.45	1.95	1.26	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.486), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.76, -0.09, 0.8, 0, respectively.

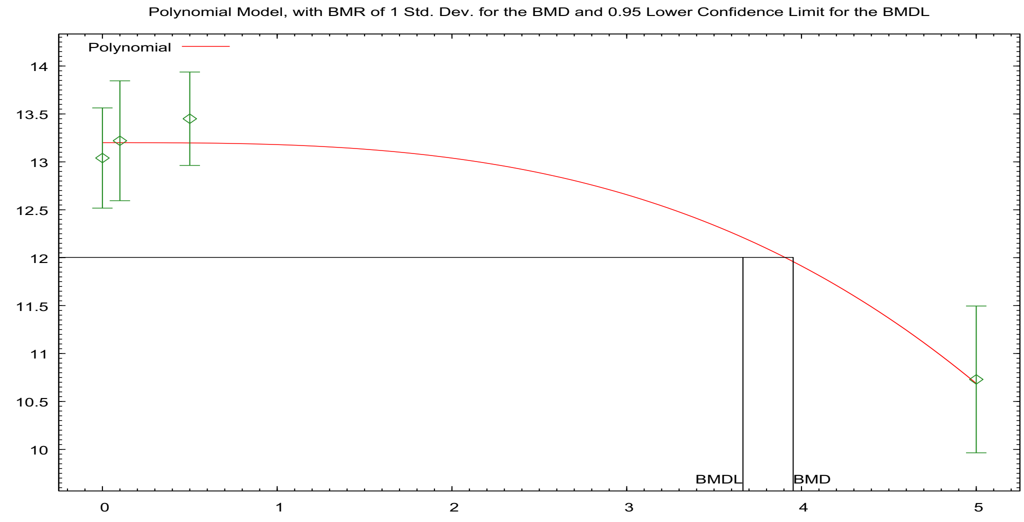

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Figure 148. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in

Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.9524

BMDL at the 95% confidence level = 3.66495

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	1.54315	1.59957
rho	n/a	0
beta_0	13.2452	13.04
beta_1	-2.55441E-24	0
beta_2	-2.52457E-26	-2.71512
beta_3	-0.0201196	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13	13.2	1.15	1.24	-0.757
0.1	18	13.2	13.2	1.26	1.24	-0.0861
0.5	23	13.4	13.2	1.13	1.24	0.8
5	18	10.7	10.7	1.54	1.24	-0.000904

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.737769	5	123.475538

A2	-55.517751	8	127.035503
A3	-56.737769	5	123.475538
fitted	-57.352978	3	120.705956
R	-78.910547	2	161.821093

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.7856	6	<0.0001
Test 2	2.44004	3	0.4862
Test 3	2.44004	3	0.4862
Test 4	1.23042	2	0.5405

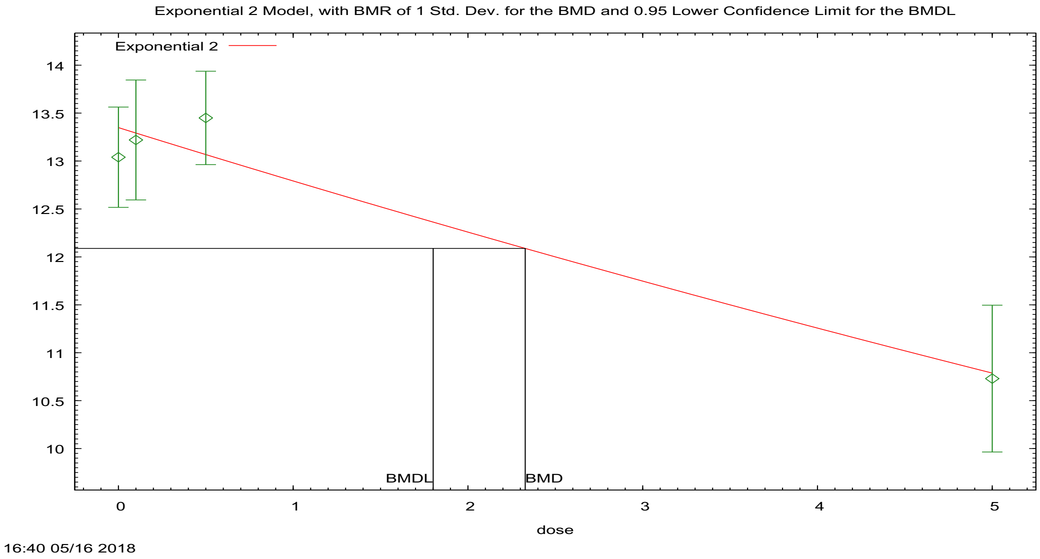


Figure 149. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.32766

BMDL at the 95% confidence level = 1.80118

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.462864	0.418444
rho	n/a	0
a	13.3488	11.9484
b	0.0426095	0.043013
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.04	13.35	1.15	1.26	-1.123
0.1	18	13.22	13.29	1.26	1.26	-0.2426
0.5	23	13.45	13.07	1.13	1.26	1.456
5	18	10.73	10.79	1.54	1.26	-0.1933

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.73777	5	123.4755
A2	-55.51775	8	127.0355
A3	-56.73777	5	123.4755
R	-78.91055	2	161.8211
2	-58.51457	3	123.0291

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.79	6	<0.0001
Test 2	2.44	3	0.4862
Test 3	2.44	3	0.4862
Test 4	3.554	2	0.1692

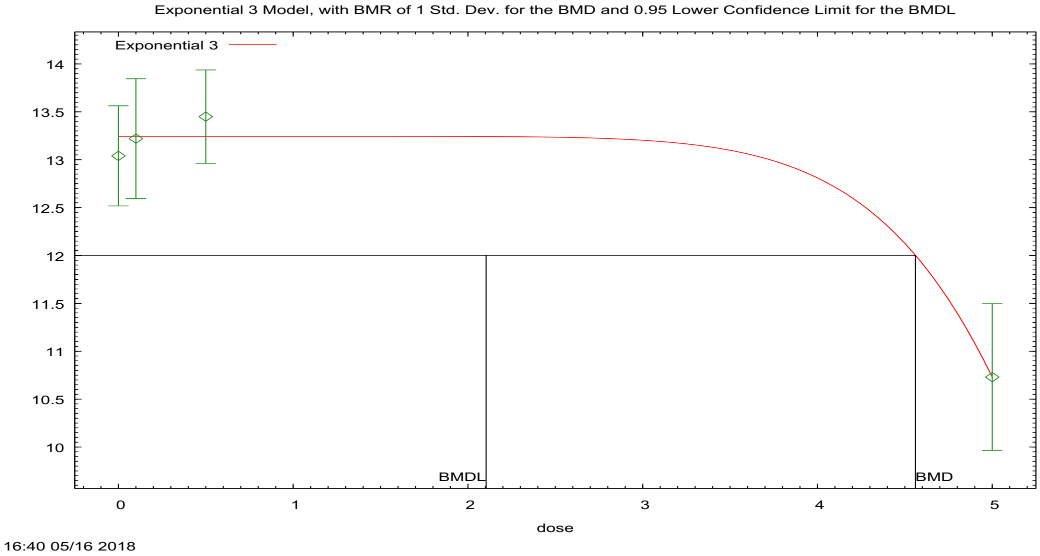


Figure 150. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.56068

BMDL at the 95% confidence level = 2.10402

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.433631	0.418444
rho	n/a	0
a	13.2444	11.9484
b	0.165623	0.043013
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.04	13.24	1.15	1.24	-0.7539
0.1	18	13.22	13.24	1.26	1.24	-0.08319
0.5	23	13.45	13.24	1.13	1.24	0.794
5	18	10.73	10.73	1.54	1.24	0.00001304

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.73777	5	123.4755
A2	-55.51775	8	127.0355
A3	-56.73777	5	123.4755
R	-78.91055	2	161.8211
3	-57.34524	4	122.6905

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.79	6	<0.0001
Test 2	2.44	3	0.4862
Test 3	2.44	3	0.4862
Test 5a	1.215	1	0.2704

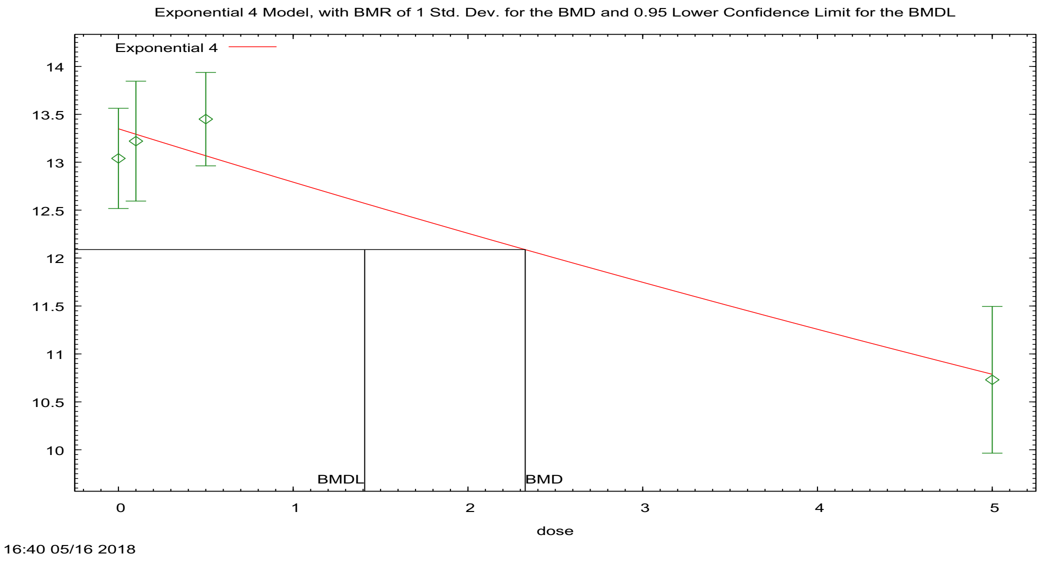


Figure 151. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.32766

BMDL at the 95% confidence level = 1.40916

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.462864	0.418444
rho	n/a	0
a	13.3488	14.1225

b	0.0426095	0.407266
c	0	0.7236
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.04	13.35	1.15	1.26	-1.123
0.1	18	13.22	13.29	1.26	1.26	-0.2426
0.5	23	13.45	13.07	1.13	1.26	1.456
5	18	10.73	10.79	1.54	1.26	-0.1933

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.73777	5	123.4755
A2	-55.51775	8	127.0355
A3	-56.73777	5	123.4755
R	-78.91055	2	161.8211
4	-58.51457	3	123.0291

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.79	6	<0.0001
Test 2	2.44	3	0.4862
Test 3	2.44	3	0.4862
Test 6a	3.554	2	0.1692

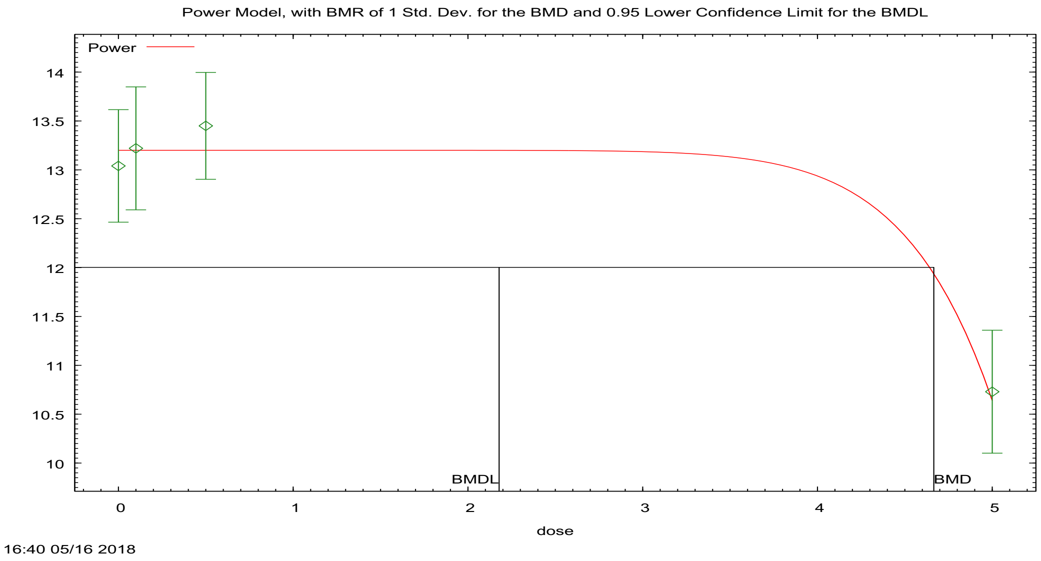


Figure 152. Plot of mean response by dose with fitted curve for Power model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.66568

BMDL at the 95% confidence level = 2.17825

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	1.54285	1.59957
rho	n/a	0
control	13.2444	10.73

slope	-0.000000189638	2.82549
power	10.19	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13	13.2	1.15	1.24	-0.754
0.1	18	13.2	13.2	1.26	1.24	-0.0832
0.5	23	13.4	13.2	1.13	1.24	0.794
5	18	10.7	10.7	1.54	1.24	-0.00000000209

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.737769	5	123.475538
A2	-55.517751	8	127.035503
A3	-56.737769	5	123.475538
fitted	-57.345245	4	122.690489
R	-78.910547	2	161.821093

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.7856	6	<0.0001
Test 2	2.44004	3	0.4862
Test 3	2.44004	3	0.4862
Test 4	1.21495	1	0.2704

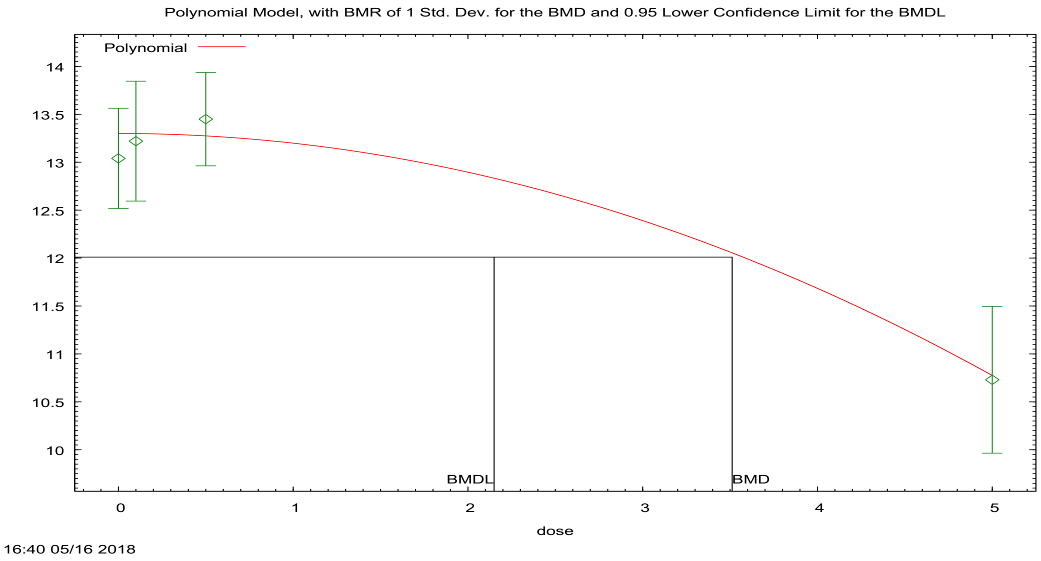


Figure 153. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.51186

BMDL at the 95% confidence level = 2.14962

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	1.54593	1.59957
rho	n/a	0
beta_0	13.2532	13.0809

beta_1	0	0
beta_2	-0.100814	-0.273596

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13	13.3	1.15	1.24	-0.786
0.1	18	13.2	13.3	1.26	1.24	-0.11
0.5	23	13.4	13.2	1.13	1.24	0.856
5	18	10.7	10.7	1.54	1.24	-0.00964

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.737769	5	123.475538
A2	-55.517751	8	127.035503
A3	-56.737769	5	123.475538
fitted	-57.425076	3	120.850152
R	-78.910547	2	161.821093

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.7856	6	<0.0001
Test 2	2.44004	3	0.4862
Test 3	2.44004	3	0.4862
Test 4	1.37461	2	0.5029

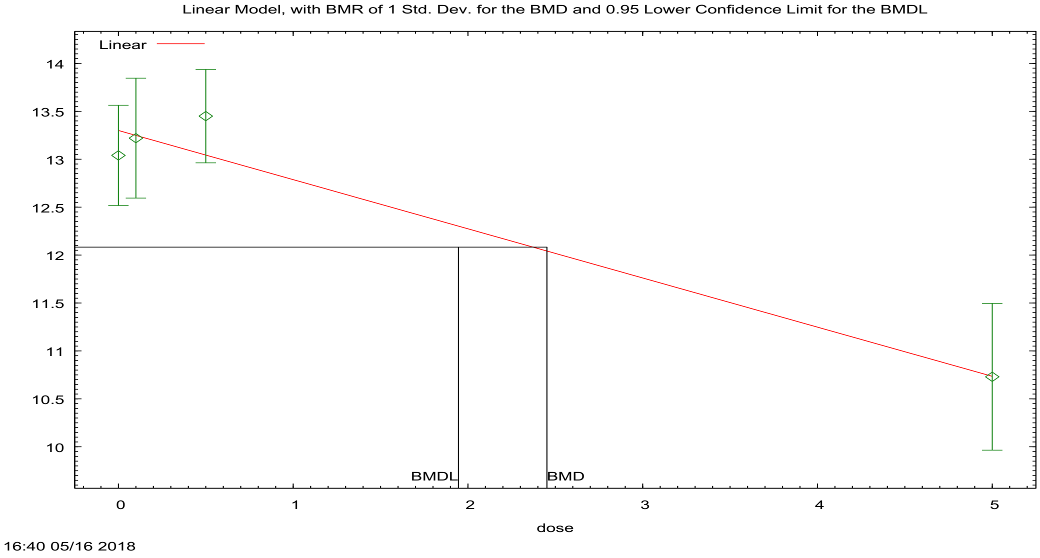


Figure 154. Plot of mean response by dose with fitted curve for Linear model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.45188

BMDL at the 95% confidence level = 1.94563

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	1.58335	1.59957
rho	n/a	0
beta_0	13.3413	13.3268

beta_1	-0.513204	-0.511998

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13	13.3	1.15	1.26	-1.1
0.1	18	13.2	13.3	1.26	1.26	-0.236
0.5	23	13.4	13.1	1.13	1.26	1.39
5	18	10.7	10.8	1.54	1.26	-0.153

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.737769	5	123.475538
A2	-55.517751	8	127.035503
A3	-56.737769	5	123.475538
fitted	-58.381829	3	122.763658
R	-78.910547	2	161.821093

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.7856	6	<0.0001
Test 2	2.44004	3	0.4862
Test 3	2.44004	3	0.4862
Test 4	3.28812	2	0.1932

BMDS WIZARD OUTPUT REPORT

BMDS Summary of Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice – Offspring Weight (g) at Postnatal Day 40 in Males

1.32. BMDS Summary of Offspring Body weight at PND40 in Males (Reproductive Mice)

Table 32. Summary of BMD Modeling Results for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.657	235.51	4.68	3.18	1.47	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.595	236.95	4.97	3.30	1.51	
Exponential (M4)	0.657	235.51	4.68	2.01	2.33	
Power	0.595	236.95	4.97	3.36	1.48	
Polynomial 3°	**0.866**	**234.96**	**4.93**	**3.36**	**1.47**	
Polynomial 2°	0.851	234.99	4.88	4.08	1.20	
Linear	0.667	235.48	4.69	3.26	1.44	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.423), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.38, -0.01, 0.38, 0, respectively.

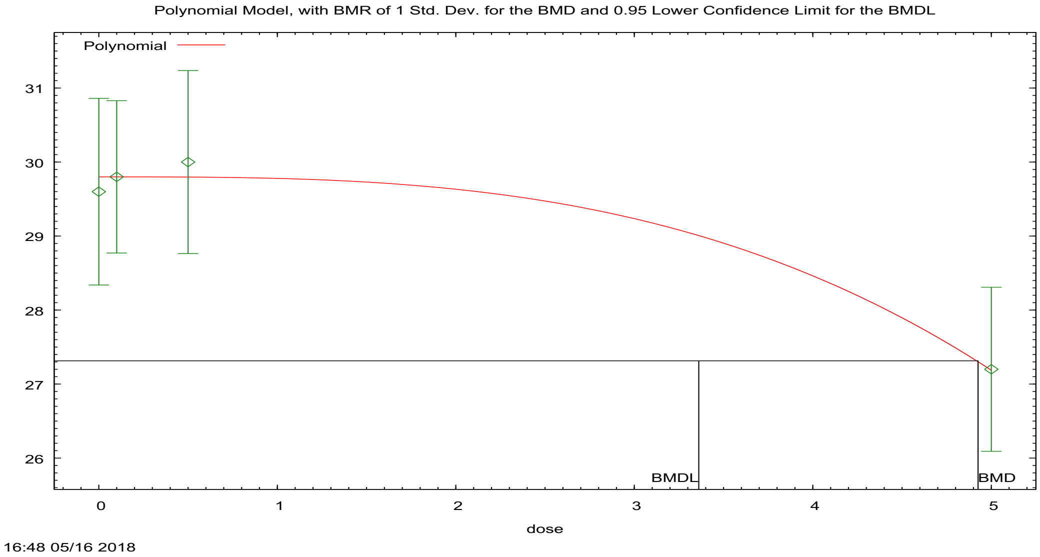


Figure 155. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.92569

BMDL at the 95% confidence level = 3.36106

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.213	6.51263
rho	n/a	0
beta_0	29.8074	29.6
beta_1	0	0
beta_2	0	-3.33252
beta_3	-0.0208569	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.8	2.77	2.49	-0.381
0.1	18	29.8	29.8	2.07	2.49	-0.0125
0.5	23	30	29.8	2.86	2.49	0.376
5	19	27.2	27.2	2.3	2.49	-0.000413

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.335534	5	238.671069
A2	-112.934283	8	241.868566
A3	-114.335534	5	238.671069
fitted	-114.479095	3	234.95819
R	-121.737289	2	247.474579

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.606	6	0.007296
Test 2	2.8025	3	0.4231
Test 3	2.8025	3	0.4231
Test 4	0.287121	2	0.8663

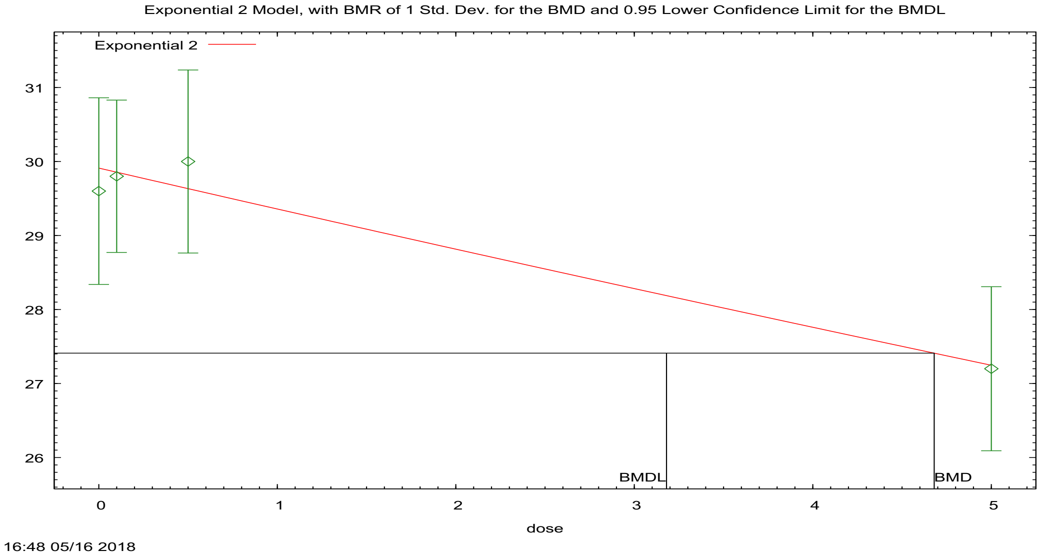


Figure 156. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.68011

BMDL at the 95% confidence level = 3.18036

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.83346	1.8231
rho	n/a	0
a	29.9113	28.4519
b	0.0186579	0.0187227
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.91	2.77	2.5	-0.5704
0.1	18	29.8	29.86	2.07	2.5	-0.09421
0.5	23	30	29.63	2.86	2.5	0.7027
5	19	27.2	27.25	2.3	2.5	-0.08207

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.3355	5	238.6711
A2	-112.9343	8	241.8686
A3	-114.3355	5	238.6711
R	-121.7373	2	247.4746
2	-114.755	3	235.5101

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.61	6	0.007296
Test 2	2.803	3	0.4231
Test 3	2.803	3	0.4231

Test 4	0.839	2	0.6574

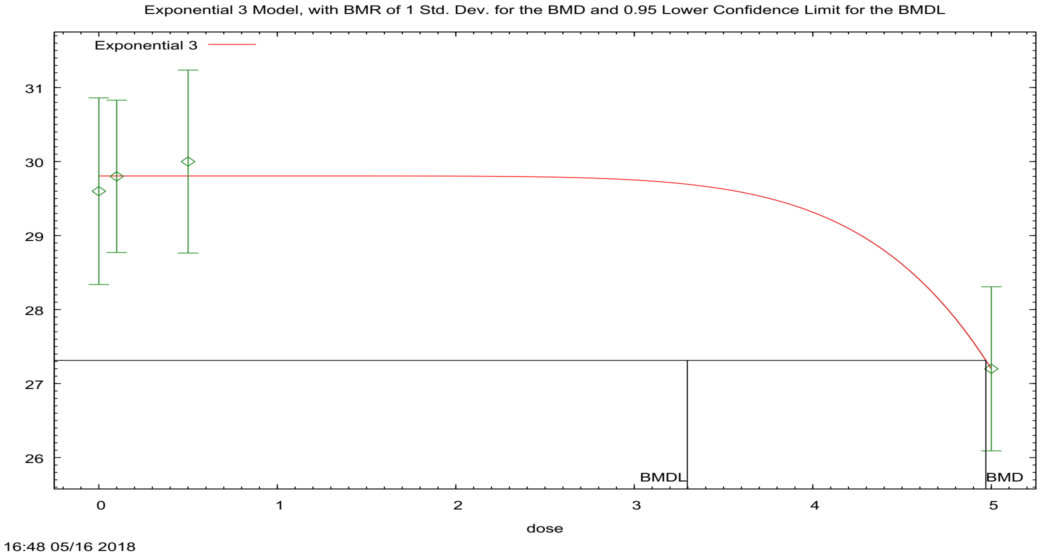


Figure 157. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.96956

BMDL at the 95% confidence level = 3.29703

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.8266	1.8231

rho	n/a	0
a	29.8065	28.4519
b	0.14635	0.0187227
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.81	2.77	2.49	-0.3796
0.1	18	29.8	29.81	2.07	2.49	-0.01098
0.5	23	30	29.81	2.86	2.49	0.3724
5	19	27.2	27.2	2.3	2.49	0.0000001374

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.3355	5	238.6711
A2	-112.9343	8	241.8686
A3	-114.3355	5	238.6711
R	-121.7373	2	247.4746
3	-114.4772	4	236.9544

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.61	6	0.007296
Test 2	2.803	3	0.4231
Test 3	2.803	3	0.4231
Test 5a	0.2834	1	0.5945

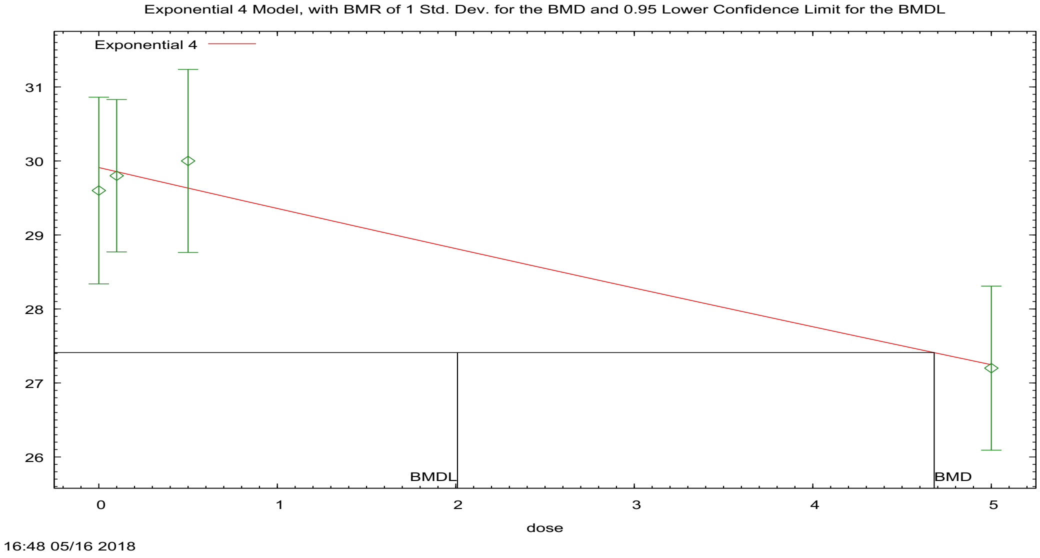


Figure 158. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.68011

BMDL at the 95% confidence level = 2.00942

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.83346	1.8231
rho	n/a	0
a	29.9113	31.5

b	0.0186579	0.297243
c	0	0.822373
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.91	2.77	2.5	-0.5704
0.1	18	29.8	29.86	2.07	2.5	-0.09421
0.5	23	30	29.63	2.86	2.5	0.7027
5	19	27.2	27.25	2.3	2.5	-0.08207

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.3355	5	238.6711
A2	-112.9343	8	241.8686
A3	-114.3355	5	238.6711
R	-121.7373	2	247.4746
4	-114.755	3	235.5101

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.61	6	0.007296
Test 2	2.803	3	0.4231
Test 3	2.803	3	0.4231
Test 6a	0.839	2	0.6574

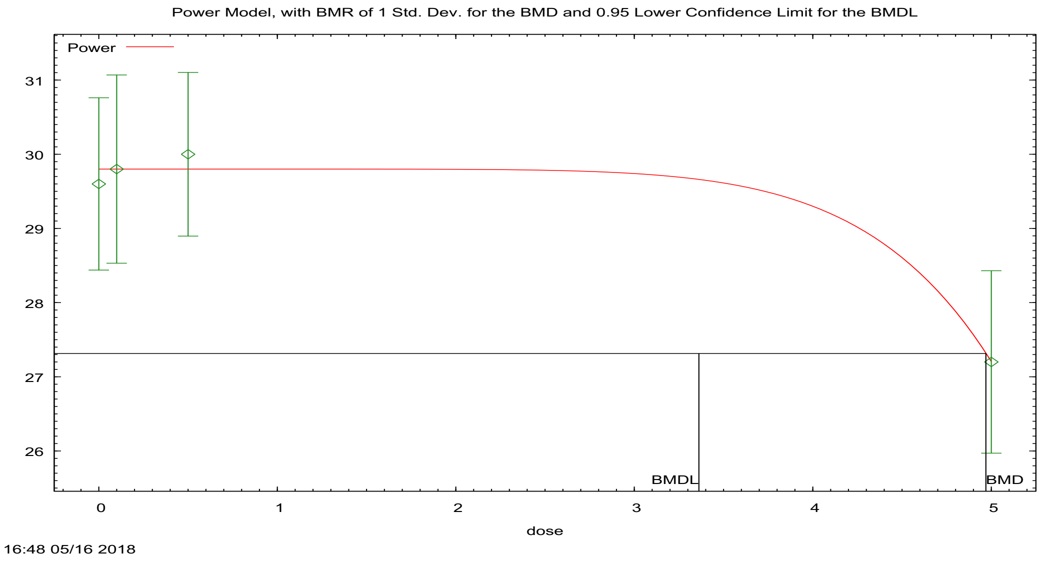


Figure 159. Plot of mean response by dose with fitted curve for Power model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.96979

BMDL at the 95% confidence level = 3.36188

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.21272	6.51263
rho	n/a	0
control	29.8065	27.2
slope	-0.0000182645	2.89081

power	7.37434	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.8	2.77	2.49	-0.38
0.1	18	29.8	29.8	2.07	2.49	-0.011
0.5	23	30	29.8	2.86	2.49	0.372
5	19	27.2	27.2	2.3	2.49	-0.0000000173

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.335534	5	238.671069
A2	-112.934283	8	241.868566
A3	-114.335534	5	238.671069
fitted	-114.477219	4	236.954439
R	-121.737289	2	247.474579

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.606	6	0.007296
Test 2	2.8025	3	0.4231
Test 3	2.8025	3	0.4231
Test 4	0.28337	1	0.5945

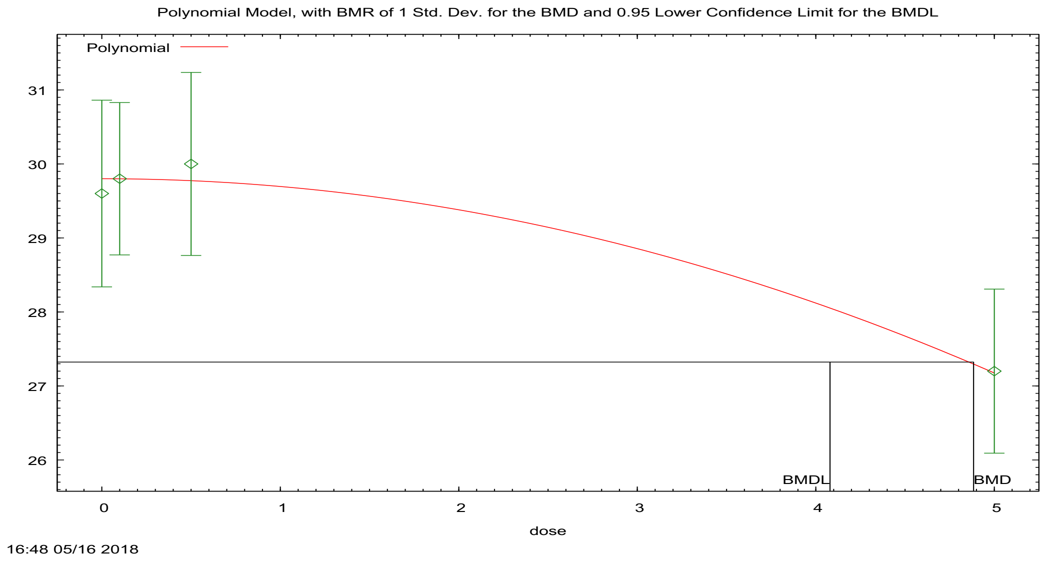


Figure 160. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.88385

BMDL at the 95% confidence level = 4.07971

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.2157	6.51263
rho	n/a	0
beta_0	29.8157	29.6512
beta_1	-1.88555E-23	0

beta_2	-0.104525	-0.27028

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.8	2.77	2.49	-0.396
0.1	18	29.8	29.8	2.07	2.49	-0.0249
0.5	23	30	29.8	2.86	2.49	0.405
5	19	27.2	27.2	2.3	2.49	-0.00444

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.335534	5	238.671069
A2	-112.934283	8	241.868566
A3	-114.335534	5	238.671069
fitted	-114.496699	3	234.993397
R	-121.737289	2	247.474579

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.606	6	0.007296
Test 2	2.8025	3	0.4231
Test 3	2.8025	3	0.4231
Test 4	0.322329	2	0.8512

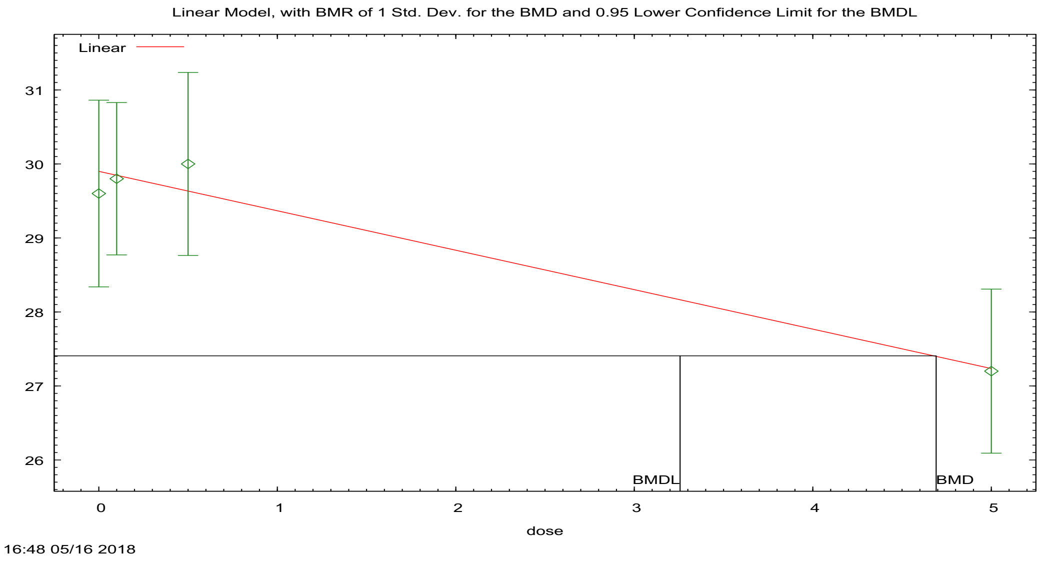


Figure 161. Plot of mean response by dose with fitted curve for Linear model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.69089

BMDL at the 95% confidence level = 3.25646

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.2532	6.51263
rho	n/a	0
beta_0	29.9078	29.8942
beta_1	-0.533085	-0.531573

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.9	2.77	2.5	-0.564
0.1	18	29.8	29.9	2.07	2.5	-0.0925
0.5	23	30	29.6	2.86	2.5	0.688
5	19	27.2	27.2	2.3	2.5	-0.0739

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.335534	5	238.671069
A2	-112.934283	8	241.868566
A3	-114.335534	5	238.671069
fitted	-114.740315	3	235.480629
R	-121.737289	2	247.474579

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.606	6	0.007296
Test 2	2.8025	3	0.4231
Test 3	2.8025	3	0.4231
Test 4	0.809561	2	0.6671

BMDS WIZARD OUTPUT REPORT

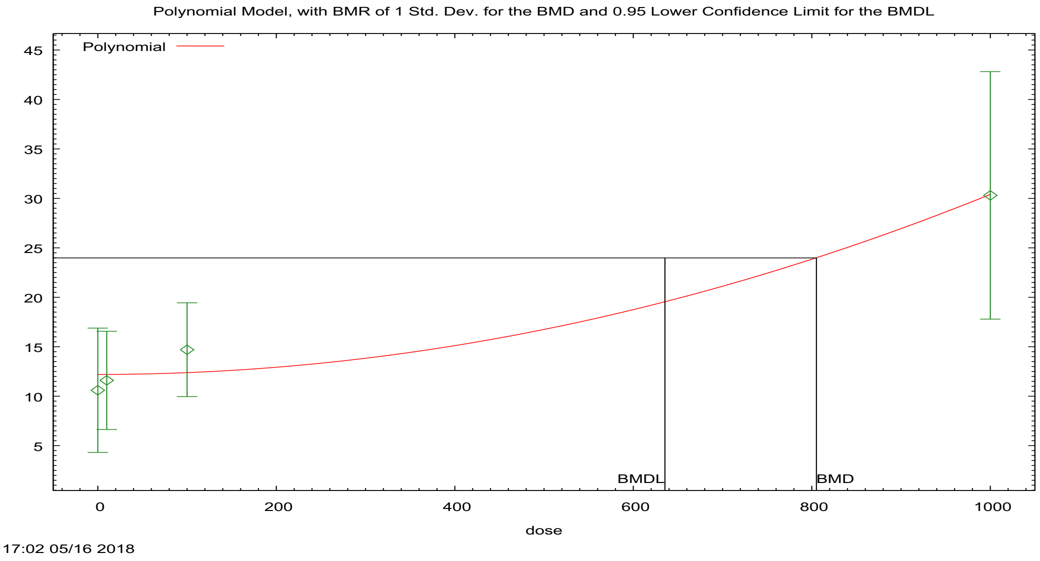
BMDS Summary of Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats – Percent per Litter with Skeletal Variations

1.33. BMDS Summary of Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats)

Table 33. Summary of BMD Modeling Results for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean

Model[a]	**Goodness of fit**		**BMD_{1SD} (mg/kg/day)**	**$BMDL_{1SD}$ (mg/kg/day)**	**BMD/BMDL**	**Basis for model selection**
	***p*-value**	**AIC**				
Exponential (M2)	0.563	547.74	716	540	1.33	Models that met inclusion criteria are presented (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.364	549.41	872	548	1.59	
Exponential (M4)	0.206	550.19	614	386	1.59	
Power	0.364	549.41	833	411	2.02	
Polynomial 3°	0.364	549.41	848	636	1.33	
Polynomial 2°	**0.661**	**547.42**	**805**	**635**	**1.27**	
Linear	0.450	548.19	614	386	1.59	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 10, 100, and 1000 mg/kg/day were -0.63, -0.23, 0.89, -0.01, respectively.


Polynomial Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

17:02 05/16 2018

Figure 162. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 805.163

BMDL at the 95% confidence level = 635.448

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.438015	5.68628
rho	1.7978	0
beta_0	12.1925	10.8806
beta_1	1.99095E-24	0.0406653
beta_2	0.0000181818	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	12.2	14.2	11.8	-0.634
10	21	11.6	12.2	10.9	11.8	-0.231
100	21	14.7	12.4	10.4	11.9	0.892
1000	21	30.3	30.4	27.5	26.8	-0.0127

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.118145	5	574.236289
A2	-267.74874	8	551.497479
A3	-269.294095	6	550.58819
fitted	-269.707549	4	547.415099

R	-290.685425	2	585.37085

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.8734	6	<0.0001
Test 2	28.7388	3	<0.0001
Test 3	3.09071	2	0.2132
Test 4	0.826909	2	0.6614

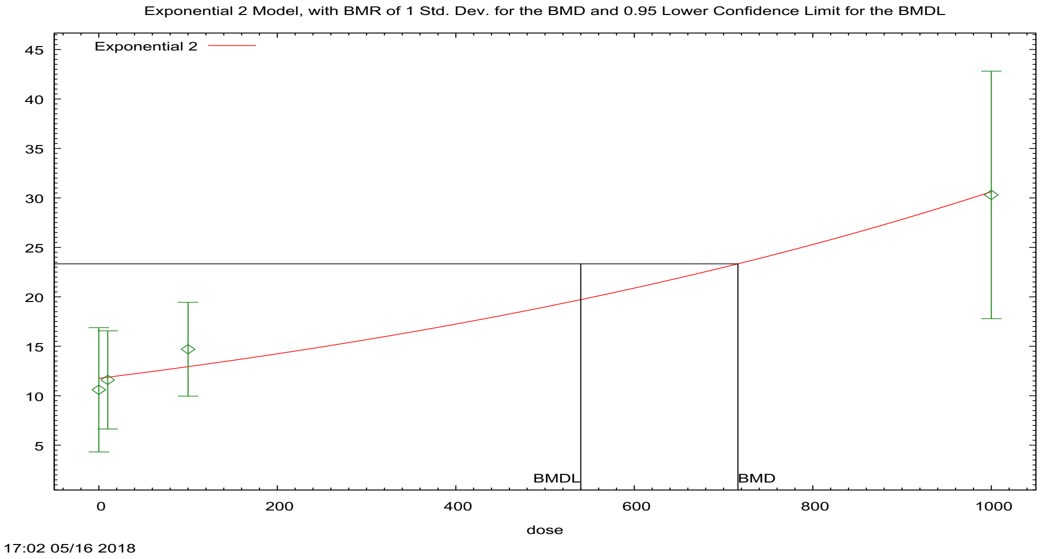


Figure 163. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 716.091

BMDL at the 95% confidence level = 540.031

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.657242	1.03331
rho	1.72078	1.58206
a	11.7578	11.6882
b	0.000957211	0.000965669
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	11.76	14.17	11.58	-0.4691
10	21	11.6	11.87	10.9	11.67	-0.1064
100	21	14.7	12.94	10.42	12.57	0.642
1000	21	30.3	30.62	27.49	26.38	-0.05599

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.1181	5	574.2363
A2	-267.7487	8	551.4975
A3	-269.2941	6	550.5882
R	-290.6854	2	585.3709
2	-269.868	4	547.736

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.87	6	<0.0001
Test 2	28.74	3	<0.0001

Test 3	3.091	2	0.2132
Test 4	1.148	2	0.5633

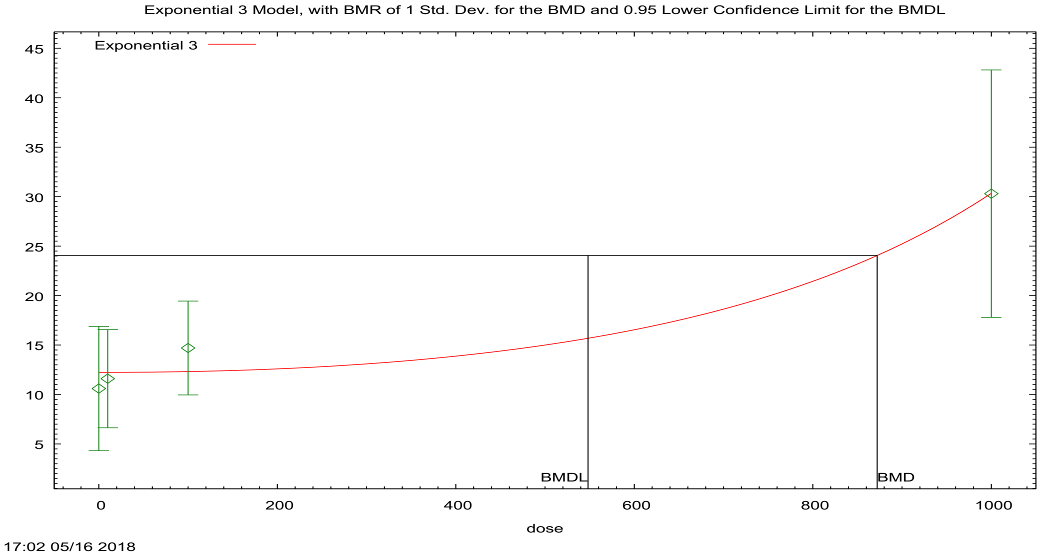


Figure 164. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 872.124

BMDL at the 95% confidence level = 548.126

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values

lnalpha	0.41575	1.03331
rho	1.80569	1.58206
a	12.2385	11.6882
b	0.000956119	0.000965669
c	n/a	0
d	2.15848	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	12.24	14.17	11.81	-0.6506
10	21	11.6	12.24	10.9	11.81	-0.2479
100	21	14.7	12.32	10.42	11.88	0.9197
1000	21	30.3	30.33	27.49	26.81	-0.00584

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.1181	5	574.2363
A2	-267.7487	8	551.4975
A3	-269.2941	6	550.5882
R	-290.6854	2	585.3709
3	-269.7063	5	549.4126

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.87	6	<0.0001
Test 2	28.74	3	<0.0001
Test 3	3.091	2	0.2132
Test 5a	0.8244	1	0.3639

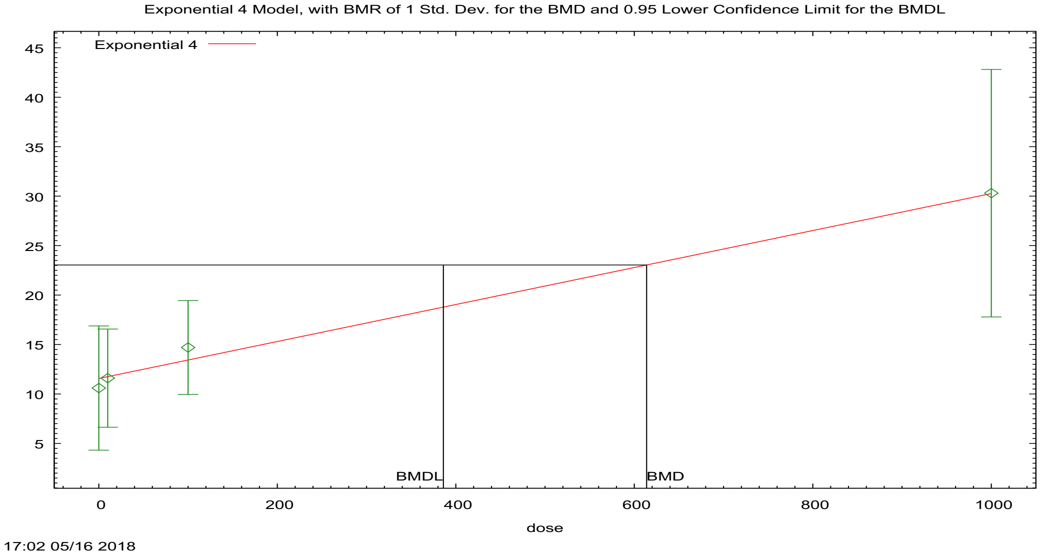


Figure 165. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 613.794

BMDL at the 95% confidence level = 386.055

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.713673	1.03331
rho	1.70232	1.58206
a	11.5638	10.07

b	0.0000000754115	0.000156222
c	21444.1	15.0447
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	11.56	14.17	11.48	-0.3939
10	21	11.6	11.75	10.9	11.64	-0.0594
100	21	14.7	13.43	10.42	13.04	0.445
1000	21	30.3	30.26	27.49	26.03	0.00661

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.1181	5	574.2363
A2	-267.7487	8	551.4975
A3	-269.2941	6	550.5882
R	-290.6854	2	585.3709
4	-270.0929	5	550.1858

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.87	6	<0.0001
Test 2	28.74	3	<0.0001
Test 3	3.091	2	0.2132
Test 6a	1.598	1	0.2062

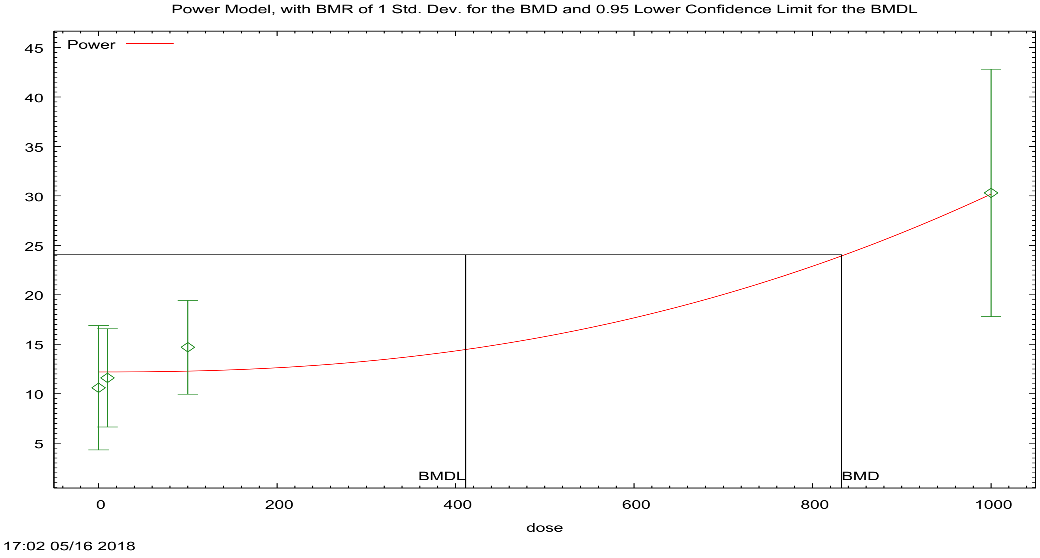


Figure 166. Plot of mean response by dose with fitted curve for Power model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 832.617

BMDL at the 95% confidence level = 411.414

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.417329	5.68628
rho	1.80513	0
control	12.2354	10.6

slope	0.00000183768	0.225303
power	2.33115	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	12.2	14.2	11.8	-0.649
10	21	11.6	12.2	10.9	11.8	-0.247
100	21	14.7	12.3	10.4	11.9	0.918
1000	21	30.3	30.3	27.5	26.8	-0.00637

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.118145	5	574.236289
A2	-267.74874	8	551.497479
A3	-269.294095	6	550.58819
fitted	-269.706226	5	549.412452
R	-290.685425	2	585.37085

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.8734	6	<0.0001
Test 2	28.7388	3	<0.0001
Test 3	3.09071	2	0.2132
Test 4	0.824262	1	0.3639

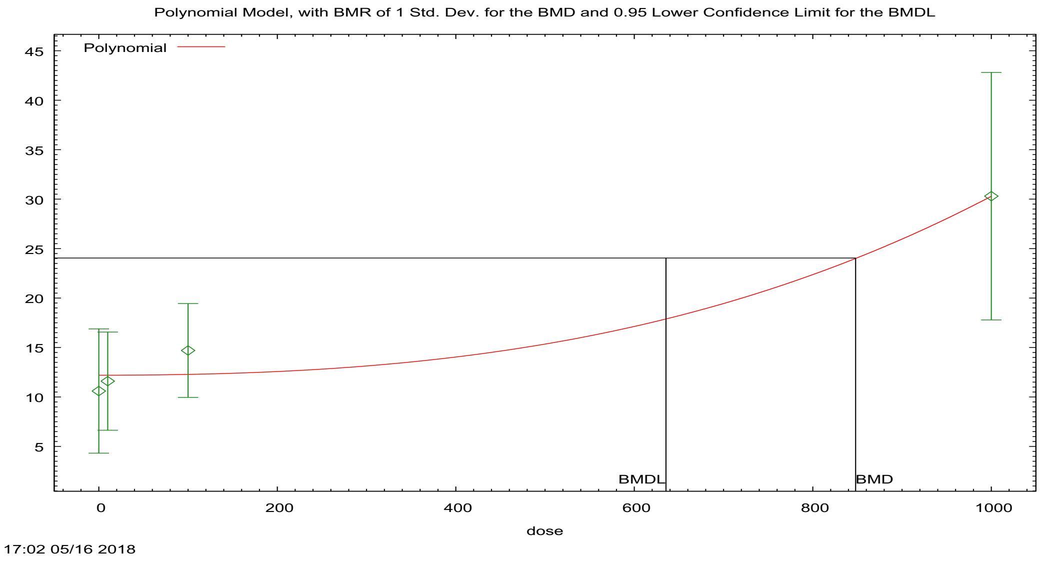


Figure 167. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 847.968

BMDL at the 95% confidence level = 635.505

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.416772	5.68628
rho	1.80533	0
beta_0	12.2364	10.6

beta_1	9.13497E-23	0.107194
beta_2	0.00000709061	0
beta_3	0.0000000110091	0.000000638272

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	12.2	14.2	11.8	-0.65
10	21	11.6	12.2	10.9	11.8	-0.247
100	21	14.7	12.3	10.4	11.9	0.919
1000	21	30.3	30.3	27.5	26.8	-0.00618

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.118145	5	574.236289
A2	-267.74874	8	551.497479
A3	-269.294095	6	550.58819
fitted	-269.706361	5	549.412722
R	-290.685425	2	585.37085

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.8734	6	<0.0001
Test 2	28.7388	3	<0.0001
Test 3	3.09071	2	0.2132
Test 4	0.824532	1	0.3639

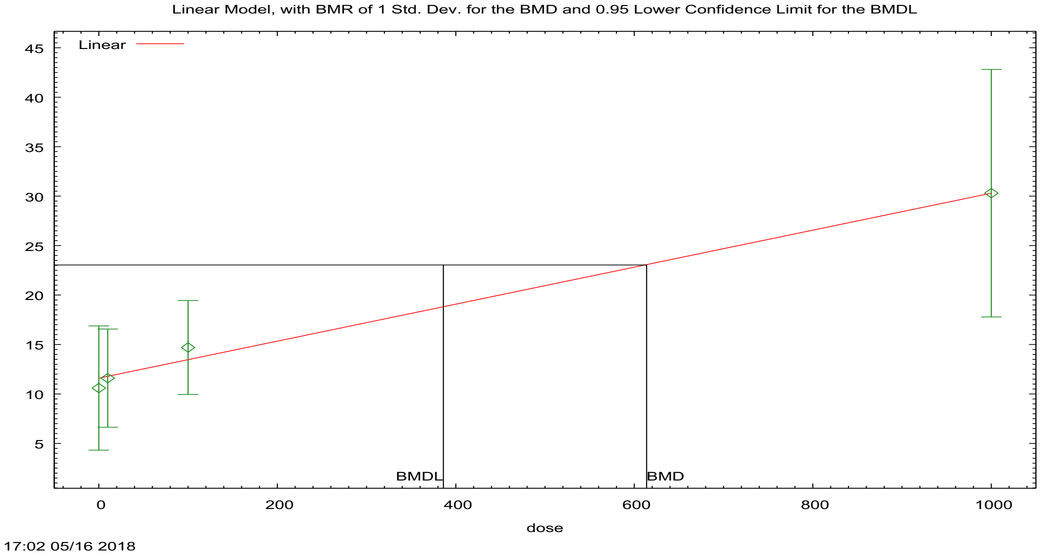


Figure 168. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 613.802

BMDL at the 95% confidence level = 386.066

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.713678	5.68628
rho	1.70231	0
beta_0	11.5638	11.5676

beta_1	0.0186987	0.0188555

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	11.6	14.2	11.5	-0.394
10	21	11.6	11.8	10.9	11.6	-0.0594
100	21	14.7	13.4	10.4	13	0.445
1000	21	30.3	30.3	27.5	26	0.0066

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.118145	5	574.236289
A2	-267.74874	8	551.497479
A3	-269.294095	6	550.58819
fitted	-270.092862	4	548.185724
R	-290.685425	2	585.37085

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.8734	6	<0.0001
Test 2	28.7388	3	<0.0001
Test 3	3.09071	2	0.2132
Test 4	1.59753	2	0.4499

Appendix C

Benchmark Dose Modeling Report for GenX Supplemental Documentation

NC DHHS

June 8, 2018

BENCHMARK DOSE MODELING REPORT FOR GENX

SUPPLEMENTAL DOCUMENTATION

Prepared by:
Occupational and Environmental Epidemiology Branch
Epidemiology Section
Division of Public Health
Department of Health and Human Services

Prepared for:
North Carolina Secretaries' Science Advisory Board

June 8, 2018

Foreword

The purpose of the supplemental documentation for the Benchmark Dose Modeling Report for GenX is to provide the North Carolina Secretaries' Science Advisory Board (SAB) with more information from the Benchmark Dose Software (BMDS) Wizard. Appendix B in the previously provided Benchmark Dose Modeling Report only included model outputs for models that met all model fit criteria. The N.C. Department of Health and Human Services (DHHS) updated the BMDS Wizard output reports to include all models that were run for each endpoint, regardless of if the model met all model fit criteria. For continuous data types, only models with appropriate variance (either constant variance or modeled variance) are included. This supplemental documentation does not alter the content or conclusions of the previously provided report, but does provide more information from the modeling software.

This supplemental documentation includes BMDS Wizard output reports for endpoints where no model outputs were included in the previous report. This is because no models met all model fit criteria and no BMDL was chosen. These endpoints include:

- Alkaline phosphatase in males (28-day mice and 2-year rat)
- Alanine aminotransferase in females (90-day mice) and males at 12 months (2-year rat)
- Sorbitol dehydrogenase in females (90-day mice)

Some endpoints were modeled with the BMDS Wizard, but no output reports for these endpoints are available because the neither constant variance nor modeled variance models fit the data, so all model output was unusable. These endpoints include:

- Hematocrit in males (90-day rat)
- Albumin to globulin ratio in males at 12 months (2-year rat)
- Alanine aminotransferase in males (28-day mice and 90-day mice)
- Sorbitol dehydrogenase in males (28-day mice and 90-day mice)
- Liver weight to brain weight in males (90-day rat) and females (reproductive mice)
- Combined fetal weights (Prenatal and developmental rat)

All data used for benchmark dose modeling can be found in Appendix A of the Benchmark Dose Modeling Report for GenX that was previously provided to the SAB.

CONTENTS

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Hemoglobin (g/dL) in Males

1.1. BMDS Summary of Hemoglobin g/dL Males (28 Day Mice GenX)

Table 1. Summary of BMD Modeling Results for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean

Model^{a}	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)^{b}	0.0321	-4.9996	20.5	13.5	1.52	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. Selected BMDL is from model with lowest AIC and lowest BMDL.
Exponential (M4) Exponential (M5)^{c}	0.241	-8.5015	2.08	0.0607	34.2	
Hill	**0.287**	**-8.7441**	**0.343**	**0.0492**	**6.97**	
Power^{d} Polynomial 3°^{e} Polynomial 2°^{f} Linear	0.0315	-4.9610	20.8	13.9	1.50	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.933), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were 0.16, -0.31, 0.79, -0.61, respectively.
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.
[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[e] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[f] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

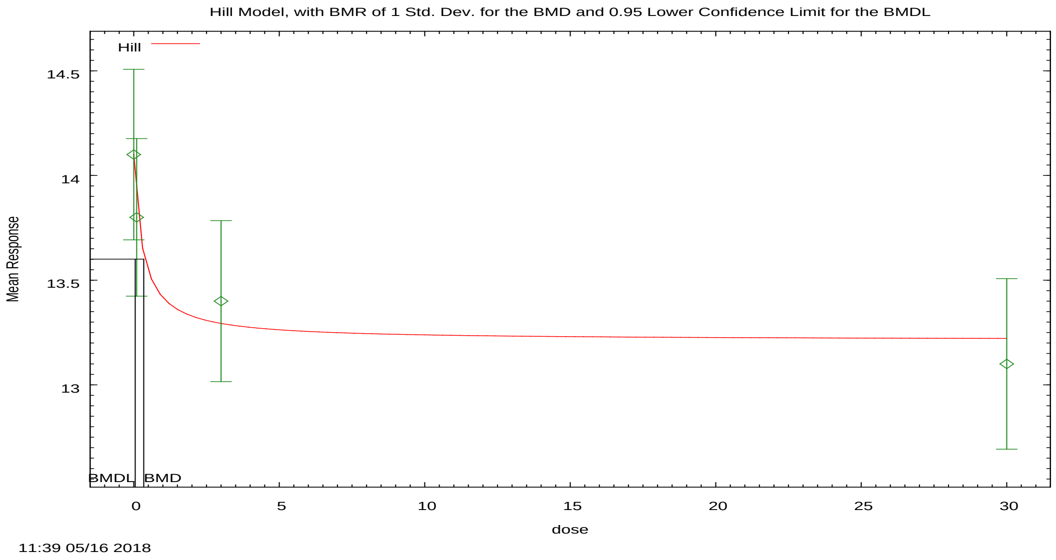

Hill Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

Figure 1. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.342989

BMDL at the 95% confidence level = 0.0491937

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.224816	0.246437
rho	n/a	0
intercept	14.0748	14.1
v	-0.887431	-1
n	1	0.796114
k	0.298961	1.55

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	14.1	0.53	0.47	0.159
0.1	8	13.8	13.9	0.45	0.47	-0.312
3	8	13.4	13.3	0.46	0.47	0.789
30	9	13.1	13.2	0.53	0.47	-0.608

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655

A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
fitted	8.372034	4	-8.744068
R	-0.034215	2	4.068429

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.3812	6	0.005347
Test 2	0.435143	3	0.9329
Test 3	0.435143	3	0.9329
Test 4	1.13359	1	0.287

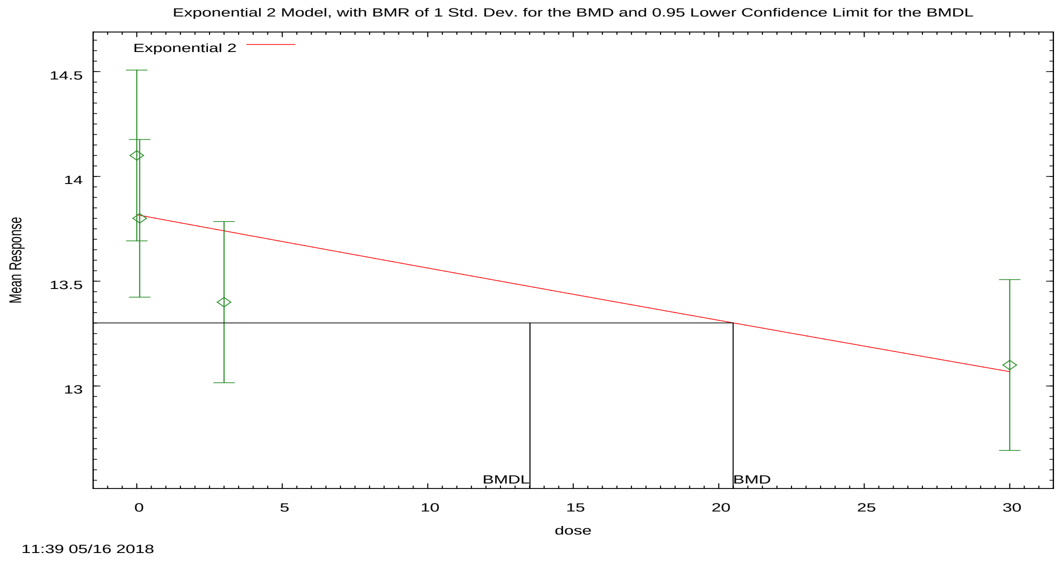


Figure 2. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 20.4946

BMDL at the 95% confidence level = 13.5131

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.32352	-1.52581
rho	n/a	0
a	13.8168	13.3792
b	0.00185691	0.00184061
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	13.82	0.53	0.52	1.647
0.1	8	13.8	13.81	0.45	0.52	-0.07817
3	8	13.4	13.74	0.46	0.52	-1.864
30	9	13.1	13.07	0.53	0.52	0.1851

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655
A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
R	-0.03421454	2	4.068429
2	5.49979	3	-4.99958

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.38	6	0.005347
Test 2	0.4351	3	0.9329

Test 3	0.4351	3	0.9329
Test 4	6.878	2	0.0321

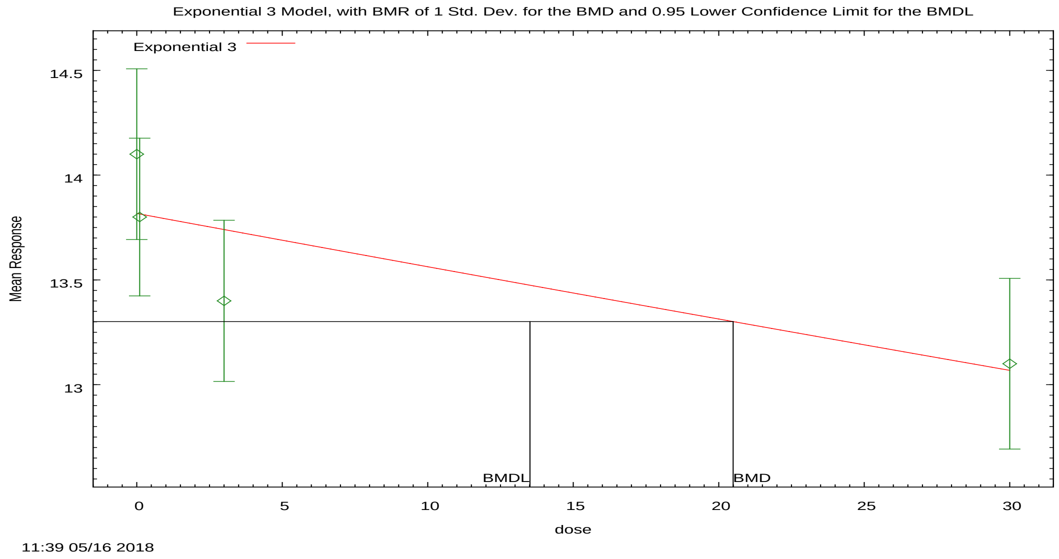


Figure 3. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 20.4946

BMDL at the 95% confidence level = 13.5131

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.32352	-1.52581
rho	n/a	0

a	13.8168	13.3792
b	0.00185691	0.00184061
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	13.82	0.53	0.52	1.647
0.1	8	13.8	13.81	0.45	0.52	-0.07817
3	8	13.4	13.74	0.46	0.52	-1.864
30	9	13.1	13.07	0.53	0.52	0.1851

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655
A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
R	-0.03421454	2	4.068429
3	5.49979	3	-4.99958

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.38	6	0.005347
Test 2	0.4351	3	0.9329
Test 3	0.4351	3	0.9329
Test 5a	6.878	2	0.0321

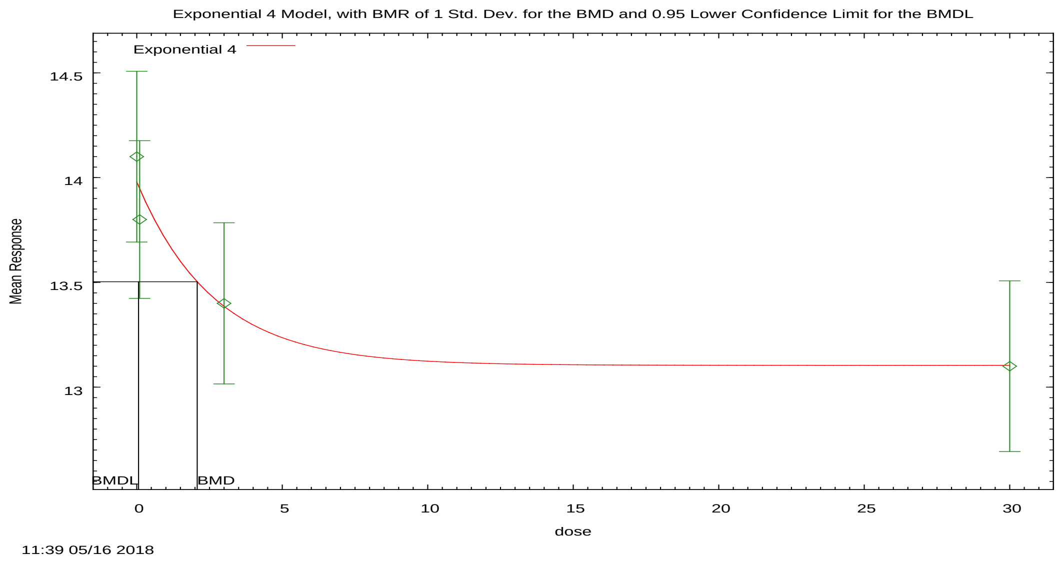


Figure 4. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.07626

BMDL at the 95% confidence level = 0.0606788

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.48534	-1.52581
rho	n/a	0
a	13.9789	14.805
b	0.378088	0.0465873
c	0.937413	0.842701

d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	13.98	0.53	0.48	0.7637
0.1	8	13.8	13.95	0.45	0.48	-0.8702
3	8	13.4	13.39	0.46	0.48	0.08685
30	9	13.1	13.1	0.53	0.48	-0.0251

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655
A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
R	-0.03421454	2	4.068429
4	8.250725	4	-8.50145

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.38	6	0.005347
Test 2	0.4351	3	0.9329
Test 3	0.4351	3	0.9329
Test 6a	1.376	1	0.2407

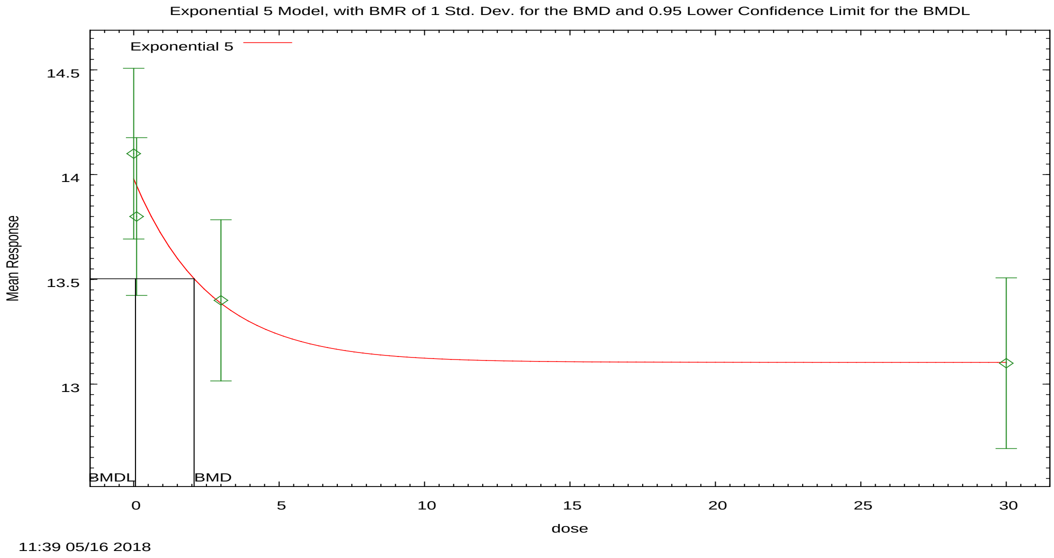


Figure 5. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.07626

BMDL at the 95% confidence level = 0.0606788

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.48534	-1.52581
rho	n/a	0
a	13.9789	14.805
b	0.378087	0.0465873
c	0.937413	0.842701

d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	13.98	0.53	0.48	0.7637
0.1	8	13.8	13.95	0.45	0.48	-0.8702
3	8	13.4	13.39	0.46	0.48	0.08685
30	9	13.1	13.1	0.53	0.48	-0.0251

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655
A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
R	-0.03421454	2	4.068429
5	8.250725	4	-8.50145

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.38	6	0.005347
Test 2	0.4351	3	0.9329
Test 3	0.4351	3	0.9329
Test 7a	1.376	1	0.2407

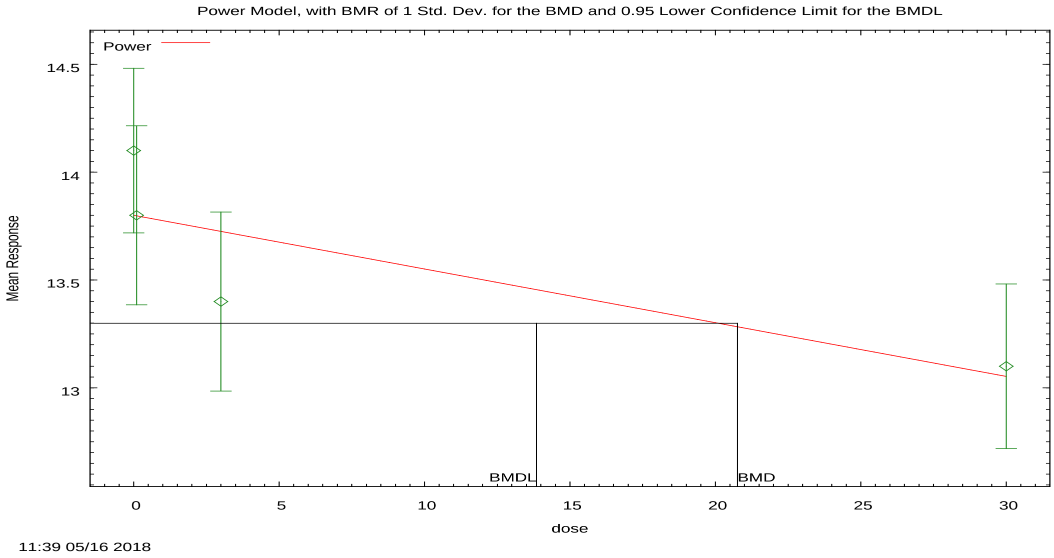


Figure 6. Plot of mean response by dose with fitted curve for Power model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 20.7618

BMDL at the 95% confidence level = 13.855

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.2665	0.246437
rho	n/a	0
control	13.8156	14.1
slope	-0.0248647	-2.33333
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	13.8	0.53	0.52	1.65
0.1	8	13.8	13.8	0.45	0.52	-0.0718
3	8	13.4	13.7	0.46	0.52	-1.87
30	9	13.1	13.1	0.53	0.52	0.176

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655
A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
fitted	5.480494	3	-4.960988
R	-0.034215	2	4.068429

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.3812	6	0.005347
Test 2	0.435143	3	0.9329
Test 3	0.435143	3	0.9329
Test 4	6.91667	2	0.03148

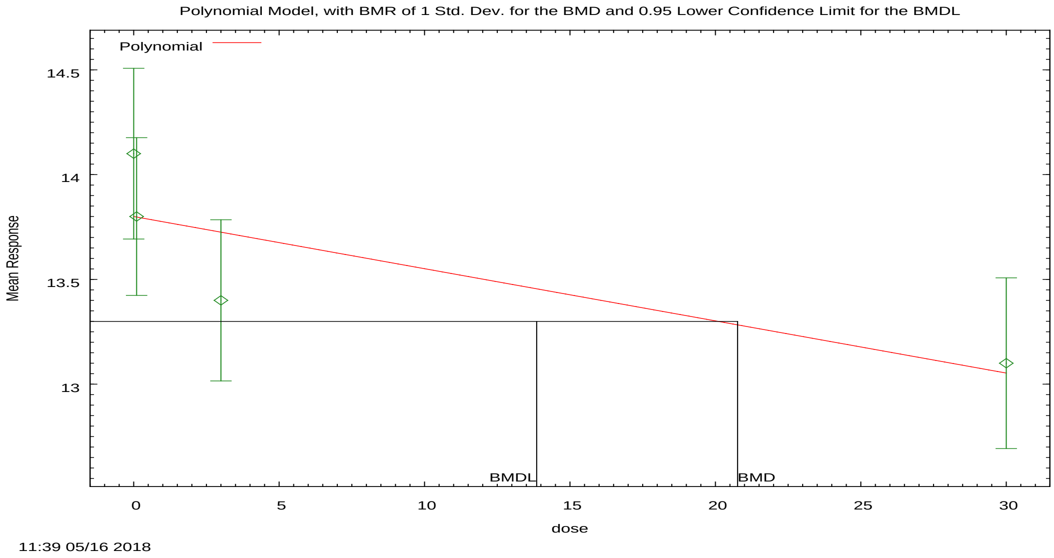


Figure 7. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 20.7618

BMDL at the 95% confidence level = 13.855

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.2665	0.246437
rho	n/a	0
beta_0	13.8156	14.1
beta_1	-0.0248647	-3.1049
beta_2	0	0

beta_3	0	-0.0316594

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	13.8	0.53	0.52	1.65
0.1	8	13.8	13.8	0.45	0.52	-0.0718
3	8	13.4	13.7	0.46	0.52	-1.87
30	9	13.1	13.1	0.53	0.52	0.176

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655
A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
fitted	5.480494	3	-4.960988
R	-0.034215	2	4.068429

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.3812	6	0.005347
Test 2	0.435143	3	0.9329
Test 3	0.435143	3	0.9329
Test 4	6.91667	2	0.03148

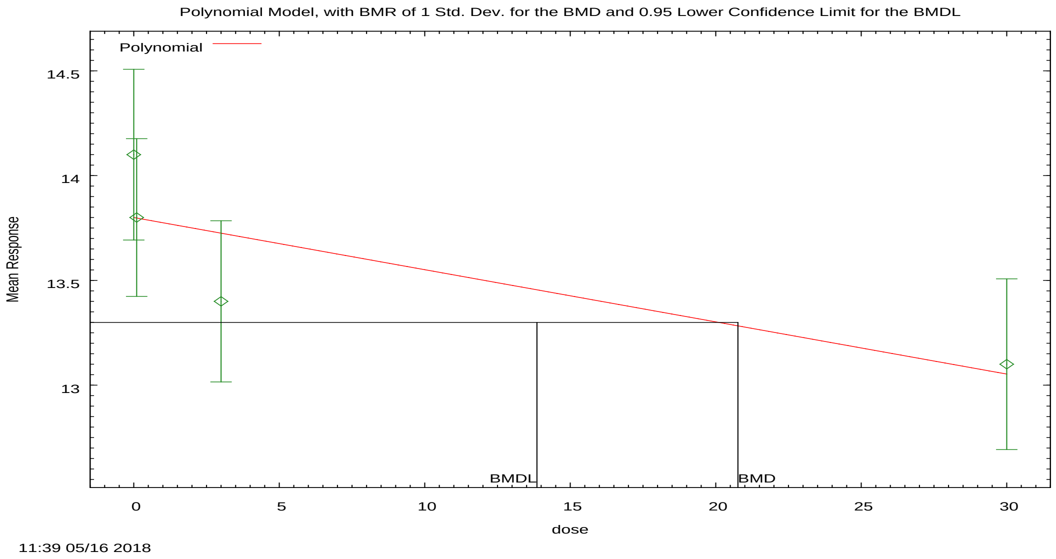


Figure 8. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 20.7618

BMDL at the 95% confidence level = 13.855

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.2665	0.246437
rho	n/a	0
beta_0	13.8156	13.9629
beta_1	-0.0248647	-0.207243
beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	13.8	0.53	0.52	1.65
0.1	8	13.8	13.8	0.45	0.52	-0.0718
3	8	13.4	13.7	0.46	0.52	-1.87
30	9	13.1	13.1	0.53	0.52	0.176

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655
A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
fitted	5.480494	3	-4.960988
R	-0.034215	2	4.068429

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.3812	6	0.005347
Test 2	0.435143	3	0.9329
Test 3	0.435143	3	0.9329
Test 4	6.91667	2	0.03148

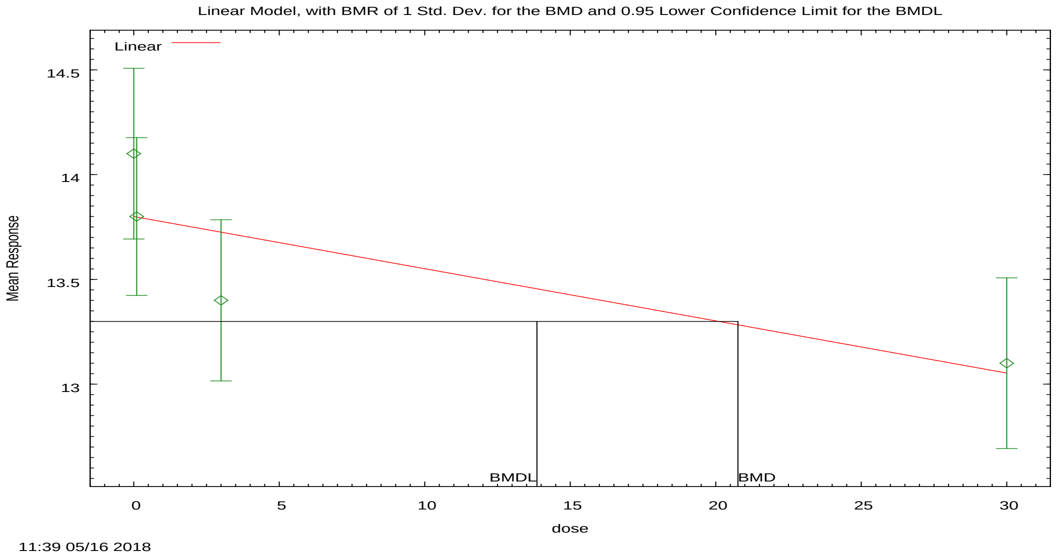


Figure 9. Plot of mean response by dose with fitted curve for Linear model with constant variance for Hemoglobin in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 20.7618

BMDL at the 95% confidence level = 13.855

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.2665	0.246437
rho	n/a	0
beta_0	13.8156	13.803
beta_1	-0.0248647	-0.0245313

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	14.1	13.8	0.53	0.52	1.65
0.1	8	13.8	13.8	0.45	0.52	-0.0718
3	8	13.4	13.7	0.46	0.52	-1.87
30	9	13.1	13.1	0.53	0.52	0.176

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	8.938828	5	-7.877655
A2	9.156399	8	-2.312799
A3	8.938828	5	-7.877655
fitted	5.480494	3	-4.960988
R	-0.034215	2	4.068429

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.3812	6	0.005347
Test 2	0.435143	3	0.9329
Test 3	0.435143	3	0.9329
Test 4	6.91667	2	0.03148

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery – Hemoglobin (g/dL) in Males

1.2. BMDS Summary of Hemoglobin (g/dL) Males (28 Day Rats GenX)

Table 2. Summary of BMD Modeling Results for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.0807	-12.891	14.0	10.3	1.36	Only one model met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from this model.
Exponential (M4)	**0.731**	**-15.807**	**2.44**	**1.19**	**2.06**	
Exponential (M5)	N/A[c]	-13.925	2.91	1.21	2.41	
Hill	N/A[c]	-13.925	2.89	0.906	3.19	
Power[d] Polynomial 3°[e] Polynomial 2°[f] Linear	0.0780	-12.824	14.3	10.6	1.35	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.383), selected model in bold; scaled residuals for selected model for doses 0, 0.3, 3, and 30 mg/kg/day were -0.22, 0.26, -0.05, 0.01, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] No available degrees of freedom to calculate a goodness of fit value.

[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[e] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[f] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

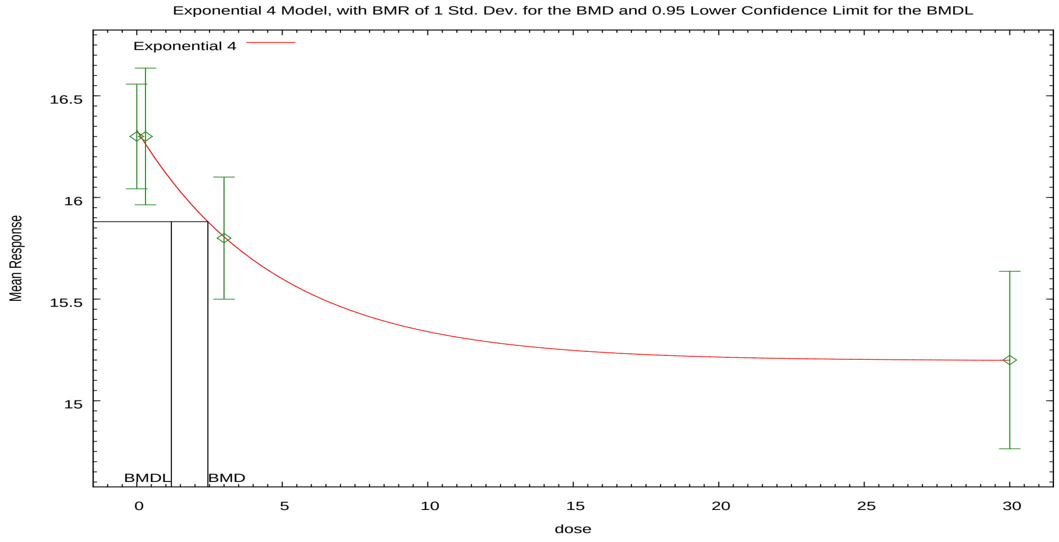


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Figure 10. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.4439

BMDL at the 95% confidence level = 1.18907

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.59517	-1.59813
rho	n/a	0
a	16.3313	17.115
b	0.207026	0.0450856
c	0.930541	0.845819
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.3	16.33	0.36	0.45	-0.2197
0.3	10	16.3	16.26	0.47	0.45	0.2599
3	10	15.8	15.81	0.42	0.45	-0.04565
30	10	15.2	15.2	0.61	0.45	0.005483

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC

A1	11.96254	5	-13.92508
A2	13.49192	8	-10.98384
A3	11.96254	5	-13.92508
R	-2.034667	2	8.069334
4	11.90349	4	-15.80699

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.05	6	<0.0001
Test 2	3.059	3	0.3827
Test 3	3.059	3	0.3827
Test 6a	0.1181	1	0.7311

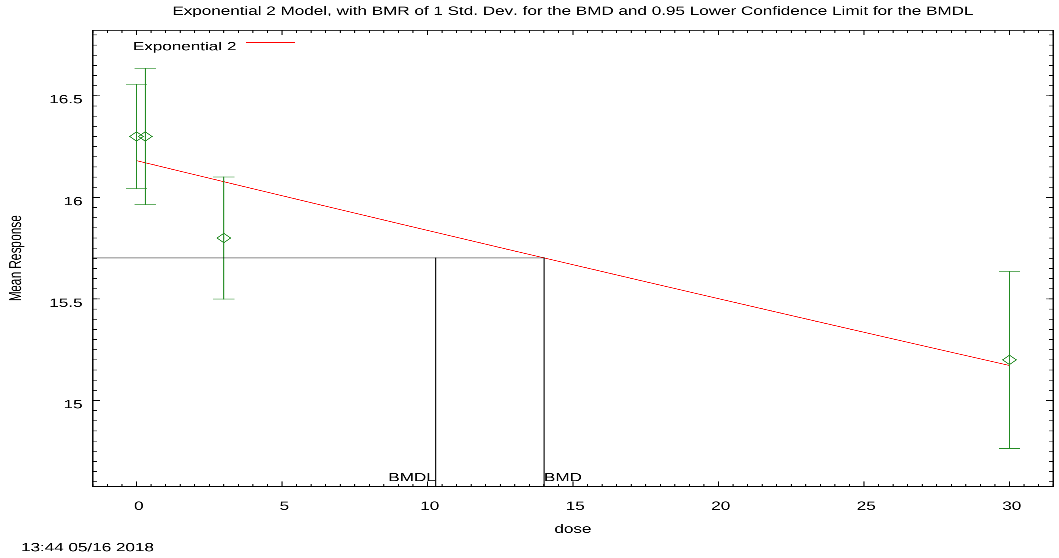

Figure 11. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 14.0048

BMDL at the 95% confidence level = 10.2849

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.47228	-1.59813
rho	n/a	0
a	16.1807	15.6136
b	0.00214552	0.00213419
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.3	16.18	0.36	0.48	0.7876
0.3	10	16.3	16.17	0.47	0.48	0.8563
3	10	15.8	16.08	0.42	0.48	-1.828
30	10	15.2	15.17	0.61	0.48	0.1846

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	11.96254	5	-13.92508
A2	13.49192	8	-10.98384
A3	11.96254	5	-13.92508
R	-2.034667	2	8.069334
2	9.445631	3	-12.89126

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	31.05	6	<0.0001
Test 2	3.059	3	0.3827
Test 3	3.059	3	0.3827
Test 4	5.034	2	0.08071

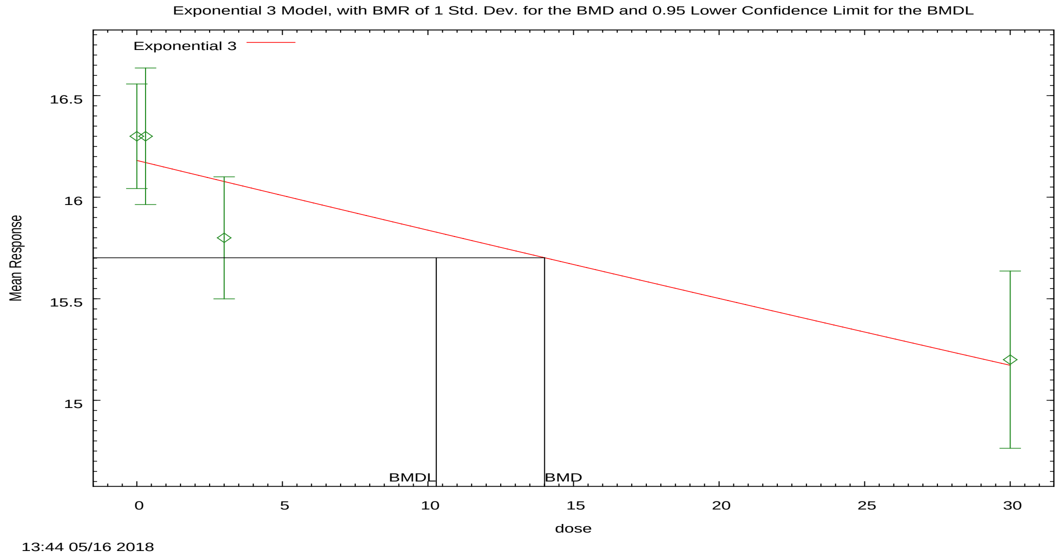

Figure 12. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 14.0048

BMDL at the 95% confidence level = 10.2849

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values

lnalpha	-1.47228	-1.59813
rho	n/a	0
a	16.1807	15.6136
b	0.00214552	0.00213419
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.3	16.18	0.36	0.48	0.7876
0.3	10	16.3	16.17	0.47	0.48	0.8563
3	10	15.8	16.08	0.42	0.48	-1.828
30	10	15.2	15.17	0.61	0.48	0.1846

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	11.96254	5	-13.92508
A2	13.49192	8	-10.98384
A3	11.96254	5	-13.92508
R	-2.034667	2	8.069334
3	9.445631	3	-12.89126

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.05	6	<0.0001
Test 2	3.059	3	0.3827
Test 3	3.059	3	0.3827
Test 5a	5.034	2	0.08071

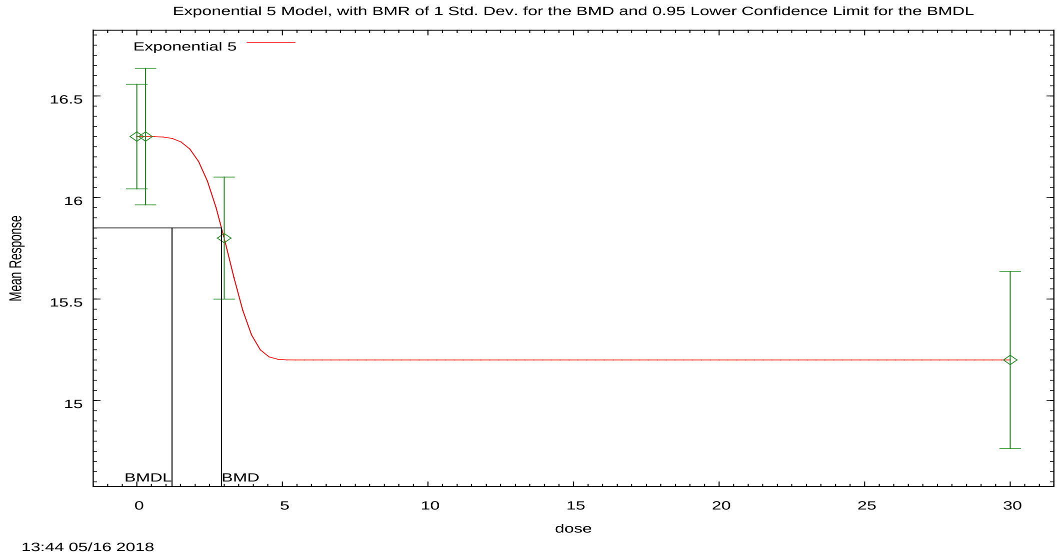

Figure 13. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.91069

BMDL at the 95% confidence level = 1.20656

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.59813	-1.59813
rho	n/a	0
a	16.3	17.115
b	0.299728	0.0450856
c	0.932515	0.845819

d	4.7112	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.3	16.3	0.36	0.45	-0.00004575
0.3	10	16.3	16.3	0.47	0.45	0.00004541
3	10	15.8	15.8	0.42	0.45	-0.0000002073
30	10	15.2	15.2	0.61	0.45	-0.0000002999

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	11.96254	5	-13.92508
A2	13.49192	8	-10.98384
A3	11.96254	5	-13.92508
R	-2.034667	2	8.069334
5	11.96254	5	-13.92508

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.05	6	<0.0001
Test 2	3.059	3	0.3827
Test 3	3.059	3	0.3827
Test 7a	0.000000004155	0	N/A

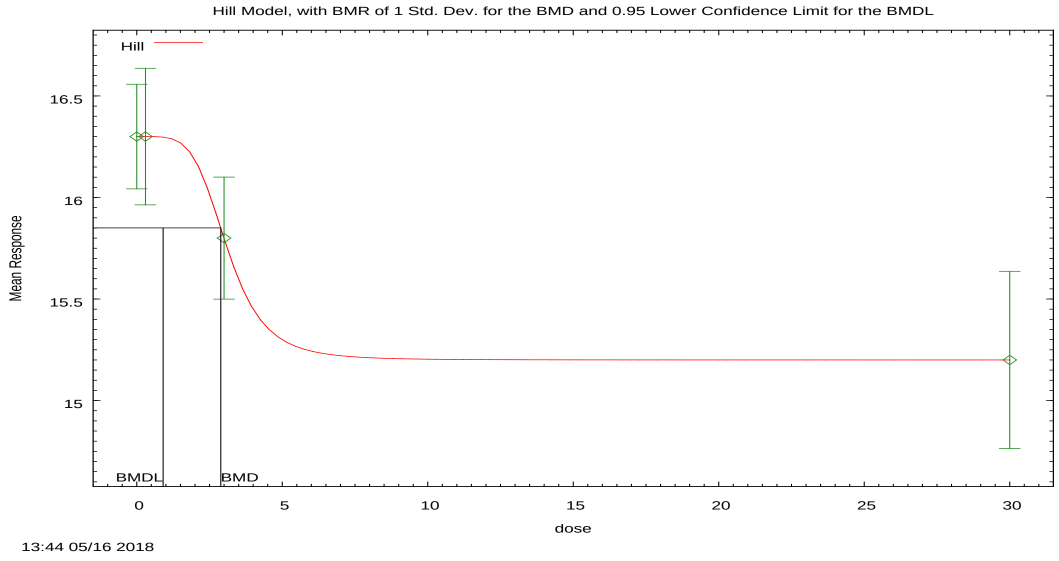

Figure 14. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.88712

BMDL at the 95% confidence level = 0.906305

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.202275	0.22475
rho	n/a	0
intercept	16.3	16.3
v	-1.10002	-1.1
n	4.85942	0.325798

k	3.11471	5.25

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.3	16.3	0.36	0.45	-0.0000442
0.3	10	16.3	16.3	0.47	0.45	0.0000449
3	10	15.8	15.8	0.42	0.45	0.00000338
30	10	15.2	15.2	0.61	0.45	0.000000875

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	11.962542	5	-13.925085
A2	13.491918	8	-10.983835
A3	11.962542	5	-13.925085
fitted	11.962542	5	-13.925085
R	-2.034667	2	8.069334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.0532	6	<0.0001
Test 2	3.05875	3	0.3827
Test 3	3.05875	3	0.3827
Test 4	0.00000000398149	0	N/A

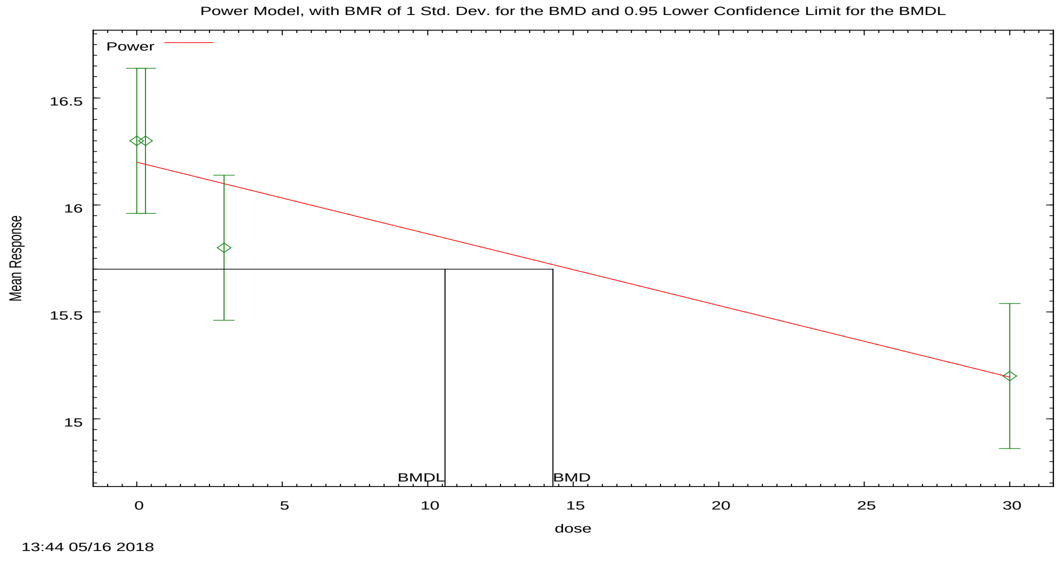

Figure 15. Plot of mean response by dose with fitted curve for Power model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 14.3009

BMDL at the 95% confidence level = 10.5936

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.229788	0.22475
rho	n/a	0
control	16.1791	16.3
slope	-0.0335197	-2.69297
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.3	16.2	0.36	0.48	0.798
0.3	10	16.3	16.2	0.47	0.48	0.864
3	10	15.8	16.1	0.42	0.48	-1.84
30	10	15.2	15.2	0.61	0.48	0.175

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	11.962542	5	-13.925085
A2	13.491918	8	-10.983835
A3	11.962542	5	-13.925085
fitted	9.41194	3	-12.823879
R	-2.034667	2	8.069334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.0532	6	<0.0001
Test 2	3.05875	3	0.3827
Test 3	3.05875	3	0.3827
Test 4	5.10121	2	0.07803

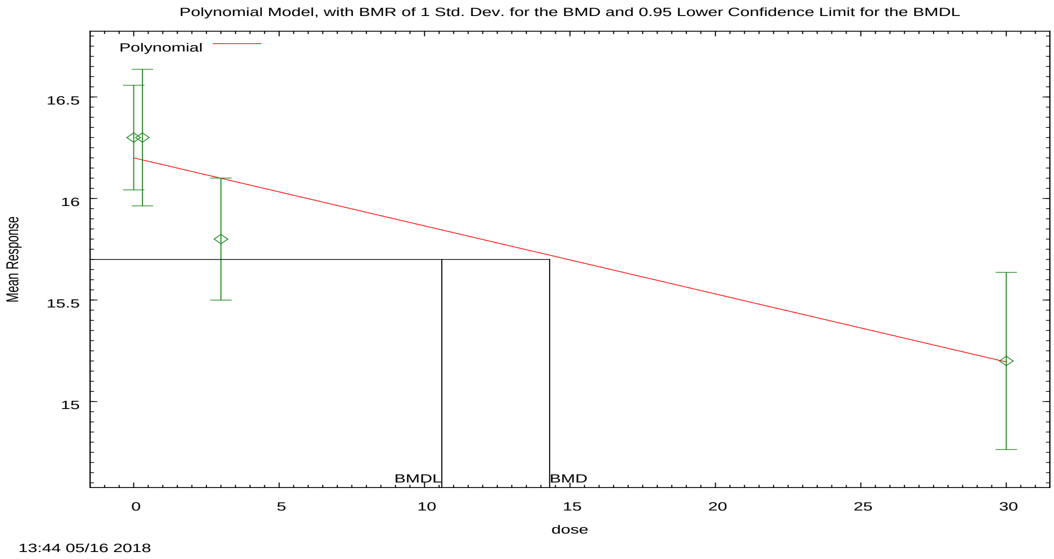

Figure 16. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 14.3009

BMDL at the 95% confidence level = 10.5936

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.229788	0.22475
rho	n/a	0
beta_0	16.1791	16.3
beta_1	-0.0335197	0
beta_2	0	-0.0691221

beta_3	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.3	16.2	0.36	0.48	0.798
0.3	10	16.3	16.2	0.47	0.48	0.864
3	10	15.8	16.1	0.42	0.48	-1.84
30	10	15.2	15.2	0.61	0.48	0.175

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	11.962542	5	-13.925085
A2	13.491918	8	-10.983835
A3	11.962542	5	-13.925085
fitted	9.41194	3	-12.823879
R	-2.034667	2	8.069334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.0532	6	<0.0001
Test 2	3.05875	3	0.3827
Test 3	3.05875	3	0.3827
Test 4	5.10121	2	0.07803

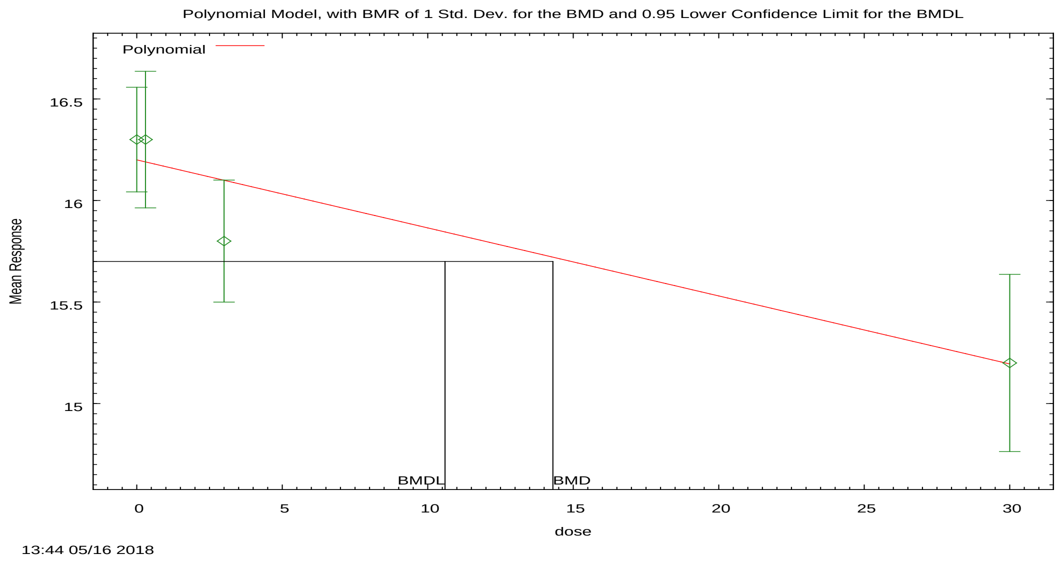

Figure 17. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 14.3009

BMDL at the 95% confidence level = 10.5936

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.229788	0.22475
rho	n/a	0
beta_0	16.1791	16.3266
beta_1	-0.0335197	-0.189646
beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.3	16.2	0.36	0.48	0.798
0.3	10	16.3	16.2	0.47	0.48	0.864
3	10	15.8	16.1	0.42	0.48	-1.84
30	10	15.2	15.2	0.61	0.48	0.175

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	11.962542	5	-13.925085
A2	13.491918	8	-10.983835
A3	11.962542	5	-13.925085
fitted	9.41194	3	-12.823879
R	-2.034667	2	8.069334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.0532	6	<0.0001
Test 2	3.05875	3	0.3827
Test 3	3.05875	3	0.3827
Test 4	5.10121	2	0.07803

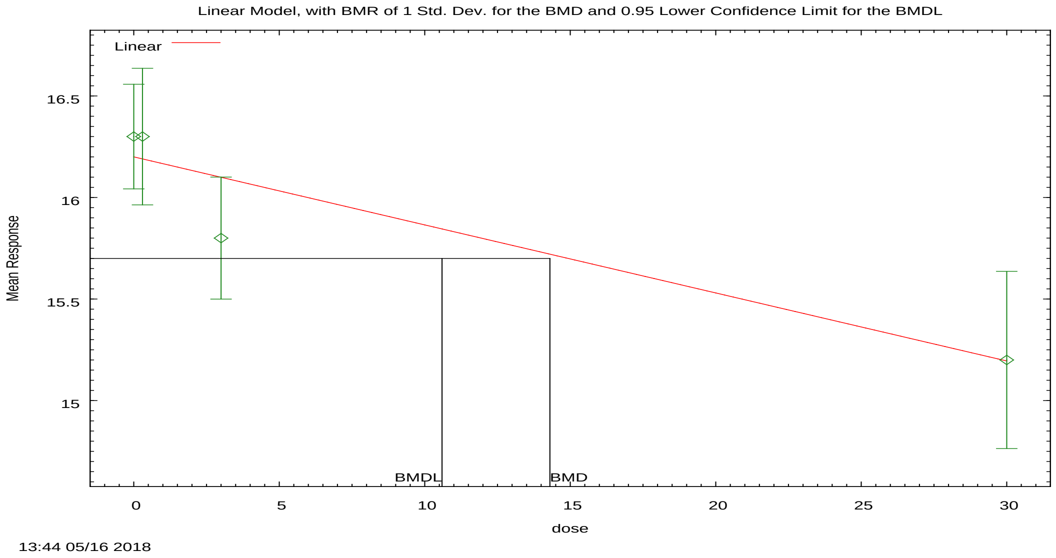

Figure 18. Plot of mean response by dose with fitted curve for Linear model with constant variance for Hemoglobin in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 14.3009

BMDL at the 95% confidence level = 10.5936

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.229788	0.22475
rho	n/a	0
beta_0	16.1791	16.1791
beta_1	-0.0335197	-0.0335197

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.3	16.2	0.36	0.48	0.798
0.3	10	16.3	16.2	0.47	0.48	0.864
3	10	15.8	16.1	0.42	0.48	-1.84
30	10	15.2	15.2	0.61	0.48	0.175

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	11.962542	5	-13.925085
A2	13.491918	8	-10.983835
A3	11.962542	5	-13.925085
fitted	9.41194	3	-12.823879
R	-2.034667	2	8.069334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.0532	6	<0.0001
Test 2	3.05875	3	0.3827
Test 3	3.05875	3	0.3827
Test 4	5.10121	2	0.07803

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery – Hemoglobin (g/dL) in Males

1.3. BMDS Summary of Hemoglobin (g/dL) Males (90 Day Rats GenX)

Table 3. Summary of BMD Modeling Results for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.0113	26.870	41.0	30.5	1.34	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. Selected BMDL is from model with lowest AIC and lowest BMDL.
Exponential (M4) Exponential (M5)[c]	0.787	19.971	5.80	3.23	1.80	
Hill	**0.798**	**19.963**	**5.15**	**2.12**	**2.42**	
Power[d] Polynomial 3°[e] Polynomial 2°[f] Linear	0.0102	27.066	42.9	32.4	1.32	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.294), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 10, and 100 mg/kg/day were 0.18, -0.18, 0.01, 0, respectively.
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.
[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[e] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[f] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

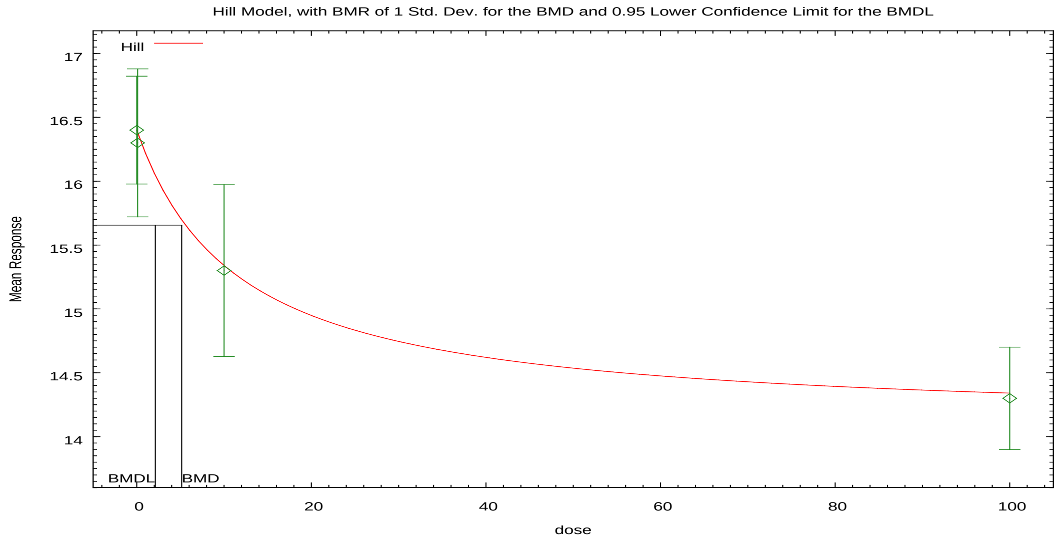

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Figure 19. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 5.14707

BMDL at the 95% confidence level = 2.12258

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.496125	0.55035
rho	n/a	0
intercept	16.3603	16.4
v	-2.30015	-2.1
n	1	1.26758
k	11.6611	9.505

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.4	0.59	0.7	0.178
0.1	10	16.3	16.3	0.81	0.7	-0.183
10	10	15.3	15.3	0.94	0.7	0.00689
100	10	14.3	14.3	0.56	0.7	-0.00182

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC

A1	-5.948773	5	21.897546
A2	-4.092313	8	24.184626
A3	-5.948773	5	21.897546
fitted	-5.981439	4	19.962879
R	-24.012887	2	52.025773

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	39.8411	6	<0.0001
Test 2	3.71292	3	0.2942
Test 3	3.71292	3	0.2942
Test 4	0.0653329	1	0.7983

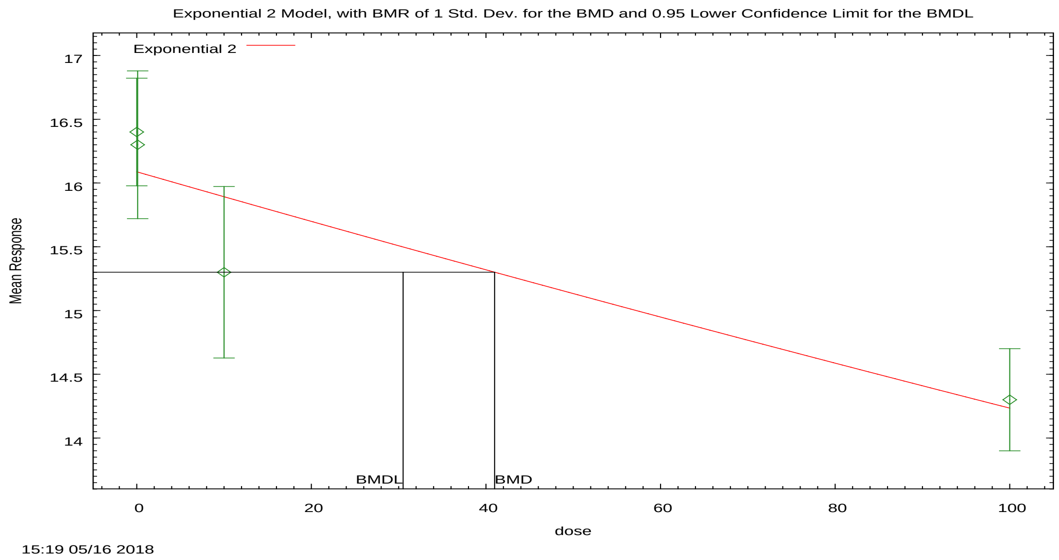

Figure 20. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 40.9903

BMDL at the 95% confidence level = 30.5103

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.478251	-0.702561
rho	n/a	0
a	16.0877	15.0423
b	0.00122412	0.00120888
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.09	0.59	0.79	1.254
0.1	10	16.3	16.09	0.81	0.79	0.8606
10	10	15.3	15.89	0.94	0.79	-2.378
100	10	14.3	14.23	0.56	0.79	0.2645

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-5.948773	5	21.89755
A2	-4.092313	8	24.18463
A3	-5.948773	5	21.89755
R	-24.01289	2	52.02577
2	-10.43498	3	26.86996

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	39.84	6	<0.0001
Test 2	3.713	3	0.2942
Test 3	3.713	3	0.2942
Test 4	8.972	2	0.01126

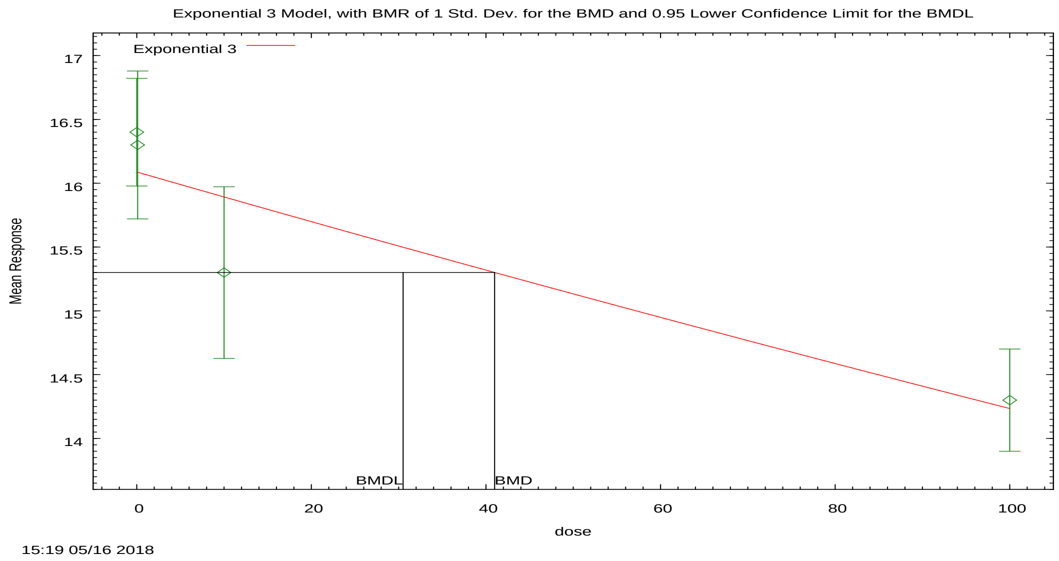

Figure 21. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 40.9903

BMDL at the 95% confidence level = 30.5103

Parameter Estimates

Variable	**Estimate**	**Default Initial Parameter Values**

lnalpha	-0.478251	-0.702561
rho	n/a	0
a	16.0877	15.0423
b	0.00122412	0.00120888
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.09	0.59	0.79	1.254
0.1	10	16.3	16.09	0.81	0.79	0.8606
10	10	15.3	15.89	0.94	0.79	-2.378
100	10	14.3	14.23	0.56	0.79	0.2645

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-5.948773	5	21.89755
A2	-4.092313	8	24.18463
A3	-5.948773	5	21.89755
R	-24.01289	2	52.02577
3	-10.43498	3	26.86996

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	39.84	6	<0.0001
Test 2	3.713	3	0.2942
Test 3	3.713	3	0.2942
Test 5a	8.972	2	0.01126

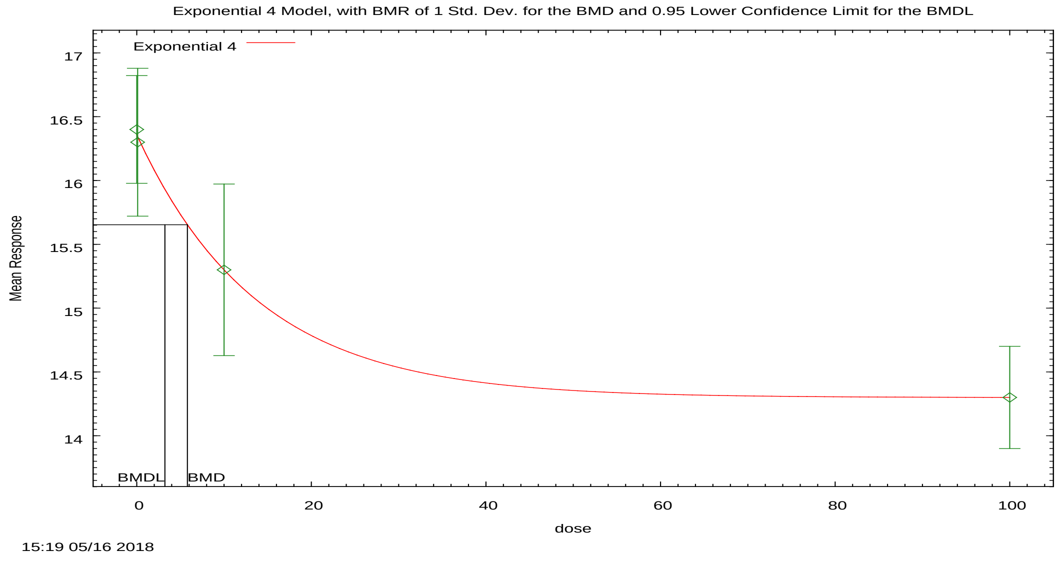

Figure 22. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 5.80078

BMDL at the 95% confidence level = 3.22524

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.700731	-0.702561
rho	n/a	0
a	16.3578	17.22
b	0.0721802	0.0172469
c	0.874119	0.790885

d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.36	0.59	0.7	0.1896
0.1	10	16.3	16.34	0.81	0.7	-0.1929
10	10	15.3	15.3	0.94	0.7	0.003951
100	10	14.3	14.3	0.56	0.7	-0.0006445

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-5.948773	5	21.89755
A2	-4.092313	8	24.18463
A3	-5.948773	5	21.89755
R	-24.01289	2	52.02577
4	-5.985381	4	19.97076

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	39.84	6	<0.0001
Test 2	3.713	3	0.2942
Test 3	3.713	3	0.2942
Test 6a	0.07322	1	0.7867

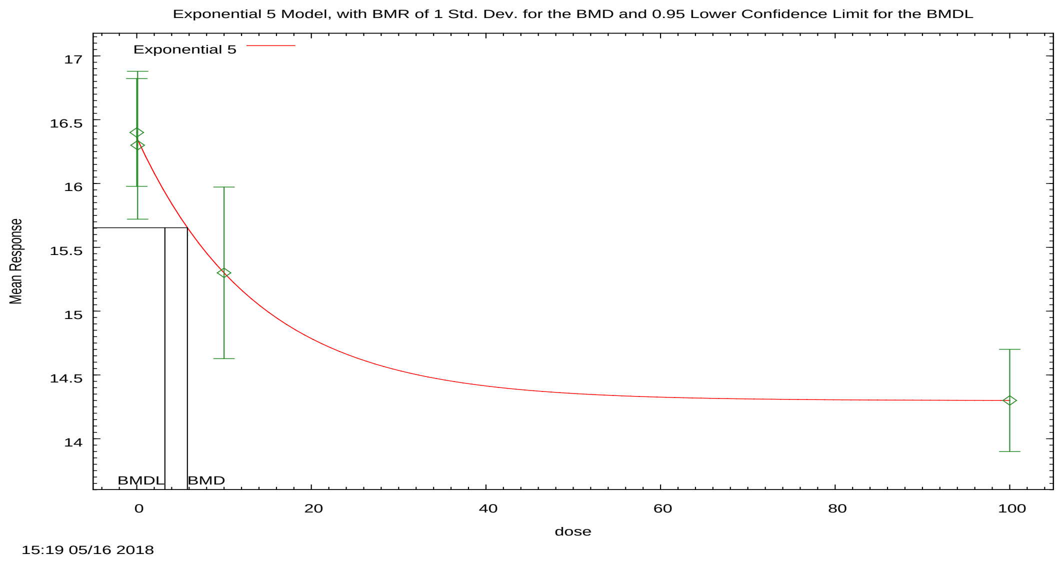

Figure 23. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 5.80078

BMDL at the 95% confidence level = 3.22524

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.700731	-0.702561
rho	n/a	0
a	16.3578	17.22
b	0.0721802	0.0172469
c	0.874119	0.790885

d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.36	0.59	0.7	0.1896
0.1	10	16.3	16.34	0.81	0.7	-0.1929
10	10	15.3	15.3	0.94	0.7	0.003951
100	10	14.3	14.3	0.56	0.7	-0.0006443

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-5.948773	5	21.89755
A2	-4.092313	8	24.18463
A3	-5.948773	5	21.89755
R	-24.01289	2	52.02577
5	-5.985381	4	19.97076

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	39.84	6	<0.0001
Test 2	3.713	3	0.2942
Test 3	3.713	3	0.2942
Test 7a	0.07322	1	0.7867

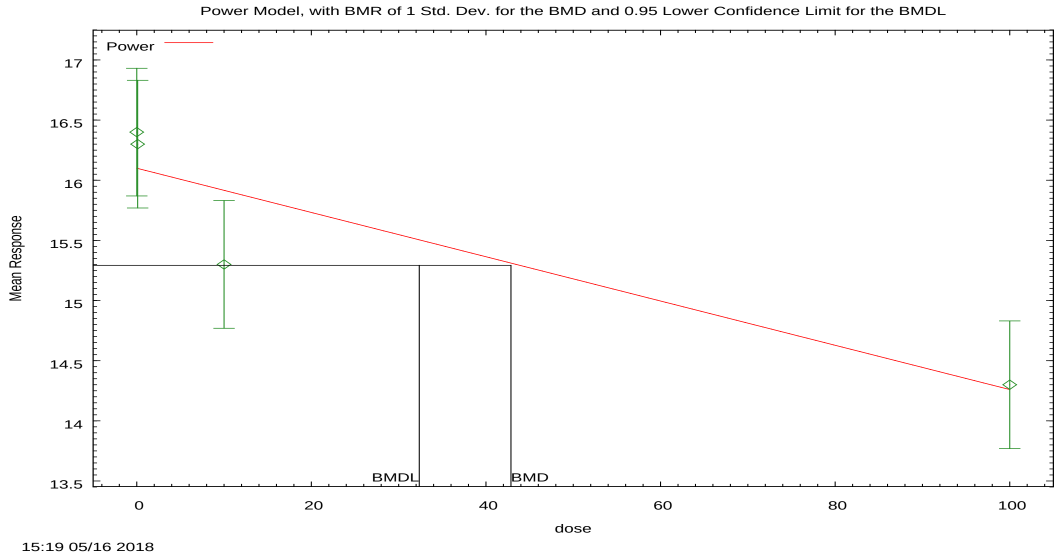

Figure 24. Plot of mean response by dose with fitted curve for Power model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 42.8617

BMDL at the 95% confidence level = 32.3608

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.62292	0.55035
rho	n/a	0
control	16.0818	16.4
slope	-0.0184139	-4.2
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.1	0.59	0.79	1.27
0.1	10	16.3	16.1	0.81	0.79	0.881
10	10	15.3	15.9	0.94	0.79	-2.39
100	10	14.3	14.2	0.56	0.79	0.239

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-5.948773	5	21.897546
A2	-4.092313	8	24.184626
A3	-5.948773	5	21.897546
fitted	-10.533249	3	27.066498
R	-24.012887	2	52.025773

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	39.8411	6	<0.0001
Test 2	3.71292	3	0.2942
Test 3	3.71292	3	0.2942
Test 4	9.16895	2	0.01021

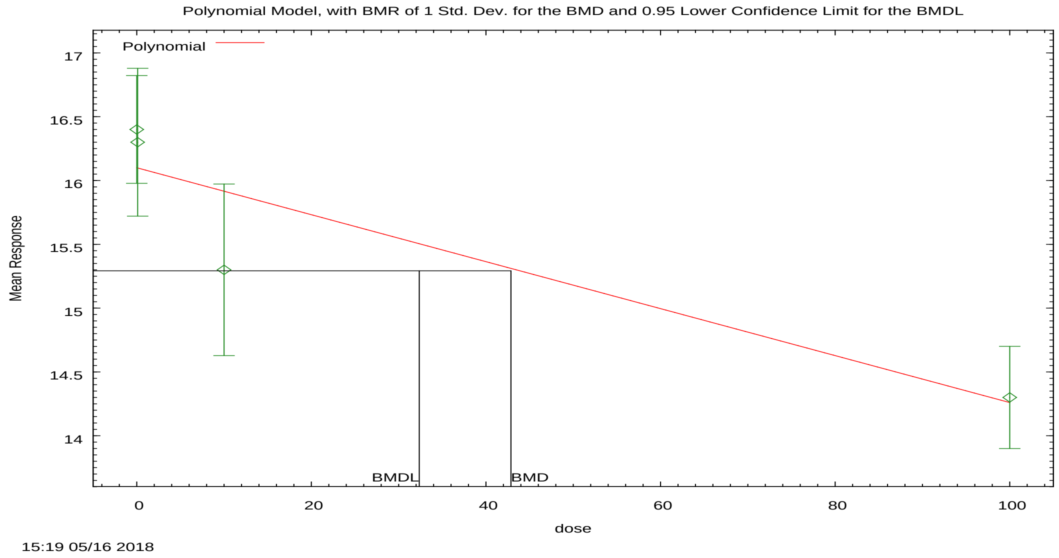

Figure 25. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 42.8617

BMDL at the 95% confidence level = 32.3608

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.62292	0.55035
rho	n/a	0
beta_0	16.0818	16.4
beta_1	-0.0184139	-1.00988
beta_2	0	0

beta_3	0	-0.000889991

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.1	0.59	0.79	1.27
0.1	10	16.3	16.1	0.81	0.79	0.881
10	10	15.3	15.9	0.94	0.79	-2.39
100	10	14.3	14.2	0.56	0.79	0.239

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-5.948773	5	21.897546
A2	-4.092313	8	24.184626
A3	-5.948773	5	21.897546
fitted	-10.533249	3	27.066498
R	-24.012887	2	52.025773

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	39.8411	6	<0.0001
Test 2	3.71292	3	0.2942
Test 3	3.71292	3	0.2942
Test 4	9.16895	2	0.01021

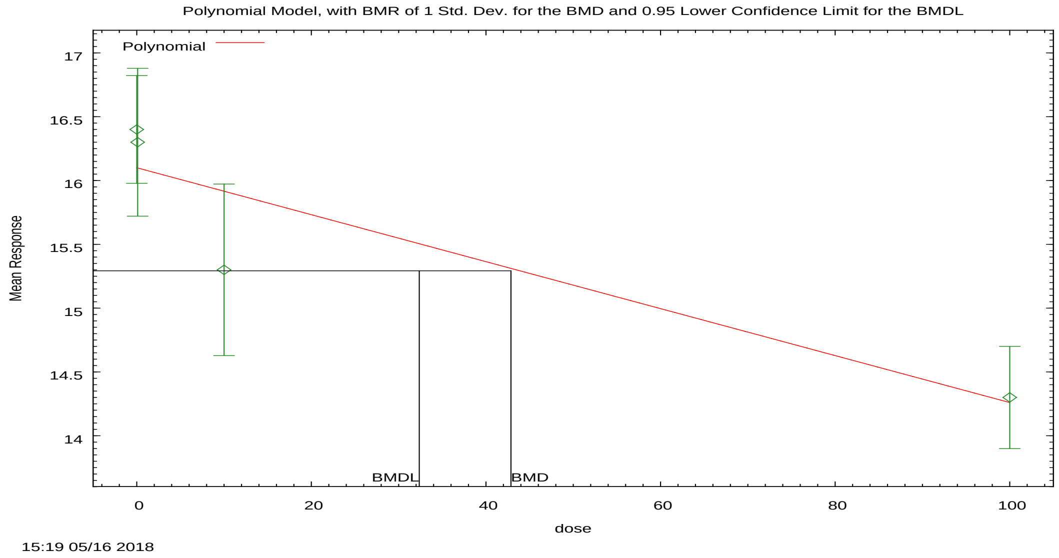

Figure 26. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 42.8617

BMDL at the 95% confidence level = 32.3608

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.62292	0.55035
rho	n/a	0
beta_0	16.0818	16.356
beta_1	-0.0184139	-0.115103
beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.1	0.59	0.79	1.27
0.1	10	16.3	16.1	0.81	0.79	0.881
10	10	15.3	15.9	0.94	0.79	-2.39
100	10	14.3	14.2	0.56	0.79	0.239

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-5.948773	5	21.897546
A2	-4.092313	8	24.184626
A3	-5.948773	5	21.897546
fitted	-10.533249	3	27.066498
R	-24.012887	2	52.025773

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	39.8411	6	<0.0001
Test 2	3.71292	3	0.2942
Test 3	3.71292	3	0.2942
Test 4	9.16895	2	0.01021

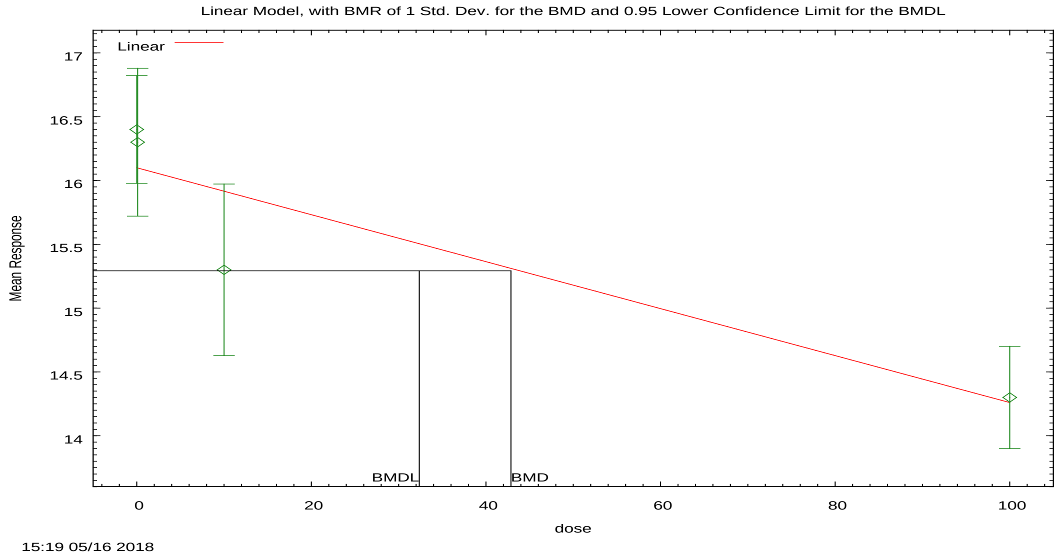

Figure 27. Plot of mean response by dose with fitted curve for Linear model with constant variance for Hemoglobin in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 42.8617

BMDL at the 95% confidence level = 32.3608

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.62292	0.55035
rho	n/a	0
beta_0	16.0818	16.0818
beta_1	-0.0184139	-0.0184139

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16.4	16.1	0.59	0.79	1.27
0.1	10	16.3	16.1	0.81	0.79	0.881
10	10	15.3	15.9	0.94	0.79	-2.39
100	10	14.3	14.2	0.56	0.79	0.239

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-5.948773	5	21.897546
A2	-4.092313	8	24.184626
A3	-5.948773	5	21.897546
fitted	-10.533249	3	27.066498
R	-24.012887	2	52.025773

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	39.8411	6	<0.0001
Test 2	3.71292	3	0.2942
Test 3	3.71292	3	0.2942
Test 4	9.16895	2	0.01021

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats – Hemoglobin (g/dL) at 6-month timepoint in Males

1.4. BMDS Summary of Hemoglobin (g/dL) Males 6 months (2 Year Rats GenX)

Table 4. Summary of BMD Modeling Results for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.439	32.762	37.1	24.5	1.51	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were not sufficiently close (> 3-fold difference), so the lowest BMDL was selected.
Exponential (M3)	0.220	34.621	46.9	24.7	1.90	
Exponential (M4)	**0.439**	**32.762**	**37.1**	**3.55**	**10.4**	
Exponential (M5)	N/A[b]	36.621	29.2	1.08	26.9	
Hill	N/A[b]	36.621	43.5	error[c]	error	
Power	0.220	34.621	46.7	25.3	1.84	
Polynomial 3°	0.471	32.621	45.4	39.8	1.14	
Polynomial 2°	0.470	32.624	43.3	25.3	1.71	
Linear	0.440	32.757	37.4	25.1	1.49	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.115), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 1, and 50 mg/kg/day were -0.03, -0.88, 0.92, -0.02, respectively.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

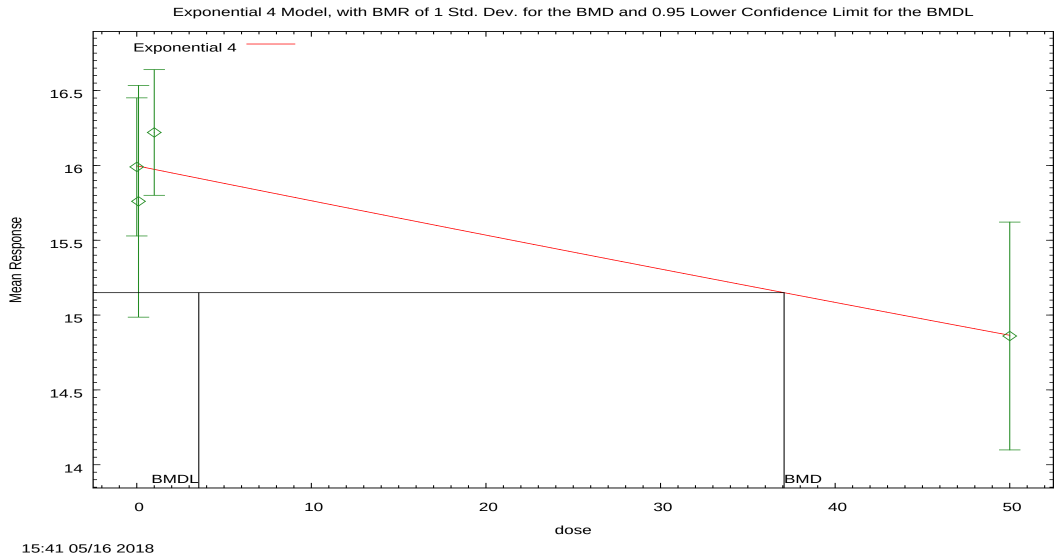

Figure 28. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hemoglobin in Males at 6 months (2-

Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 37.0764

BMDL at the 95% confidence level = 3.55258

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.330954	-0.372125
rho	n/a	0
a	15.997	17.031
b	0.00146813	0.0282075
c	0	0.830978
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	15.99	16	0.64	0.85	-0.02616
0.1	10	15.76	15.99	1.08	0.85	-0.8756
1	10	16.22	15.97	0.59	0.85	0.9196
50	10	14.86	14.86	1.06	0.85	-0.01788

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.5575	5	35.115
A2	-9.588901	8	35.1778

A3	-12.5575	5	35.115
R	-19.08199	2	42.16398
4	-13.38092	3	32.76184

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.99	6	0.004187
Test 2	5.937	3	0.1147
Test 3	5.937	3	0.1147
Test 6a	1.647	2	0.4389

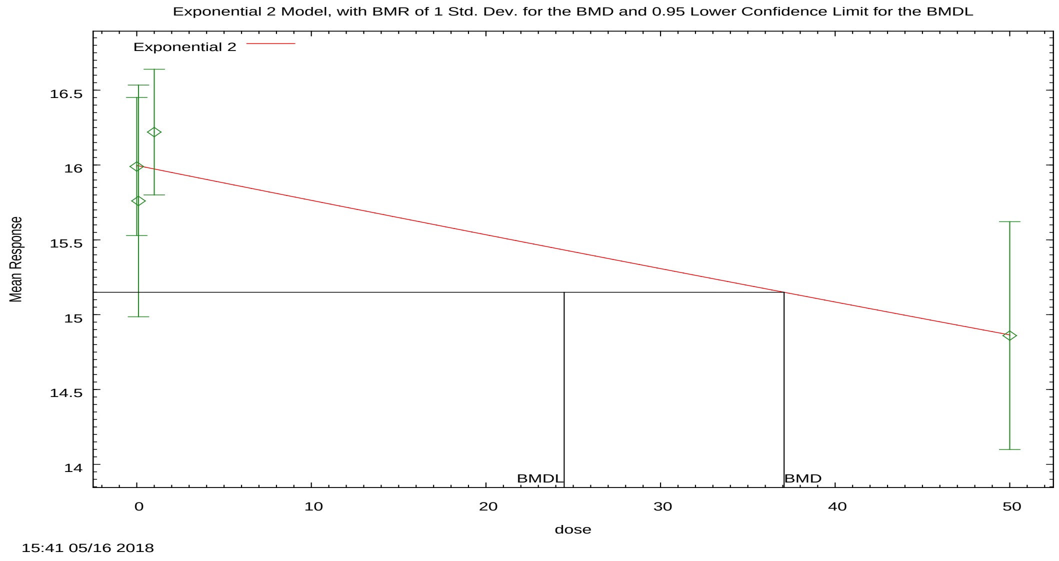

Figure 29. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 37.0764

BMDL at the 95% confidence level = 24.4798

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.330954	-0.372125
rho	n/a	0
a	15.997	15.4073
b	0.00146813	0.00146778
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	15.99	16	0.64	0.85	-0.02617
0.1	10	15.76	15.99	1.08	0.85	-0.8756
1	10	16.22	15.97	0.59	0.85	0.9196
50	10	14.86	14.86	1.06	0.85	-0.01788

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.5575	5	35.115
A2	-9.588901	8	35.1778
A3	-12.5575	5	35.115
R	-19.08199	2	42.16398
2	-13.38092	3	32.76184

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.99	6	0.004187
Test 2	5.937	3	0.1147

Test 3	5.937	3	0.1147
Test 4	1.647	2	0.4389

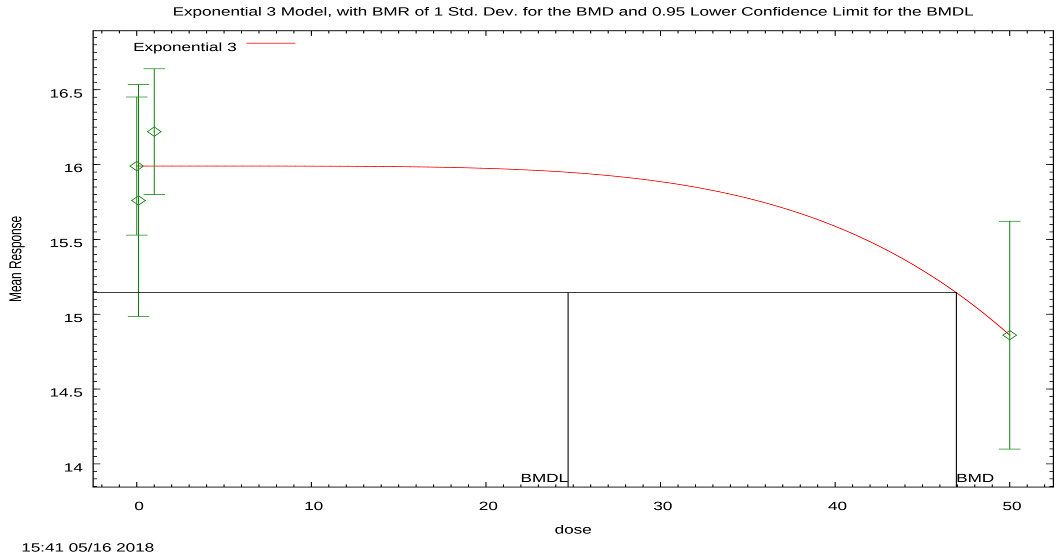

Figure 30. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 46.9404

BMDL at the 95% confidence level = 24.704

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.334469	-0.372125

rho	n/a	0
a	15.99	15.4073
b	0.0115132	0.00146778
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	15.99	15.99	0.64	0.85	-0.000000004659
0.1	10	15.76	15.99	1.08	0.85	-0.8597
1	10	16.22	15.99	0.59	0.85	0.8597
50	10	14.86	14.86	1.06	0.85	0.00000003753

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.5575	5	35.115
A2	-9.588901	8	35.1778
A3	-12.5575	5	35.115
R	-19.08199	2	42.16398
3	-13.31062	4	34.62125

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.99	6	0.004187
Test 2	5.937	3	0.1147
Test 3	5.937	3	0.1147
Test 5a	1.506	1	0.2197

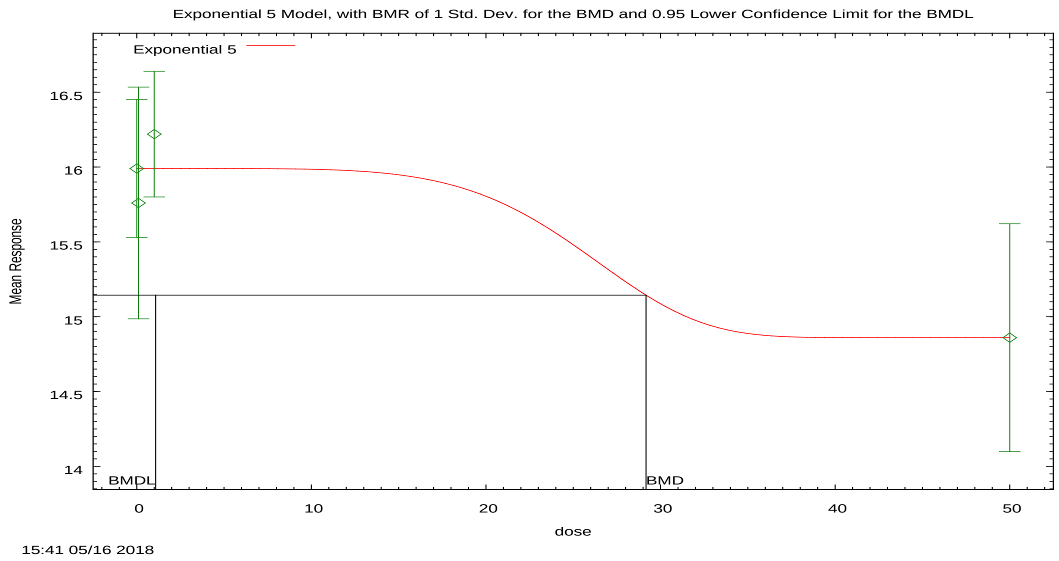

Figure 31. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 29.1698

BMDL at the 95% confidence level = 1.08248

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.334469	-0.372125
rho	n/a	0
a	15.99	17.031
b	0.0363876	0.0282075

c	0.929331	0.830978
d	5.41582	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	15.99	15.99	0.64	0.85	-0.00000009368
0.1	10	15.76	15.99	1.08	0.85	-0.8597
1	10	16.22	15.99	0.59	0.85	0.8597
50	10	14.86	14.86	1.06	0.85	-0.0000002029

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.5575	5	35.115
A2	-9.588901	8	35.1778
A3	-12.5575	5	35.115
R	-19.08199	2	42.16398
5	-13.31062	5	36.62125

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.99	6	0.004187
Test 2	5.937	3	0.1147
Test 3	5.937	3	0.1147
Test 7a	1.506	0	N/A

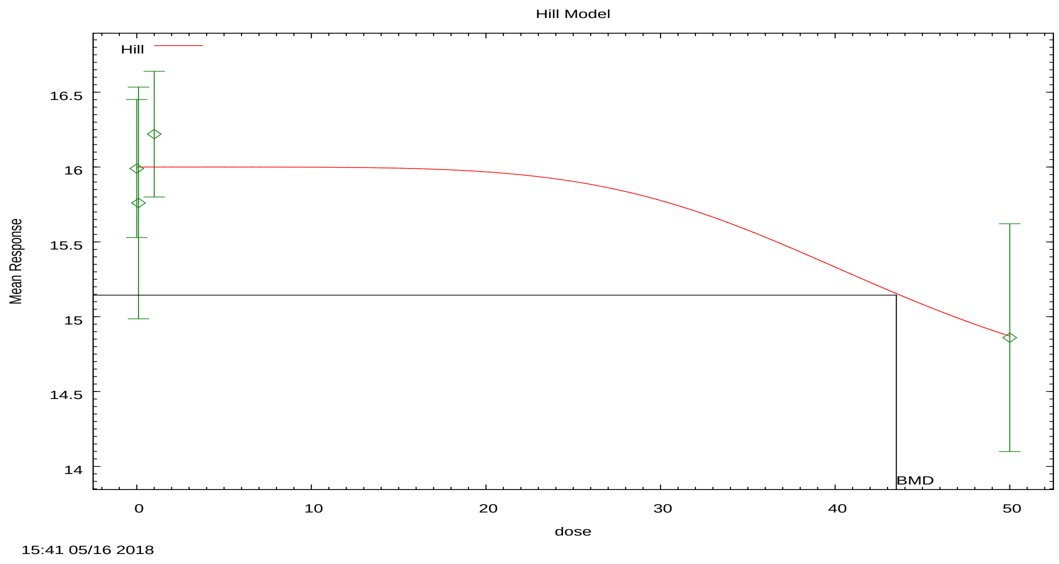

Figure 32. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 43.5036

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.715718	0.765854
rho	n/a	0
intercept	15.99	15.99
v	-1.67847	-1.13

n	5.07771	0.239697
k	43.3656	29.6434

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16	16	0.64	0.85	-0.0000000173
0.1	10	15.8	16	1.08	0.85	-0.86
1	10	16.2	16	0.59	0.85	0.86
50	10	14.9	14.9	1.06	0.85	0.000000308

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.557502	5	35.115004
A2	-9.588901	8	35.177802
A3	-12.557502	5	35.115004
fitted	-13.310623	5	36.621247
R	-19.081988	2	42.163976

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.9862	6	0.004187
Test 2	5.9372	3	0.1147
Test 3	5.9372	3	0.1147
Test 4	1.50624	0	N/A

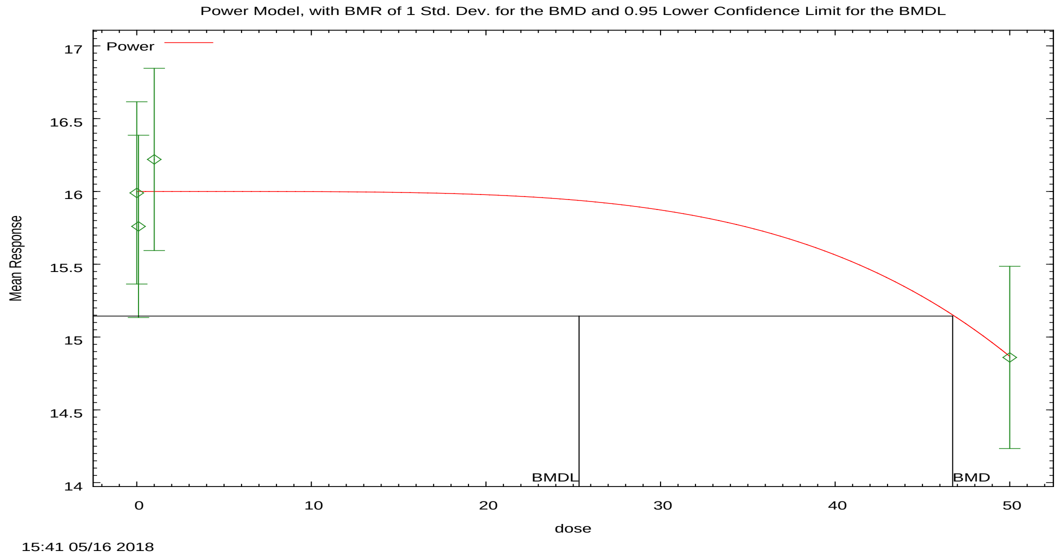

Figure 33. Plot of mean response by dose with fitted curve for Power model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 46.7298

BMDL at the 95% confidence level = 25.3338

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.715718	0.765854
rho	n/a	0
control	15.99	14.86
slope	-0.0000000606318	1.36
power	4.27929	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16	16	0.64	0.85	-0.0000000602
0.1	10	15.8	16	1.08	0.85	-0.86
1	10	16.2	16	0.59	0.85	0.86
50	10	14.9	14.9	1.06	0.85	-0.0000000458

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.557502	5	35.115004
A2	-9.588901	8	35.177802
A3	-12.557502	5	35.115004
fitted	-13.310623	4	34.621247
R	-19.081988	2	42.163976

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.9862	6	0.004187
Test 2	5.9372	3	0.1147
Test 3	5.9372	3	0.1147
Test 4	1.50624	1	0.2197

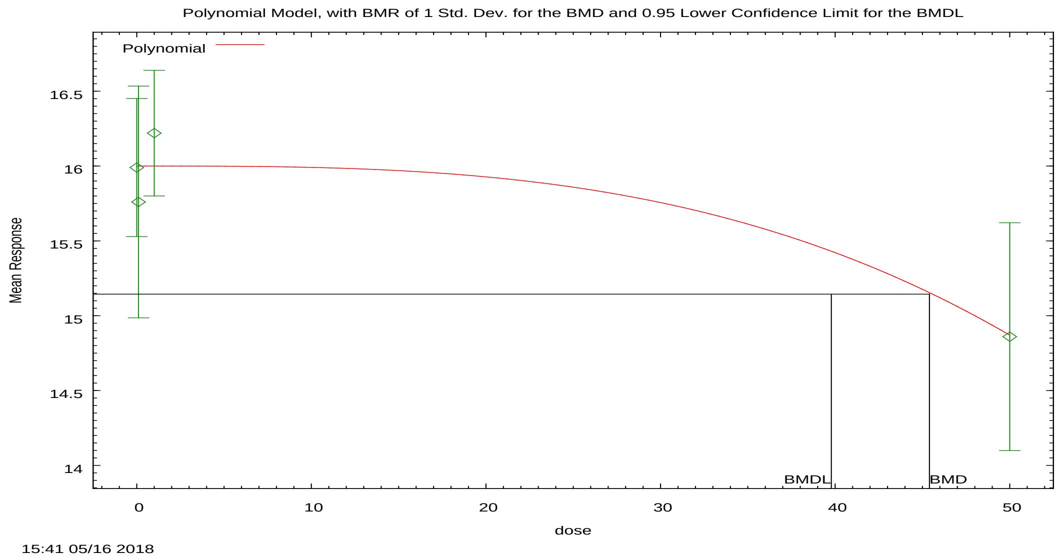

Figure 34. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 45.4012

BMDL at the 95% confidence level = 39.7802

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.715719	0.765854
rho	n/a	0
beta_0	15.99	15.99
beta_1	-8.20886E-24	-2.58676
beta_2	-9.65457E-27	0

beta_3	-0.00000904001	-0.0564382

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16	16	0.64	0.85	-0.00000858
0.1	10	15.8	16	1.08	0.85	-0.86
1	10	16.2	16	0.59	0.85	0.86
50	10	14.9	14.9	1.06	0.85	-0.00000577

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.557502	5	35.115004
A2	-9.588901	8	35.177802
A3	-12.557502	5	35.115004
fitted	-13.310652	3	32.621305
R	-19.081988	2	42.163976

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.9862	6	0.004187
Test 2	5.9372	3	0.1147
Test 3	5.9372	3	0.1147
Test 4	1.5063	2	0.4709

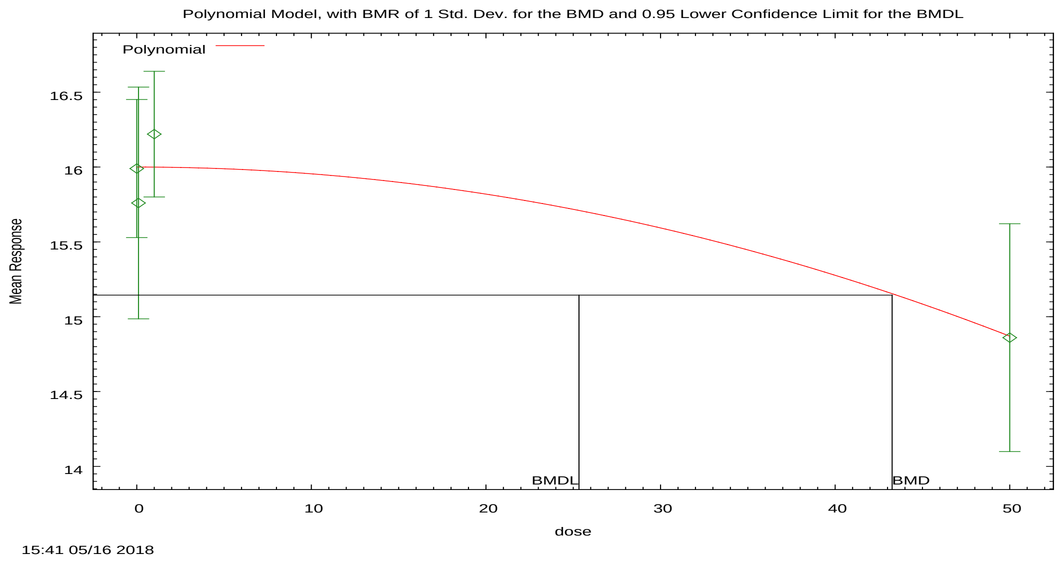

Figure 35. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 43.2632

BMDL at the 95% confidence level = 25.3293

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.71577	0.765854
rho	n/a	0
beta_0	15.9901	15.8647
beta_1	0	0
beta_2	-0.000452012	-0.00737093

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16	16	0.64	0.85	-0.000454
0.1	10	15.8	16	1.08	0.85	-0.86
1	10	16.2	16	0.59	0.85	0.861
50	10	14.9	14.9	1.06	0.85	-0.00034

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.557502	5	35.115004
A2	-9.588901	8	35.177802
A3	-12.557502	5	35.115004
fitted	-13.312062	3	32.624125
R	-19.081988	2	42.163976

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.9862	6	0.004187
Test 2	5.9372	3	0.1147
Test 3	5.9372	3	0.1147
Test 4	1.50912	2	0.4702

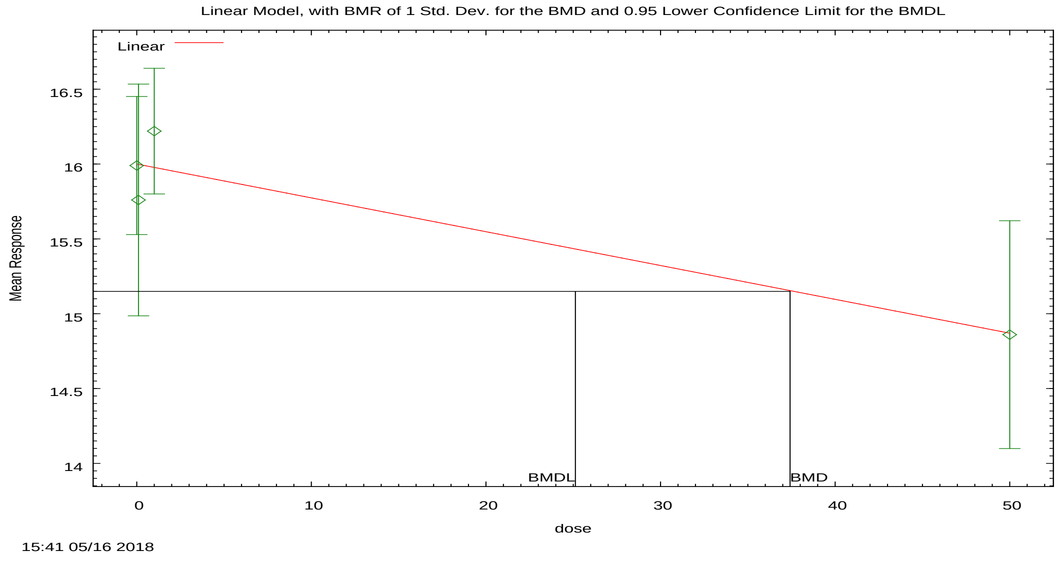

Figure 36. Plot of mean response by dose with fitted curve for Linear model with constant variance for Hemoglobin in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 37.4185

BMDL at the 95% confidence level = 25.1224

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.718147	0.765854
rho	n/a	0
beta_0	15.9968	15.9968
beta_1	-0.0226475	-0.0226475

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	16	16	0.64	0.85	-0.0255
0.1	10	15.8	16	1.08	0.85	-0.875
1	10	16.2	16	0.59	0.85	0.917
50	10	14.9	14.9	1.06	0.85	-0.0166

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-12.557502	5	35.115004
A2	-9.588901	8	35.177802
A3	-12.557502	5	35.115004
fitted	-13.378368	3	32.756735
R	-19.081988	2	42.163976

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	18.9862	6	0.004187
Test 2	5.9372	3	0.1147
Test 3	5.9372	3	0.1147
Test 4	1.64173	2	0.4401

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Hematocrit (%) in Males

1.5. BMDS Summary of Hematocrit (%) Males (28 Day Mice GenX)

Table 5. Summary of BMD Modeling Results for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	BMDL_{1SD} (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.0259	68.525	26.6	16.2	1.64	Only one model met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from this model.
Exponential (M4)	0.0743	66.399	2.55	0.00599	426	
Exponential (M5)	0.0743	66.399	2.55	0.00658	388	
Hill	**0.416**	**63.876**	**0.122**	**0.00589**	**20.7**	
Power[c] Polynomial 3°[d] Polynomial 2°[e] Linear	0.0256	68.545	26.8	16.5	1.62	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.555), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were 0.01, -0.06, 0.61, -0.53, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[d] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[e] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

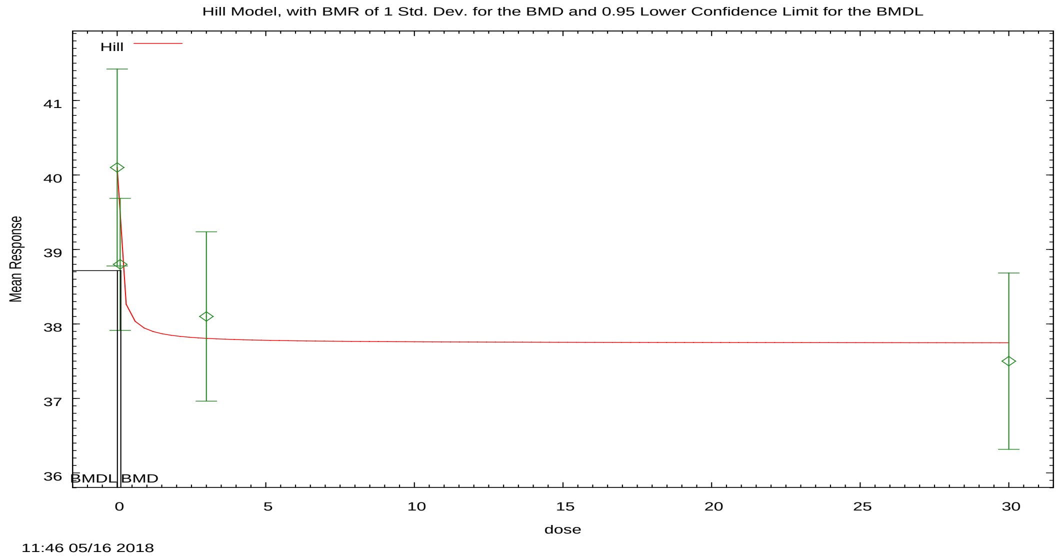

Figure 37. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.121759

BMDL at the 95% confidence level = 0.00588873

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	1.90295	2.11508
rho	n/a	0
intercept	40.0946	40.1
v	-2.35783	-2.6
n	1	0.176992
k	0.0863544	0.1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	40.1	40.1	1.72	1.38	0.0117
0.1	8	38.8	38.8	1.06	1.38	-0.0602
3	8	38.1	37.8	1.36	1.38	0.609
30	9	37.5	37.7	1.54	1.38	-0.53

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC

A1	-27.606801	5	65.213603
A2	-26.564691	8	69.129382
A3	-27.606801	5	65.213603
fitted	-27.937879	4	63.875758
R	-34.799167	2	73.598334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.469	6	0.01145
Test 2	2.08422	3	0.5551
Test 3	2.08422	3	0.5551
Test 4	0.662155	1	0.4158

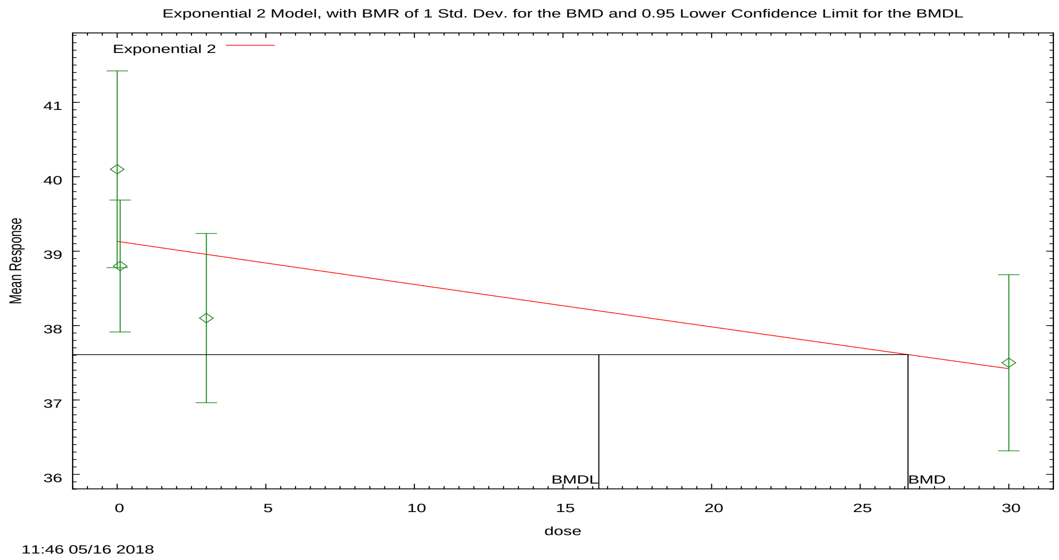

Figure 38. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 26.6079

BMDL at the 95% confidence level = 16.2043

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.838957	0.623929
rho	n/a	0
a	39.1306	38.1316
b	0.00149016	0.00147576
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	40.1	39.13	1.72	1.52	1.912
0.1	8	38.8	39.12	1.06	1.52	-0.6038
3	8	38.1	38.96	1.36	1.52	-1.592
30	9	37.5	37.42	1.54	1.52	0.1582

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-27.6068	5	65.2136
A2	-26.56469	8	69.12938
A3	-27.6068	5	65.2136
R	-34.79917	2	73.59833
2	-31.26227	3	68.52455

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	16.47	6	0.01145
Test 2	2.084	3	0.5551
Test 3	2.084	3	0.5551
Test 4	7.311	2	0.02585

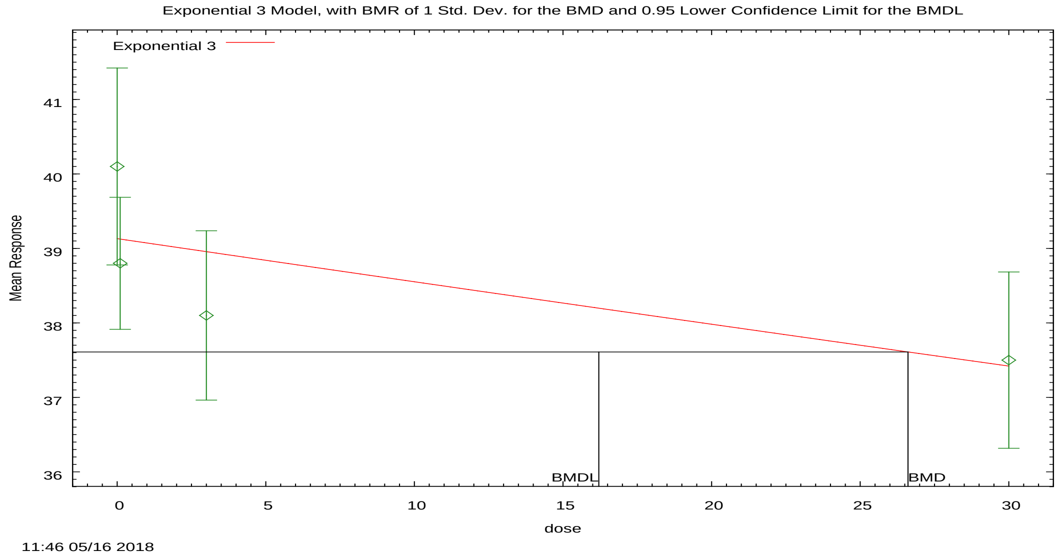

Figure 39. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 26.6079

BMDL at the 95% confidence level = 16.2043

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values

lnalpha	0.838957	0.623929
rho	n/a	0
a	39.1306	38.1316
b	0.00149016	0.00147576
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	40.1	39.13	1.72	1.52	1.912
0.1	8	38.8	39.12	1.06	1.52	-0.6038
3	8	38.1	38.96	1.36	1.52	-1.592
30	9	37.5	37.42	1.54	1.52	0.1582

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-27.6068	5	65.2136
A2	-26.56469	8	69.12938
A3	-27.6068	5	65.2136
R	-34.79917	2	73.59833
3	-31.26227	3	68.52455

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.47	6	0.01145
Test 2	2.084	3	0.5551
Test 3	2.084	3	0.5551
Test 5a	7.311	2	0.02585

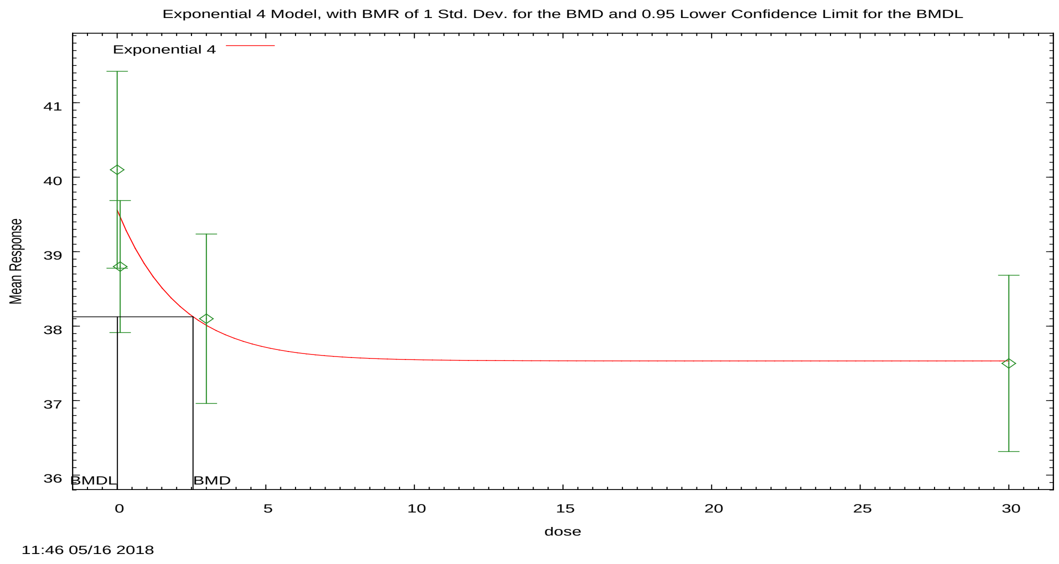

Figure 40. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.55178

BMDL at the 95% confidence level = 0.00599229

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.717617	0.623929
rho	n/a	0
a	39.5575	42.105
b	0.481184	0.0454117
c	0.948817	0.84822

d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	40.1	39.56	1.72	1.43	1.137
0.1	8	38.8	39.46	1.06	1.43	-1.309
3	8	38.1	38.01	1.36	1.43	0.1761
30	9	37.5	37.53	1.54	1.43	-0.06887

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-27.6068	5	65.2136
A2	-26.56469	8	69.12938
A3	-27.6068	5	65.2136
R	-34.79917	2	73.59833
4	-29.19949	4	66.39898

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.47	6	0.01145
Test 2	2.084	3	0.5551
Test 3	2.084	3	0.5551
Test 6a	3.185	1	0.0743

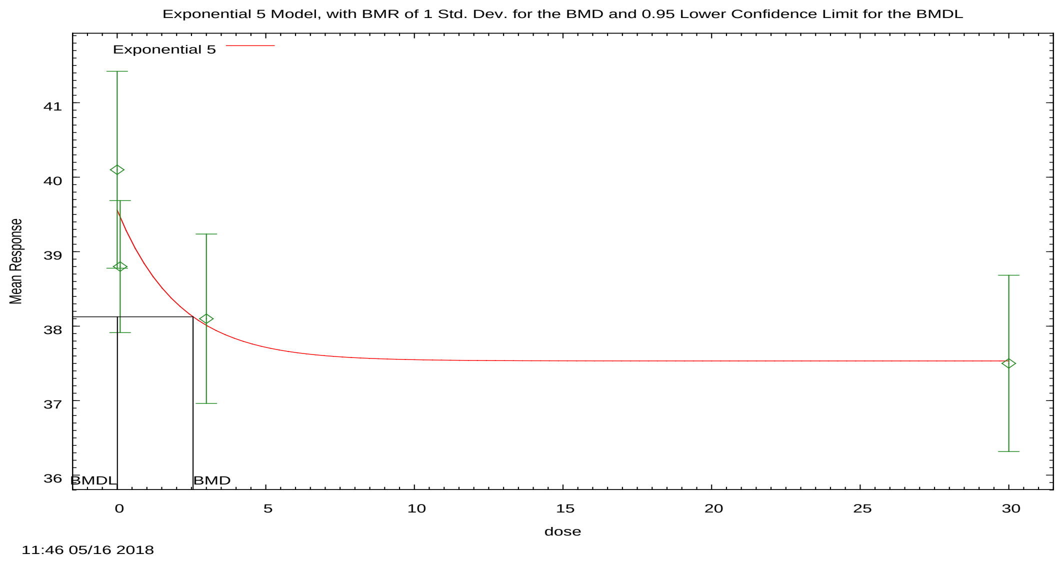

Figure 41. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.55177

BMDL at the 95% confidence level = 0.00657763

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.717617	0.623929
rho	n/a	0
a	39.5575	42.105
b	0.481185	0.0454117
c	0.948817	0.84822

d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	40.1	39.56	1.72	1.43	1.137
0.1	8	38.8	39.46	1.06	1.43	-1.309
3	8	38.1	38.01	1.36	1.43	0.1761
30	9	37.5	37.53	1.54	1.43	-0.06887

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-27.6068	5	65.2136
A2	-26.56469	8	69.12938
A3	-27.6068	5	65.2136
R	-34.79917	2	73.59833
5	-29.19949	4	66.39898

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.47	6	0.01145
Test 2	2.084	3	0.5551
Test 3	2.084	3	0.5551
Test 7a	3.185	1	0.0743

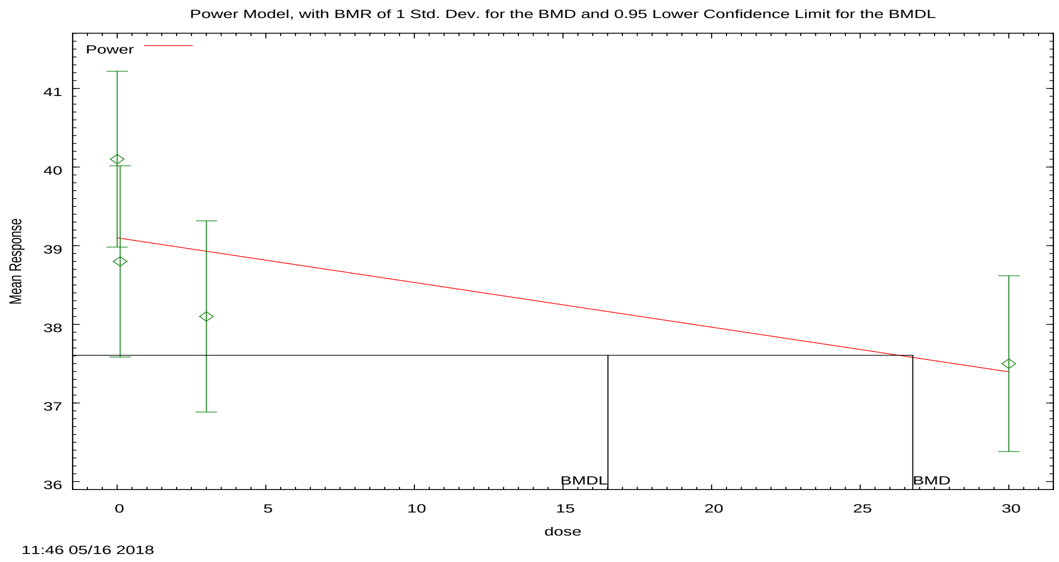

Figure 42. Plot of mean response by dose with fitted curve for Power model with constant variance for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 26.7678

BMDL at the 95% confidence level = 16.5116

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.31536	2.11508
rho	n/a	0
control	39.1282	40.1
slope	-0.0568457	-5.63333
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	40.1	39.1	1.72	1.52	1.92
0.1	8	38.8	39.1	1.06	1.52	-0.599
3	8	38.1	39	1.36	1.52	-1.59
30	9	37.5	37.4	1.54	1.52	0.152

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-27.606801	5	65.213603
A2	-26.564691	8	69.129382
A3	-27.606801	5	65.213603
fitted	-31.272636	3	68.545272
R	-34.799167	2	73.598334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.469	6	0.01145
Test 2	2.08422	3	0.5551
Test 3	2.08422	3	0.5551
Test 4	7.33167	2	0.02558

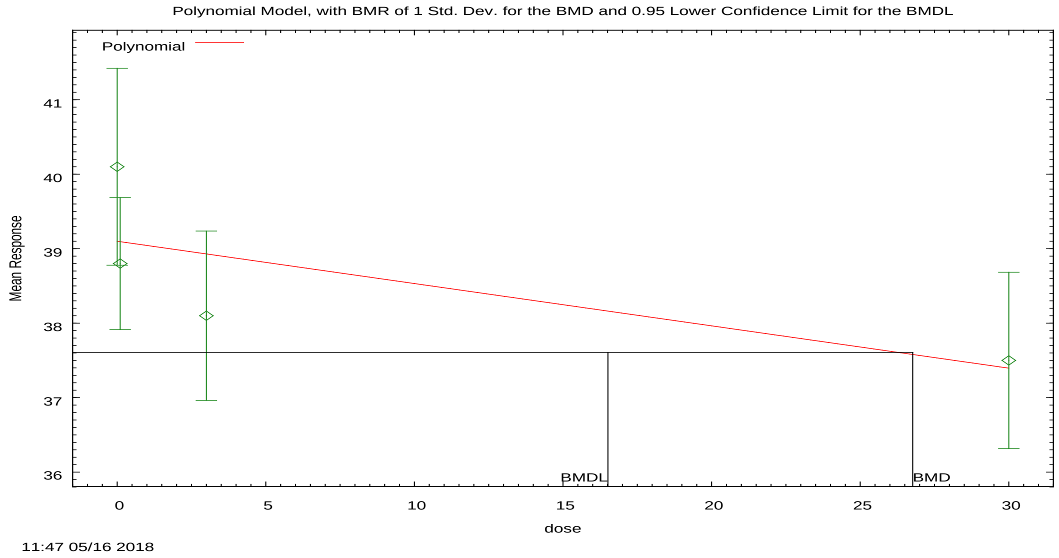

Figure 43. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 26.7678

BMDL at the 95% confidence level = 16.5116

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.31536	2.11508
rho	n/a	0
beta_0	39.1282	40.1
beta_1	-0.0568457	-13.4677
beta_2	0	0

beta_3	0	-0.141518

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	40.1	39.1	1.72	1.52	1.92
0.1	8	38.8	39.1	1.06	1.52	-0.599
3	8	38.1	39	1.36	1.52	-1.59
30	9	37.5	37.4	1.54	1.52	0.152

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-27.606801	5	65.213603
A2	-26.564691	8	69.129382
A3	-27.606801	5	65.213603
fitted	-31.272636	3	68.545272
R	-34.799167	2	73.598334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.469	6	0.01145
Test 2	2.08422	3	0.5551
Test 3	2.08422	3	0.5551
Test 4	7.33167	2	0.02558

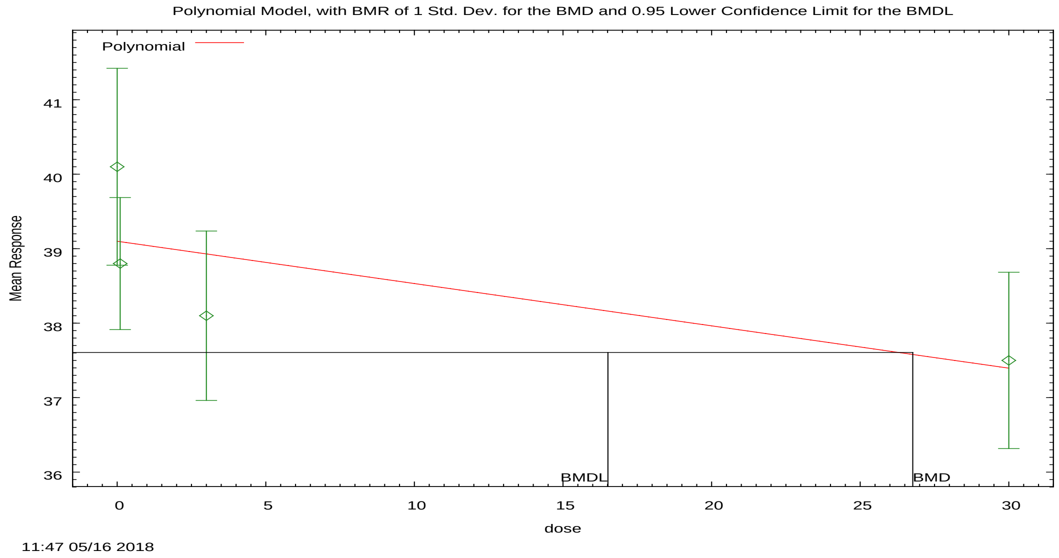

Figure 44. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 26.7678

BMDL at the 95% confidence level = 16.5116

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.31536	2.11508
rho	n/a	0
beta_0	39.1282	39.4873
beta_1	-0.0568457	-0.515152
beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	40.1	39.1	1.72	1.52	1.92
0.1	8	38.8	39.1	1.06	1.52	-0.599
3	8	38.1	39	1.36	1.52	-1.59
30	9	37.5	37.4	1.54	1.52	0.152

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-27.606801	5	65.213603
A2	-26.564691	8	69.129382
A3	-27.606801	5	65.213603
fitted	-31.272636	3	68.545272
R	-34.799167	2	73.598334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.469	6	0.01145
Test 2	2.08422	3	0.5551
Test 3	2.08422	3	0.5551
Test 4	7.33167	2	0.02558

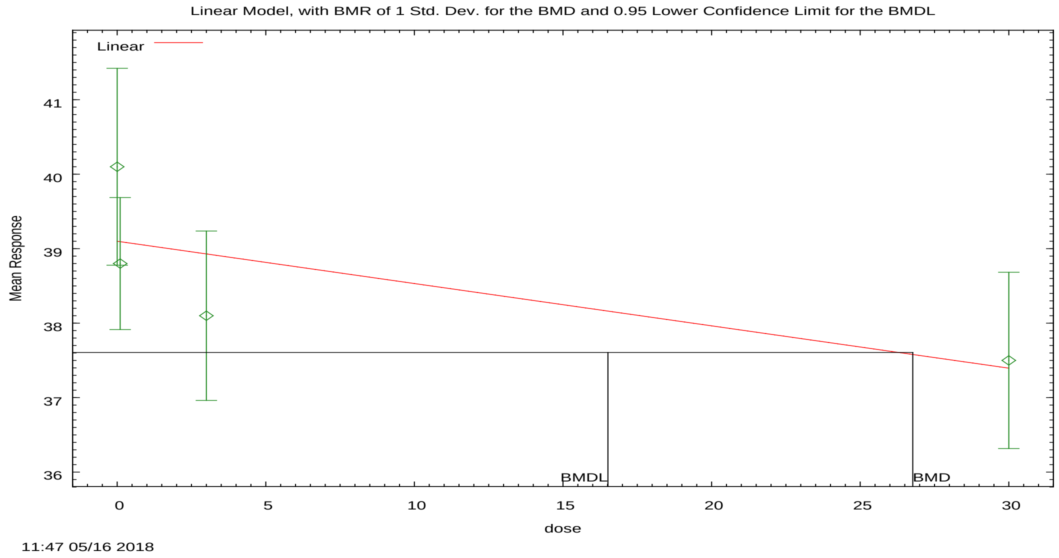

Figure 45. Plot of mean response by dose with fitted curve for Linear model with constant variance for Hematocrit in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 26.7678

BMDL at the 95% confidence level = 16.5116

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.31536	2.11508
rho	n/a	0
beta_0	39.1282	39.085
beta_1	-0.0568457	-0.055593

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	9	40.1	39.1	1.72	1.52	1.92
0.1	8	38.8	39.1	1.06	1.52	-0.599
3	8	38.1	39	1.36	1.52	-1.59
30	9	37.5	37.4	1.54	1.52	0.152

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-27.606801	5	65.213603
A2	-26.564691	8	69.129382
A3	-27.606801	5	65.213603
fitted	-31.272636	3	68.545272
R	-34.799167	2	73.598334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.469	6	0.01145
Test 2	2.08422	3	0.5551
Test 3	2.08422	3	0.5551
Test 4	7.33167	2	0.02558

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery – Hematocrit (%) in Males

1.6. BMDS Summary of Hematocrit (%) Males (28 Day Rats GenX)

Table 6. Summary of BMD Modeling Results for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.0164	83.111	16.2	11.6	1.41	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. Selected BMDL is from model with lowest AIC and lowest BMDL.
Exponential (M4) Exponential (M5)[c]	0.53	77.289	1.76	0.738	2.39	
Hill	**0.676**	**77.070**	**1.35**	**0.357**	**3.78**	
Power[d] Polynomial 3°[e] Polynomial 2°[f] Linear	0.0159	83.185	16.6	11.9	1.39	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.908), selected model in bold; scaled residuals for selected model for doses 0, 0.3, 3, and 30 mg/kg/day were 0.22, -0.32, 0.15, -0.05, respectively.
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.
[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[e] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[f] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

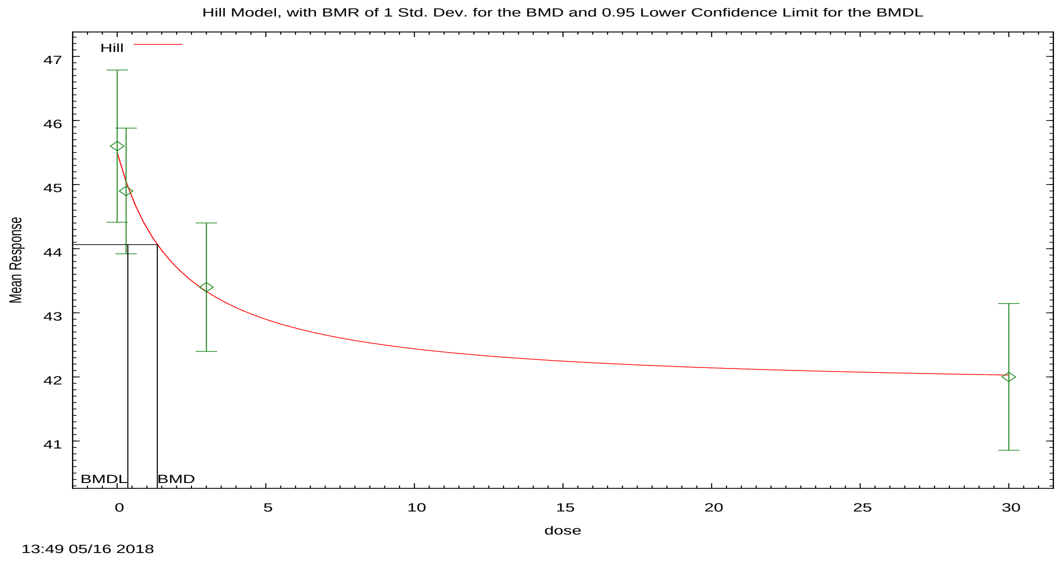

Figure 46. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.35004

BMDL at the 95% confidence level = 0.357169

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.06835	2.28813
rho	n/a	0
intercept	45.501	45.6
v	-3.72485	-3.6
n	1	1.17389
k	2.14654	2.28

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	45.5	1.66	1.44	0.218
0.3	10	44.9	45	1.37	1.44	-0.317
3	10	43.4	43.3	1.4	1.44	0.154
30	10	42	42	1.6	1.44	-0.0548

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.447444	5	78.894888
A2	-34.173832	8	84.347664
A3	-34.447444	5	78.894888
fitted	-34.535063	4	77.070127
R	-47.681776	2	99.363552

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.0159	6	0.0001438
Test 2	0.547224	3	0.9084
Test 3	0.547224	3	0.9084
Test 4	0.175239	1	0.6755

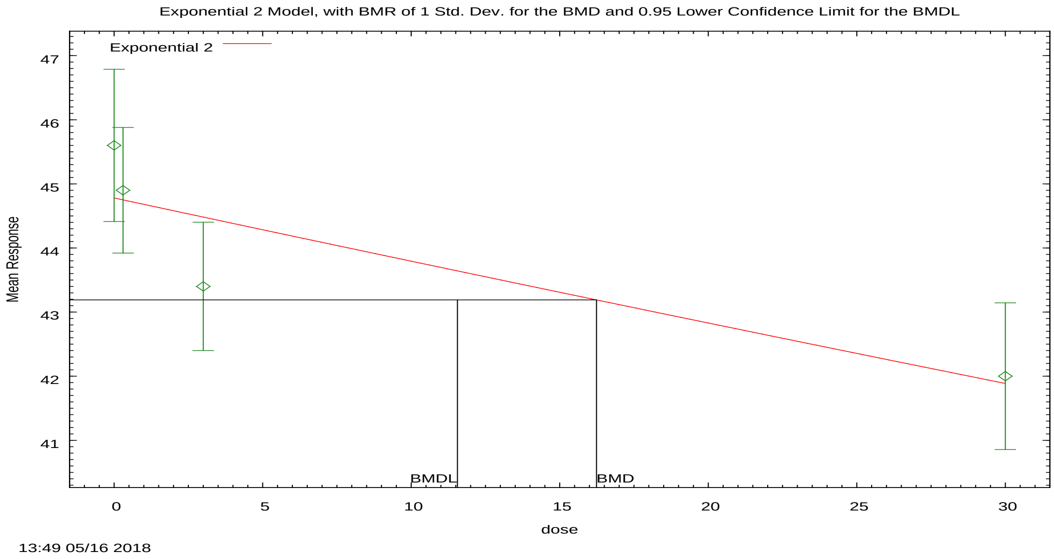

Figure 47. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 16.2379

BMDL at the 95% confidence level = 11.5562

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.92777	0.722372
rho	n/a	0
a	44.7804	43.1524
b	0.00222676	0.00220782
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	44.78	1.66	1.59	1.63
0.3	10	44.9	44.75	1.37	1.59	0.2973
3	10	43.4	44.48	1.4	1.59	-2.152
30	10	42	41.89	1.6	1.59	0.2254

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.44744	5	78.89489
A2	-34.17383	8	84.34766
A3	-34.44744	5	78.89489
R	-47.68178	2	99.36355
2	-38.5554	3	83.11081

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.02	6	0.0001438
Test 2	0.5472	3	0.9084
Test 3	0.5472	3	0.9084
Test 4	8.216	2	0.01644

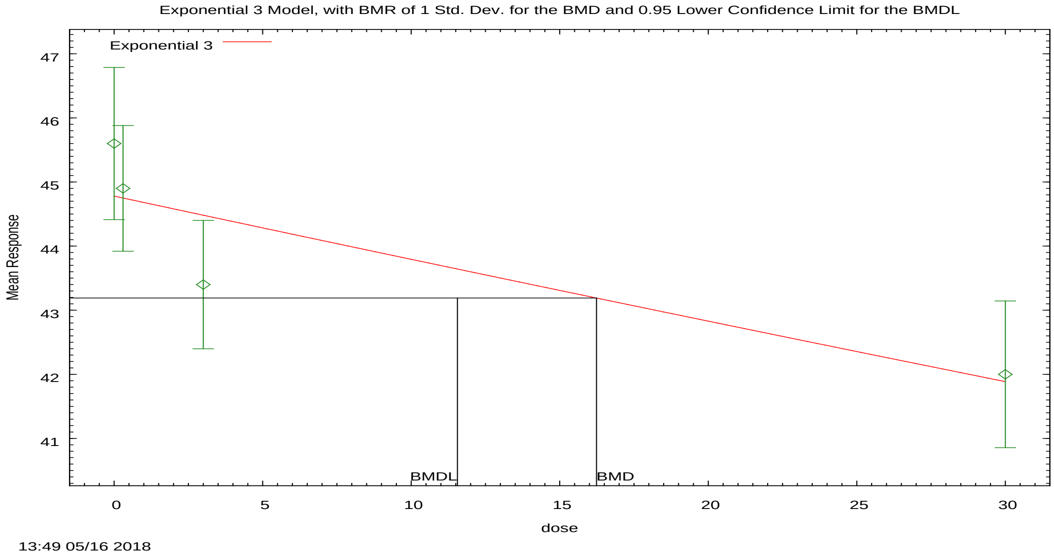

Figure 48. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 16.2379

BMDL at the 95% confidence level = 11.5562

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.92777	0.722372
rho	n/a	0
a	44.7804	43.1524
b	0.00222676	0.00220782
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	44.78	1.66	1.59	1.63
0.3	10	44.9	44.75	1.37	1.59	0.2973
3	10	43.4	44.48	1.4	1.59	-2.152
30	10	42	41.89	1.6	1.59	0.2254

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.44744	5	78.89489
A2	-34.17383	8	84.34766
A3	-34.44744	5	78.89489
R	-47.68178	2	99.36355
3	-38.5554	3	83.11081

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.02	6	0.0001438
Test 2	0.5472	3	0.9084
Test 3	0.5472	3	0.9084
Test 5a	8.216	2	0.01644

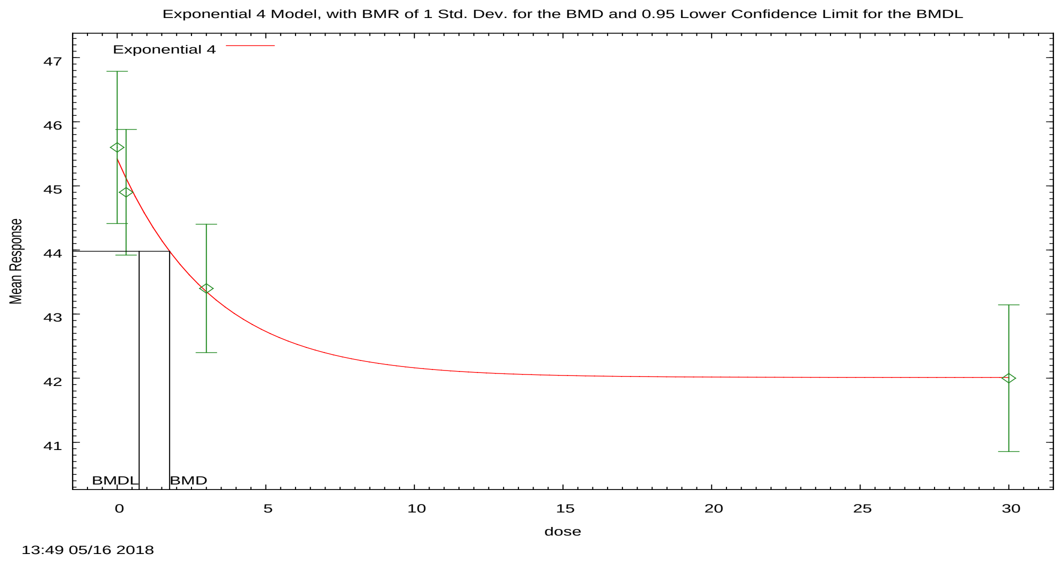

Figure 49. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.76258

BMDL at the 95% confidence level = 0.738122

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.732232	0.722372
rho	n/a	0
a	45.4219	47.88
b	0.31179	0.0481796
c	0.924905	0.835422

d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	45.42	1.66	1.44	0.3906
0.3	10	44.9	45.12	1.37	1.44	-0.4765
3	10	43.4	43.35	1.4	1.44	0.1106
30	10	42	42.01	1.6	1.44	-0.02467

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.44744	5	78.89489
A2	-34.17383	8	84.34766
A3	-34.44744	5	78.89489
R	-47.68178	2	99.36355
4	-34.64464	4	77.28927

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.02	6	0.0001438
Test 2	0.5472	3	0.9084
Test 3	0.5472	3	0.9084
Test 6a	0.3944	1	0.53

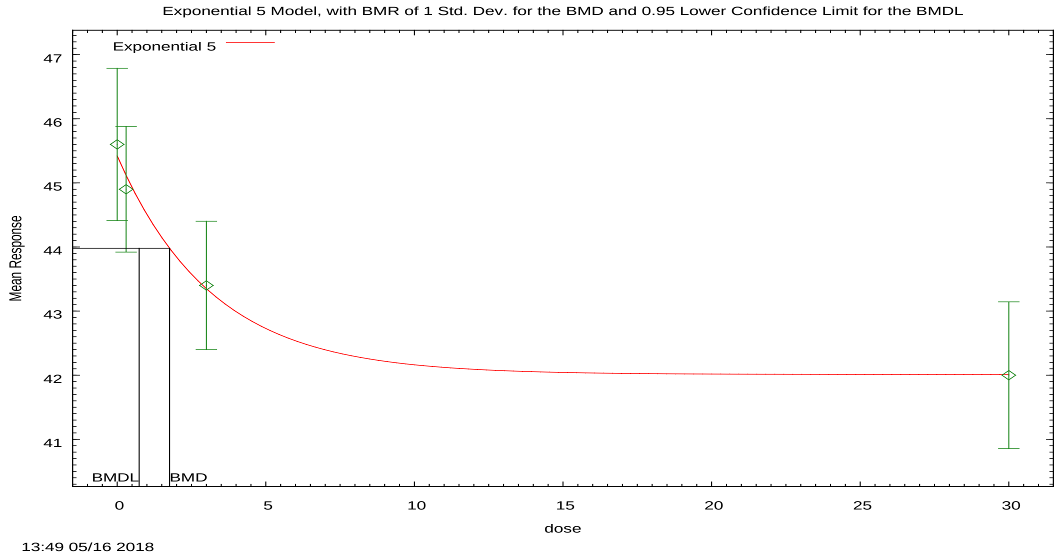

Figure 50. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.76258

BMDL at the 95% confidence level = 0.738122

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.732232	0.722372
rho	n/a	0
a	45.4219	47.88
b	0.31179	0.0481796
c	0.924905	0.835422

d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	45.42	1.66	1.44	0.3906
0.3	10	44.9	45.12	1.37	1.44	-0.4765
3	10	43.4	43.35	1.4	1.44	0.1106
30	10	42	42.01	1.6	1.44	-0.02467

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.44744	5	78.89489
A2	-34.17383	8	84.34766
A3	-34.44744	5	78.89489
R	-47.68178	2	99.36355
5	-34.64464	4	77.28927

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.02	6	0.0001438
Test 2	0.5472	3	0.9084
Test 3	0.5472	3	0.9084
Test 7a	0.3944	1	0.53

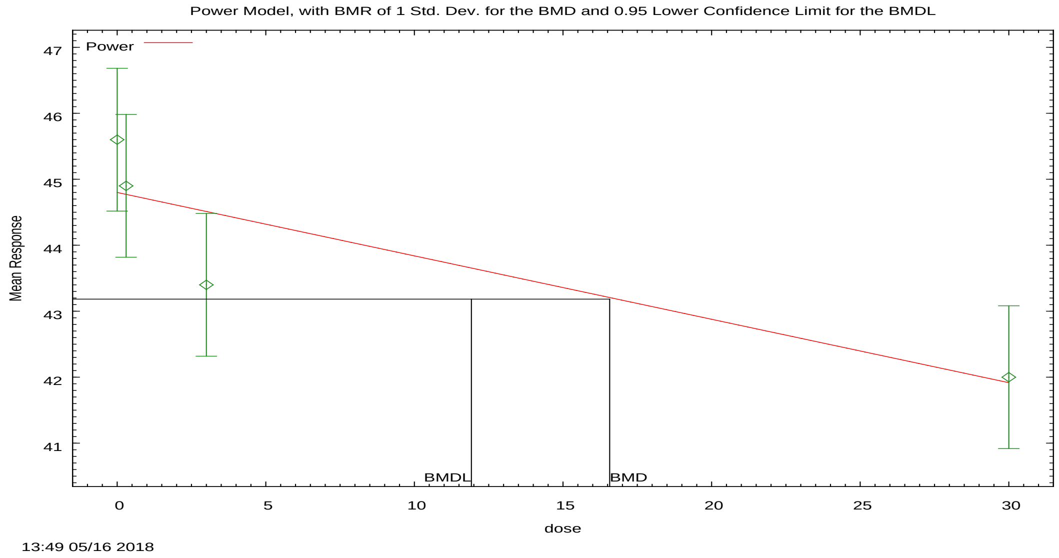

Figure 51. Plot of mean response by dose with fitted curve for Power model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 16.5698

BMDL at the 95% confidence level = 11.9179

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.53353	2.28813
rho	n/a	0
control	44.7747	45.6
slope	-0.0960605	-10.5553
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	44.8	1.66	1.59	1.64
0.3	10	44.9	44.7	1.37	1.59	0.306
3	10	43.4	44.5	1.4	1.59	-2.16
30	10	42	41.9	1.6	1.59	0.213

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.447444	5	78.894888
A2	-34.173832	8	84.347664
A3	-34.447444	5	78.894888
fitted	-38.592269	3	83.184538
R	-47.681776	2	99.363552

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.0159	6	0.0001438
Test 2	0.547224	3	0.9084
Test 3	0.547224	3	0.9084
Test 4	8.28965	2	0.01585

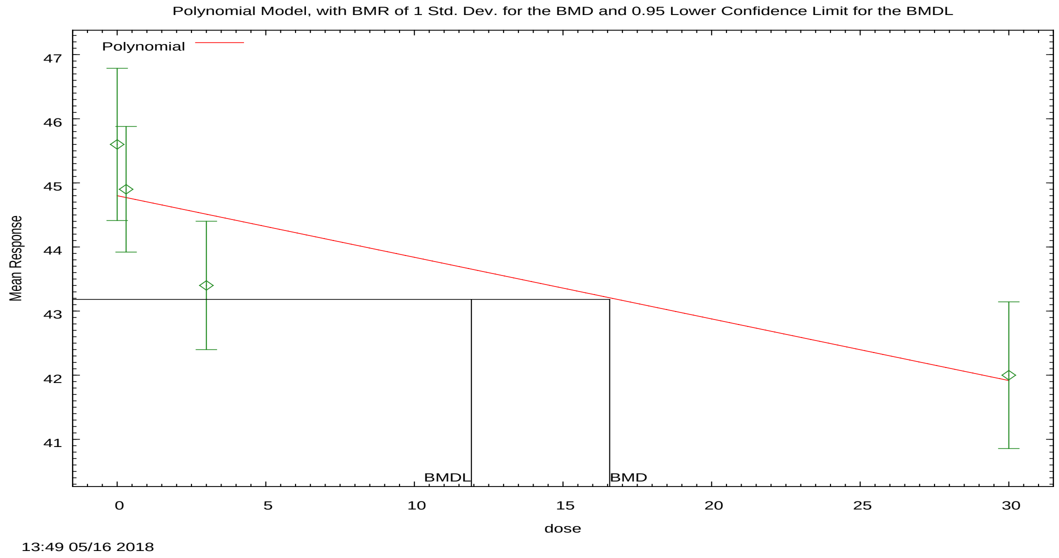

Figure 52. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 16.5698

BMDL at the 95% confidence level = 11.9179

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.53353	2.28813
rho	n/a	0
beta_0	44.7747	45.6
beta_1	-0.0960604	-2.52838
beta_2	0	0

beta_3	0	-0.0191878

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	44.8	1.66	1.59	1.64
0.3	10	44.9	44.7	1.37	1.59	0.306
3	10	43.4	44.5	1.4	1.59	-2.16
30	10	42	41.9	1.6	1.59	0.213

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.447444	5	78.894888
A2	-34.173832	8	84.347664
A3	-34.447444	5	78.894888
fitted	-38.592269	3	83.184538
R	-47.681776	2	99.363552

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.0159	6	0.0001438
Test 2	0.547224	3	0.9084
Test 3	0.547224	3	0.9084
Test 4	8.28965	2	0.01585

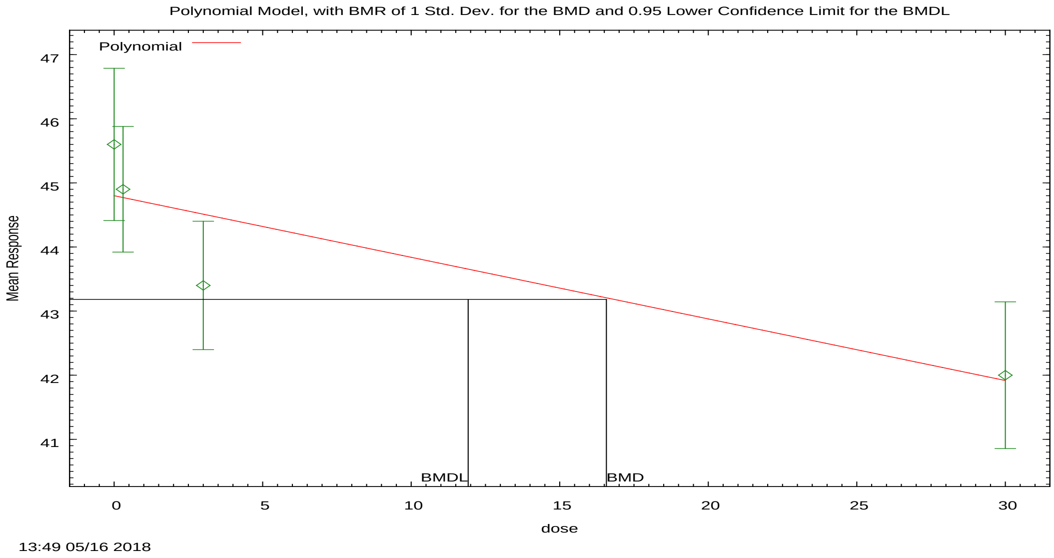

Figure 53. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 16.5698

BMDL at the 95% confidence level = 11.9179

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.53353	2.28813
rho	n/a	0
beta_0	44.7747	45.3723
beta_1	-0.0960605	-0.728393
beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	44.8	1.66	1.59	1.64
0.3	10	44.9	44.7	1.37	1.59	0.306
3	10	43.4	44.5	1.4	1.59	-2.16
30	10	42	41.9	1.6	1.59	0.213

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.447444	5	78.894888
A2	-34.173832	8	84.347664
A3	-34.447444	5	78.894888
fitted	-38.592269	3	83.184538
R	-47.681776	2	99.363552

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.0159	6	0.0001438
Test 2	0.547224	3	0.9084
Test 3	0.547224	3	0.9084
Test 4	8.28965	2	0.01585

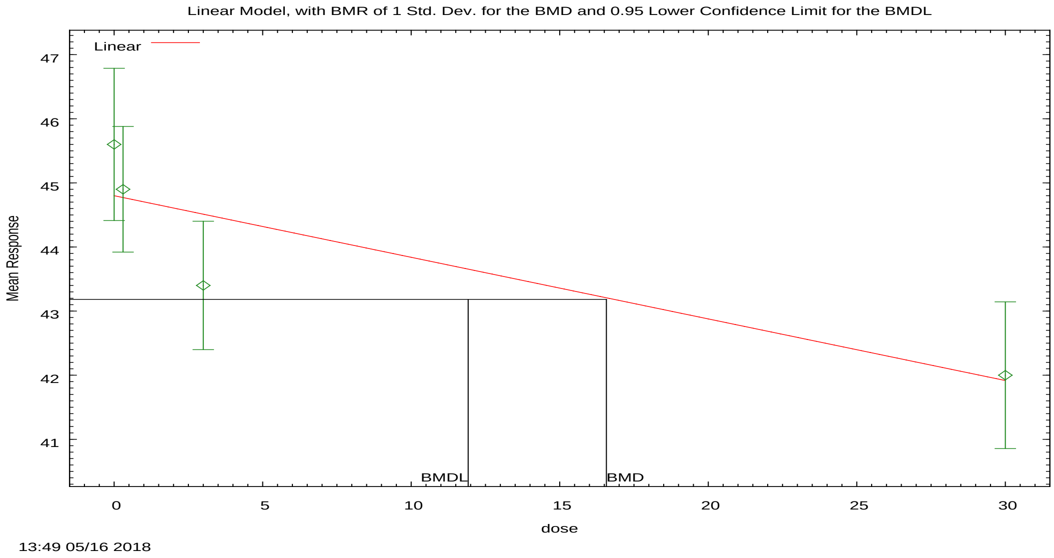

Figure 54. Plot of mean response by dose with fitted curve for Linear model with constant variance for Hematocrit in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 16.5698

BMDL at the 95% confidence level = 11.9179

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.53353	2.28813
rho	n/a	0
beta_0	44.7747	44.7747
beta_1	-0.0960605	-0.0960605

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	45.6	44.8	1.66	1.59	1.64
0.3	10	44.9	44.7	1.37	1.59	0.306
3	10	43.4	44.5	1.4	1.59	-2.16
30	10	42	41.9	1.6	1.59	0.213

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.447444	5	78.894888
A2	-34.173832	8	84.347664
A3	-34.447444	5	78.894888
fitted	-38.592269	3	83.184538
R	-47.681776	2	99.363552

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.0159	6	0.0001438
Test 2	0.547224	3	0.9084
Test 3	0.547224	3	0.9084
Test 4	8.28965	2	0.01585

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats – Hematocrit (%) at 6-month timepoint in Males

1.7. BMDS Summary of Hematocrit (%) Males 6 months (2 Year Rats GenX)

Table 7. Summary of BMD Modeling Results for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.435	120.46	36.9	24.4	1.51	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.219	122.31	46.8	24.7	1.90	
Exponential (M4)	0.197	122.46	36.9	24.4	1.51	
Exponential (M5)	N/A[b]	124.31	36.2	1.08	33.3	
Hill	N/A[b]	124.31	42.1	error[c]	error	
Power	0.219	122.31	46.4	25.3	1.84	
Polynomial 3°	**0.469**	**120.31**	**45.3**	**25.3**	**1.79**	
Polynomial 2°	0.468	120.31	43.2	35.4	1.22	
Linear	0.436	120.46	37.3	25.1	1.49	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.339), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 1, and 50 mg/kg/day were -0.12, -0.8, 0.92, 0, respectively.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

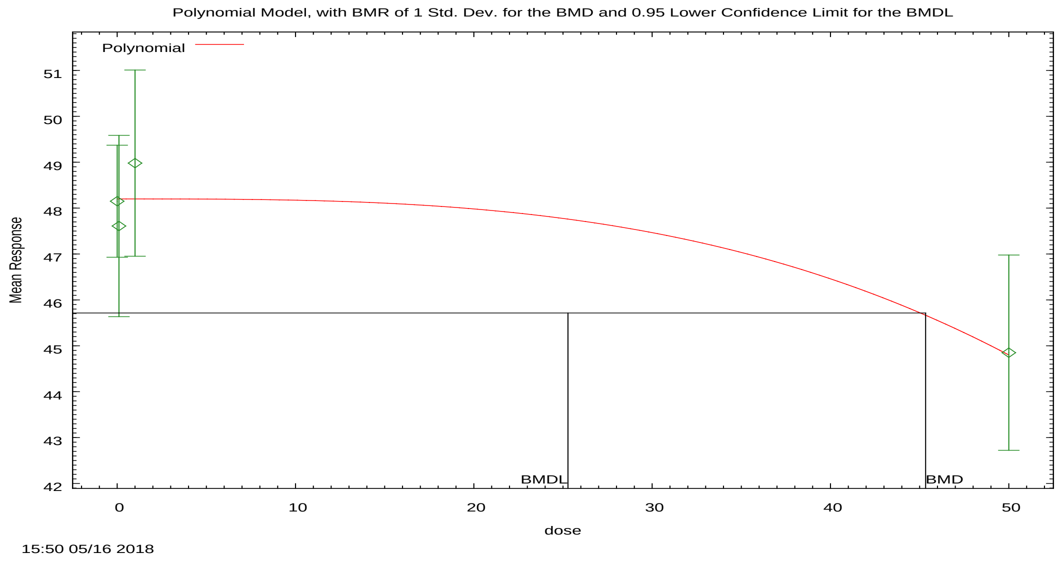

Figure 55. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 45.3334

BMDL at the 95% confidence level = 25.279

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.40912	6.85666
rho	n/a	0
beta_0	48.2467	48.15
beta_1	0	-6.10613
beta_2	-5.6392E-25	0
beta_3	-0.0000271733	-0.139088

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.1	48.2	1.71	2.53	-0.121
0.1	10	47.6	48.2	2.76	2.53	-0.795
1	10	49	48.2	2.84	2.53	0.916
50	10	44.9	44.9	2.97	2.53	-0.00000696

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.397207	5	122.794415
A2	-54.716879	8	125.433759
A3	-56.397207	5	122.794415

fitted	-57.15445	3	120.3089
R	-62.970874	2	129.941748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.508	6	0.01127
Test 2	3.36066	3	0.3393
Test 3	3.36066	3	0.3393
Test 4	1.51449	2	0.469

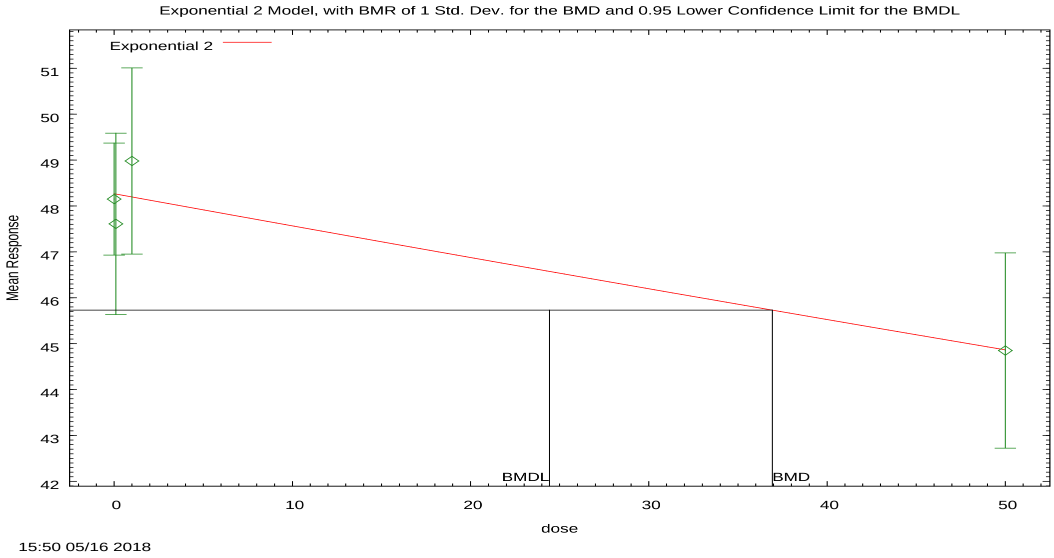

Figure 56. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 36.9284

BMDL at the 95% confidence level = 24.4126

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.86153	1.81986
rho	n/a	0
a	48.2674	46.4954
b	0.00146177	0.00146151
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.15	48.27	1.71	2.54	-0.1464
0.1	10	47.61	48.26	2.76	2.54	-0.8108
1	10	48.98	48.2	2.84	2.54	0.9763
50	10	44.85	44.87	2.97	2.54	-0.01923

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.39721	5	122.7944
A2	-54.71688	8	125.4338
A3	-56.39721	5	122.7944
R	-62.97087	2	129.9417
2	-57.23054	3	120.4611

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.51	6	0.01127
Test 2	3.361	3	0.3393
Test 3	3.361	3	0.3393

Test 4	1.667	2	0.4346

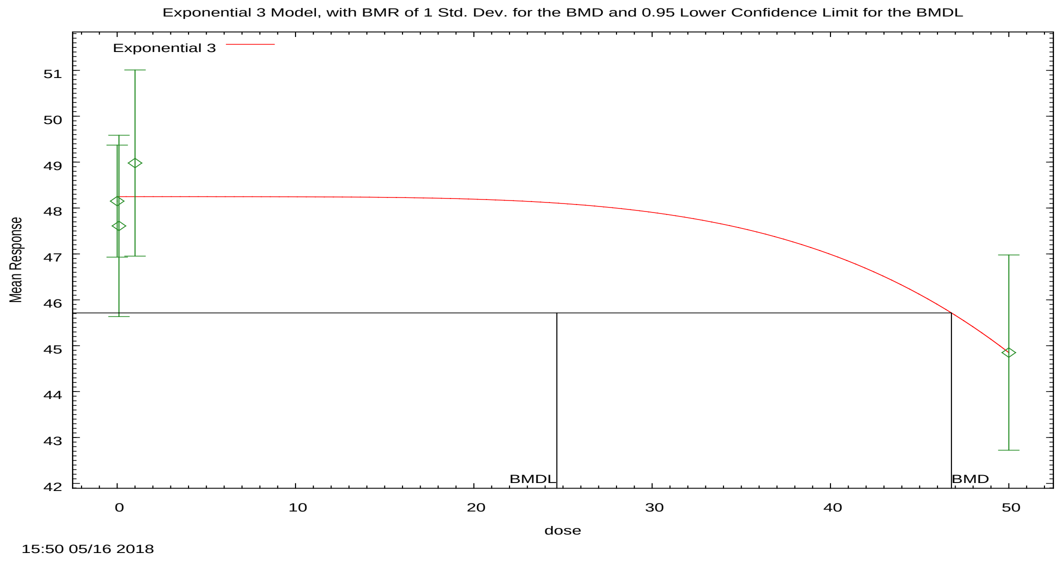

Figure 57. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 46.7835

BMDL at the 95% confidence level = 24.6546

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.85772	1.81986
rho	n/a	0

a	48.2467	46.4954
b	0.0112697	0.00146151
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.15	48.25	1.71	2.53	-0.1207
0.1	10	47.61	48.25	2.76	2.53	-0.7953
1	10	48.98	48.25	2.84	2.53	0.916
50	10	44.85	44.85	2.97	2.53	-0.0000000655

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.39721	5	122.7944
A2	-54.71688	8	125.4338
A3	-56.39721	5	122.7944
R	-62.97087	2	129.9417
3	-57.15442	4	122.3088

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.51	6	0.01127
Test 2	3.361	3	0.3393
Test 3	3.361	3	0.3393
Test 5a	1.514	1	0.2185

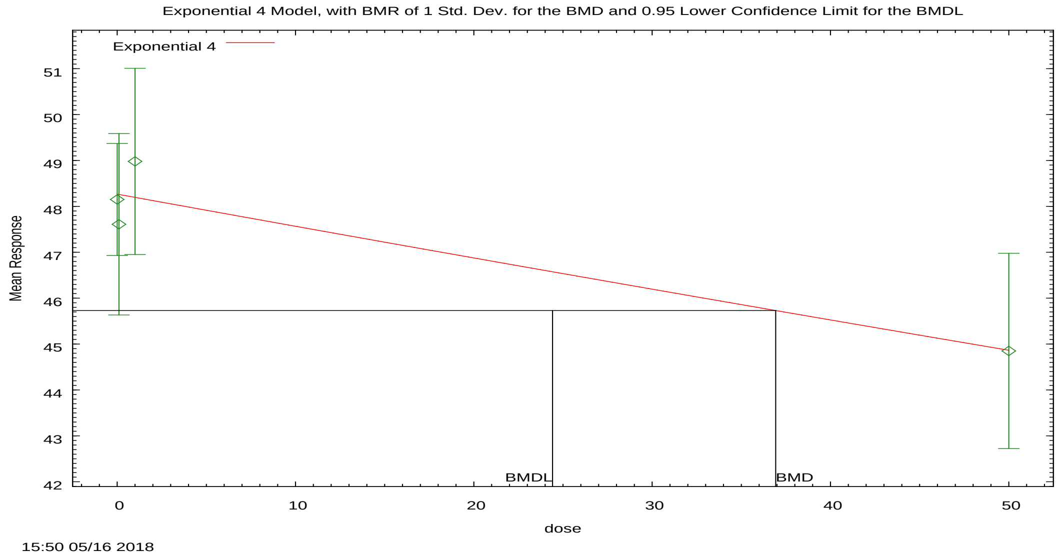

Figure 58. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 36.9284

BMDL at the 95% confidence level = 24.4126

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.86153	1.81986
rho	n/a	0
a	48.2674	51.429
b	0.00146177	0.0282678

c	0.000000000174759	0.830549
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.15	48.27	1.71	2.54	-0.1464
0.1	10	47.61	48.26	2.76	2.54	-0.8108
1	10	48.98	48.2	2.84	2.54	0.9763
50	10	44.85	44.87	2.97	2.54	-0.01923

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.39721	5	122.7944
A2	-54.71688	8	125.4338
A3	-56.39721	5	122.7944
R	-62.97087	2	129.9417
4	-57.23054	4	122.4611

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.51	6	0.01127
Test 2	3.361	3	0.3393
Test 3	3.361	3	0.3393
Test 6a	1.667	1	0.1967

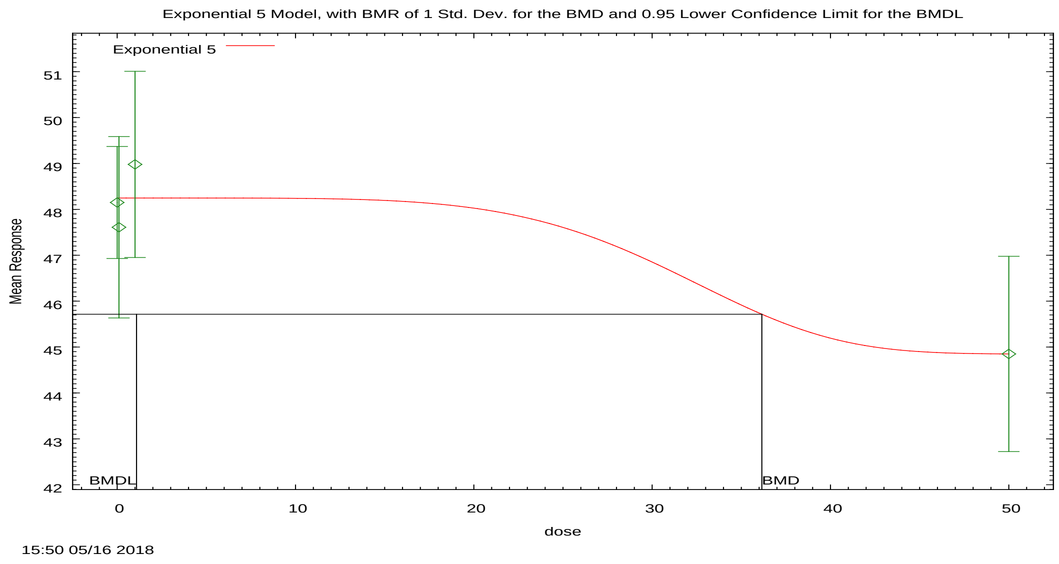

Figure 59. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 36.151

BMDL at the 95% confidence level = 1.08483

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.85772	1.81986
rho	n/a	0
a	48.2467	51.429
b	0.0294062	0.0282678

c	0.929541	0.830549
d	5.09304	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.15	48.25	1.71	2.53	-0.1207
0.1	10	47.61	48.25	2.76	2.53	-0.7953
1	10	48.98	48.25	2.84	2.53	0.916
50	10	44.85	44.85	2.97	2.53	-0.00000001585

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.39721	5	122.7944
A2	-54.71688	8	125.4338
A3	-56.39721	5	122.7944
R	-62.97087	2	129.9417
5	-57.15442	5	124.3088

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.51	6	0.01127
Test 2	3.361	3	0.3393
Test 3	3.361	3	0.3393
Test 7a	1.514	0	N/A

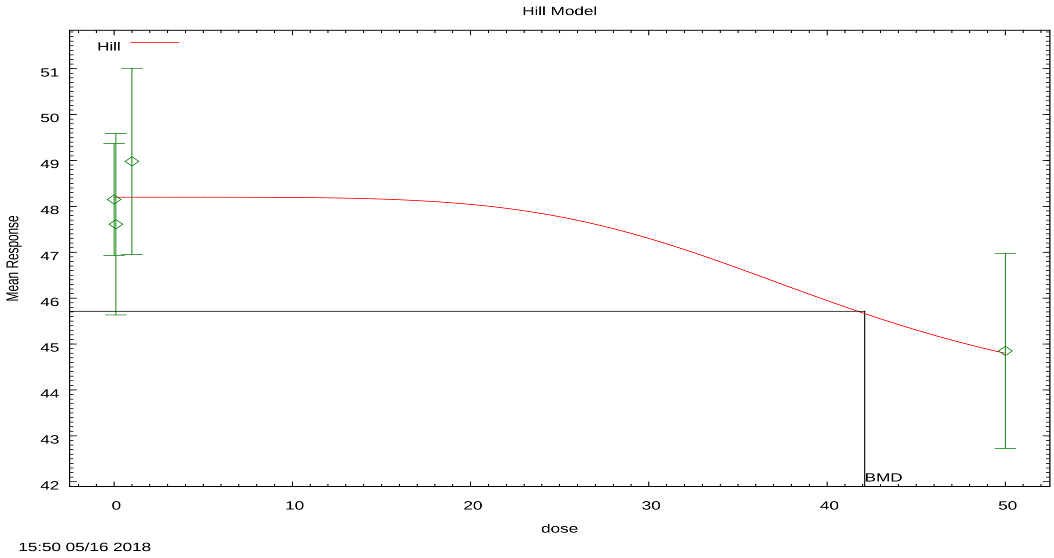

Figure 60. Plot of mean response by dose with fitted curve for Hill model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 42.1125

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.40911	6.85666
rho	n/a	0
intercept	48.2467	48.15
v	-4.66716	-3.3

n	4.73703	0.285322
k	40.6267	30.4237

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.1	48.2	1.71	2.53	-0.121
0.1	10	47.6	48.2	2.76	2.53	-0.795
1	10	49	48.2	2.84	2.53	0.916
50	10	44.9	44.8	2.97	2.53	0.000000279

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.397207	5	122.794415
A2	-54.716879	8	125.433759
A3	-56.397207	5	122.794415
fitted	-57.154419	5	124.308838
R	-62.970874	2	129.941748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.508	6	0.01127
Test 2	3.36066	3	0.3393
Test 3	3.36066	3	0.3393
Test 4	1.51442	0	N/A

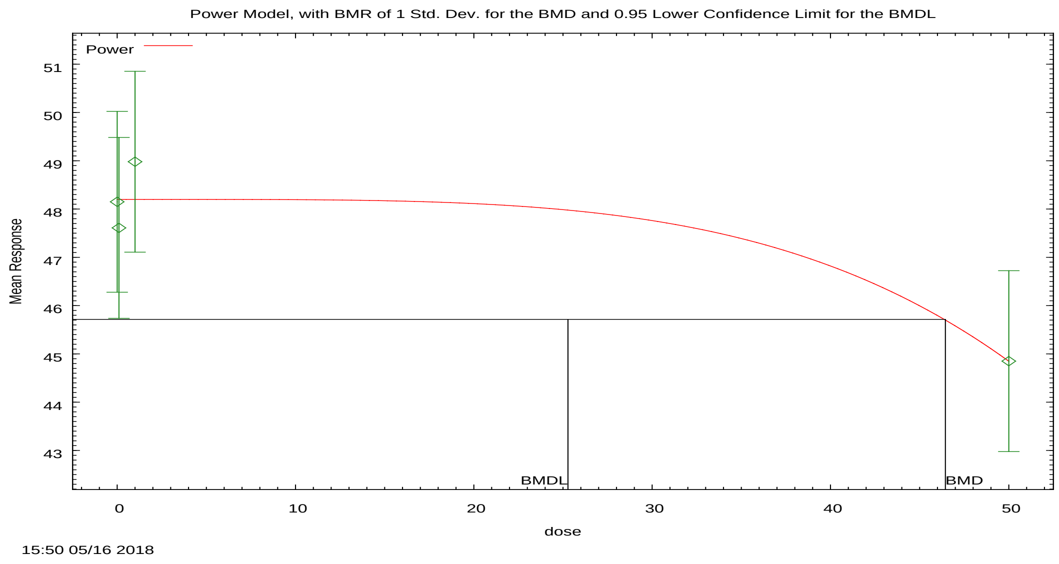

Figure 61. Plot of mean response by dose with fitted curve for Power model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 46.4432

BMDL at the 95% confidence level = 25.2791

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.40911	6.85666
rho	n/a	0
control	48.2467	44.85
slope	-0.000000580442	4.13
power	3.98317	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.1	48.2	1.71	2.53	-0.121
0.1	10	47.6	48.2	2.76	2.53	-0.795
1	10	49	48.2	2.84	2.53	0.916
50	10	44.9	44.9	2.97	2.53	-0.000000144

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.397207	5	122.794415
A2	-54.716879	8	125.433759
A3	-56.397207	5	122.794415
fitted	-57.154419	4	122.308839
R	-62.970874	2	129.941748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.508	6	0.01127
Test 2	3.36066	3	0.3393
Test 3	3.36066	3	0.3393
Test 4	1.51442	1	0.2185

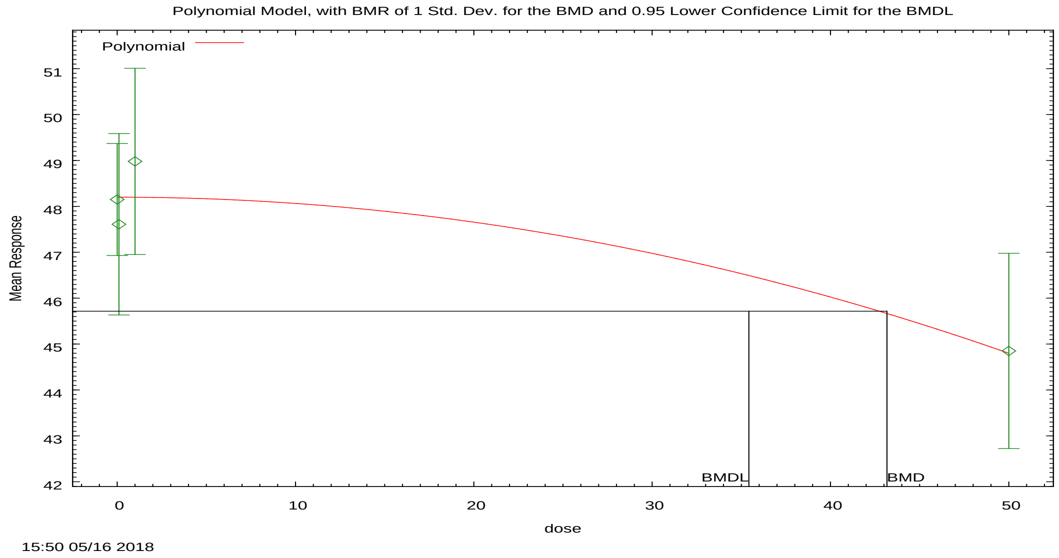

Figure 62. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 43.1665

BMDL at the 95% confidence level = 35.4249

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.40961	6.85666
rho	n/a	0
beta_0	48.247	47.8412
beta_1	-9.04729E-26	0
beta_2	-0.00135869	-0.0237465

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.1	48.2	1.71	2.53	-0.121
0.1	10	47.6	48.2	2.76	2.53	-0.796
1	10	49	48.2	2.84	2.53	0.917
50	10	44.9	44.9	2.97	2.53	-0.000364

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.397207	5	122.794415
A2	-54.716879	8	125.433759
A3	-56.397207	5	122.794415
fitted	-57.155961	3	120.311922
R	-62.970874	2	129.941748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.508	6	0.01127
Test 2	3.36066	3	0.3393
Test 3	3.36066	3	0.3393
Test 4	1.51751	2	0.4682

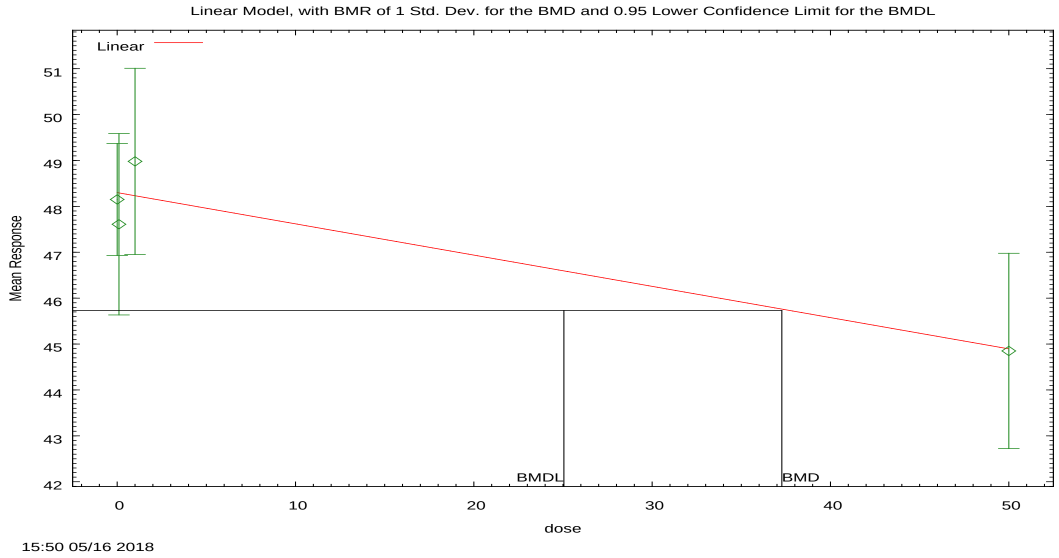

Figure 63. Plot of mean response by dose with fitted curve for Linear model with constant variance for Hematocrit in Males at 6 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 37.2705

BMDL at the 95% confidence level = 25.0508

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.43267	6.85666
rho	n/a	0
beta_0	48.2668	48.2668
beta_1	-0.0680504	-0.0680504

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	48.1	48.3	1.71	2.54	-0.146
0.1	10	47.6	48.3	2.76	2.54	-0.81
1	10	49	48.2	2.84	2.54	0.974
50	10	44.9	44.9	2.97	2.54	-0.0179

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.397207	5	122.794415
A2	-54.716879	8	125.433759
A3	-56.397207	5	122.794415
fitted	-57.227793	3	120.455586
R	-62.970874	2	129.941748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.508	6	0.01127
Test 2	3.36066	3	0.3393
Test 3	3.36066	3	0.3393
Test 4	1.66117	2	0.4358

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Albumin to Globulin Ratio in Males

1.8. BMDS Summary of Albumin to Globulin Ratio Males (28 Day Mice GenX)

Table 8. Summary of BMD Modeling Results for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	<0.0001	-73.454	10.3	7.79	1.32	Only one model met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from this model.
Exponential (M4) Exponential (M5)[c]	**0.999**	**-93.451**	**0.775**	**0.464**	**1.67**	
Hill	N/A[d]	-91.451	0.705	0.313	2.25	
Power[e] Polynomial 2°[f] Linear[g]	<0.0001	-74.496	8.72	6.25	1.40	
Polynomial 3°[h]	<0.0001	-74.496	8.72	6.25	1.40	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0996), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were 0, 0.06, -0.15, 0.09, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[d] No available degrees of freedom to calculate a goodness of fit value.

[e] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[f] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[g] The Linear model may appear equivalent to the Polynomial 3° model, however differences exist in digits not displayed in the table.

[h] The Polynomial 3° model may appear equivalent to the Power model, however differences exist in digits not displayed in the table. This also applies to the Polynomial 2° model. This also applies to the Linear model.

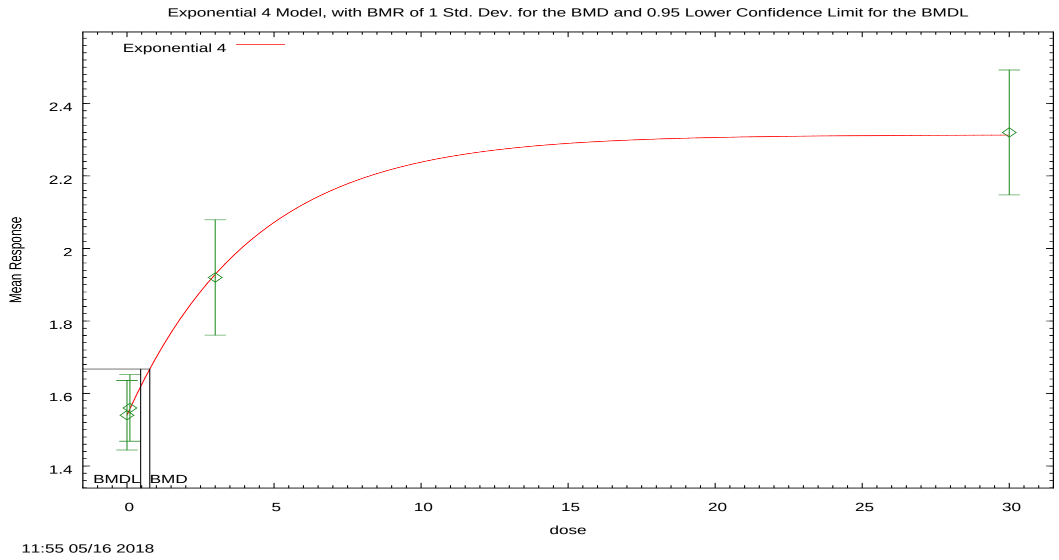

Figure 64. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.774566

BMDL at the 95% confidence level = 0.464264

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.54159	-5.41198
rho	3.29978	3.23182
a	1.53988	1.463
b	0.232774	0.0722953
c	1.50243	1.66507
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.54	0.13	0.13	0.003022
0.1	10	1.56	1.56	0.13	0.13	0.05642
3	10	1.92	1.93	0.22	0.19	-0.1489
30	10	2.32	2.31	0.24	0.25	0.09068

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.91325	5	-87.82651
A2	52.04398	8	-88.08796
A3	51.72568	6	-91.45137
R	20.32428	2	-36.64857
4	51.72568	5	-93.45137

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.44	6	<0.0001
Test 2	6.261	3	0.09956
Test 3	0.6366	2	0.7274
Test 6a	0.0000004765	1	0.9994

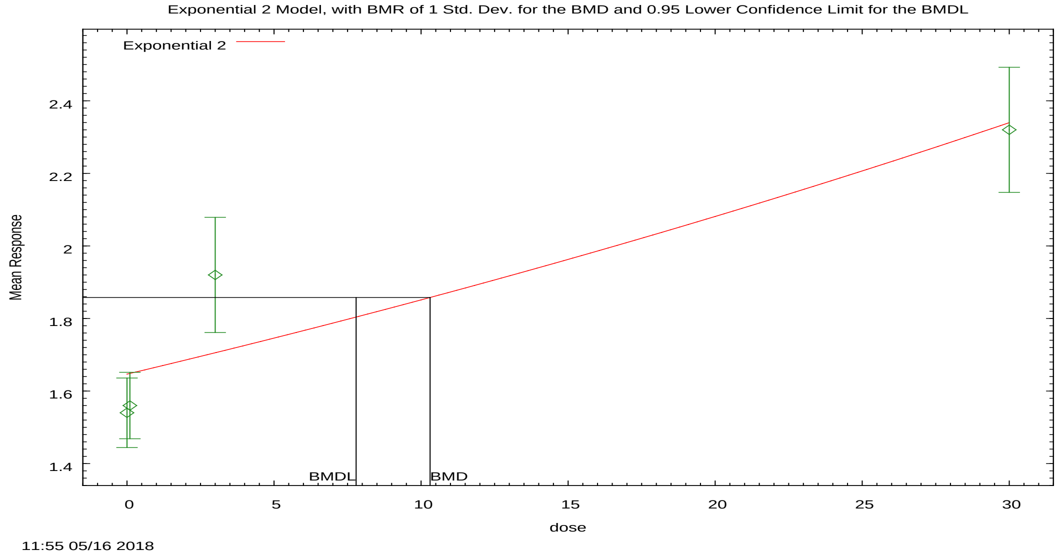

Figure 65. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 10.3062

BMDL at the 95% confidence level = 7.79109

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.48813	-5.41198
rho	0.758549	3.23182
a	1.64655	1.63743
b	0.01171	0.0120196
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.65	0.13	0.21	-1.595
0.1	10	1.56	1.65	0.13	0.21	-1.324
3	10	1.92	1.7	0.22	0.21	3.17
30	10	2.32	2.34	0.24	0.24	-0.257

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.91325	5	-87.82651
A2	52.04398	8	-88.08796
A3	51.72568	6	-91.45137
R	20.32428	2	-36.64857
2	40.72708	4	-73.45417

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.44	6	<0.0001
Test 2	6.261	3	0.09956
Test 3	0.6366	2	0.7274
Test 4	22	2	<0.0001

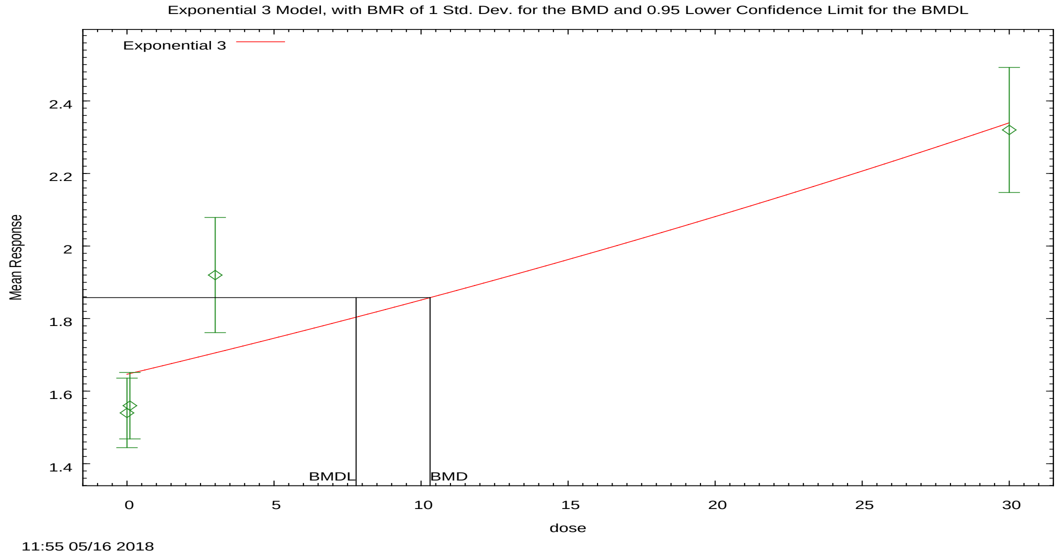

Figure 66. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 10.3062

BMDL at the 95% confidence level = 7.79109

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.48813	-5.41198
rho	0.758548	3.23182
a	1.64655	1.63743
b	0.01171	0.0120196
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.65	0.13	0.21	-1.595
0.1	10	1.56	1.65	0.13	0.21	-1.324
3	10	1.92	1.7	0.22	0.21	3.17
30	10	2.32	2.34	0.24	0.24	-0.257

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.91325	5	-87.82651
A2	52.04398	8	-88.08796
A3	51.72568	6	-91.45137
R	20.32428	2	-36.64857
3	40.72708	4	-73.45417

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.44	6	<0.0001
Test 2	6.261	3	0.09956
Test 3	0.6366	2	0.7274
Test 5a	22	2	<0.0001

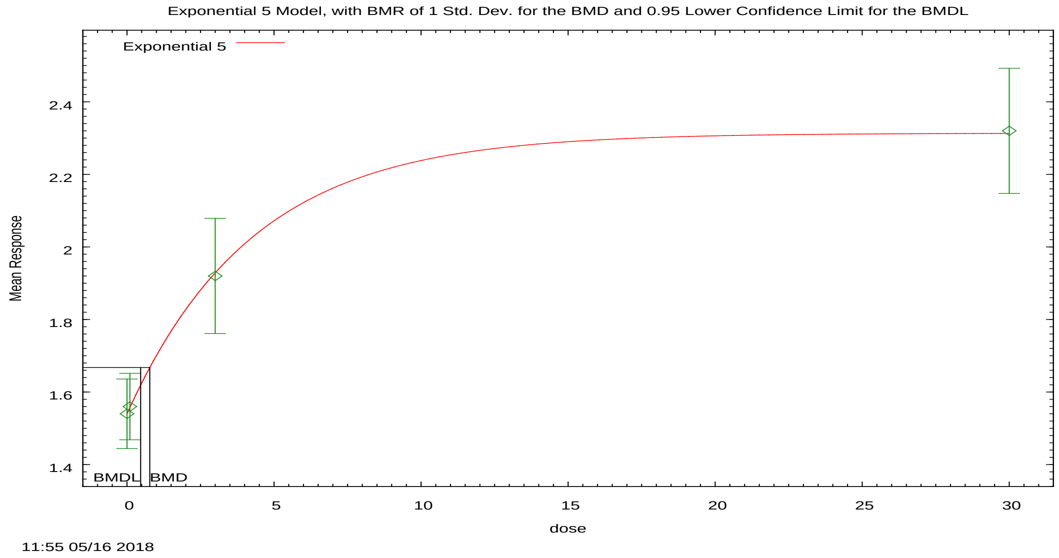

Figure 67. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.774566

BMDL at the 95% confidence level = 0.464264

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.54159	-5.41198
rho	3.29978	3.23182
a	1.53988	1.463
b	0.232774	0.0722953

c	1.50243	1.66507
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.54	0.13	0.13	0.003022
0.1	10	1.56	1.56	0.13	0.13	0.05642
3	10	1.92	1.93	0.22	0.19	-0.1489
30	10	2.32	2.31	0.24	0.25	0.09068

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.91325	5	-87.82651
A2	52.04398	8	-88.08796
A3	51.72568	6	-91.45137
R	20.32428	2	-36.64857
5	51.72568	5	-93.45137

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.44	6	<0.0001
Test 2	6.261	3	0.09956
Test 3	0.6366	2	0.7274
Test 7a	0.0000004765	1	0.9994

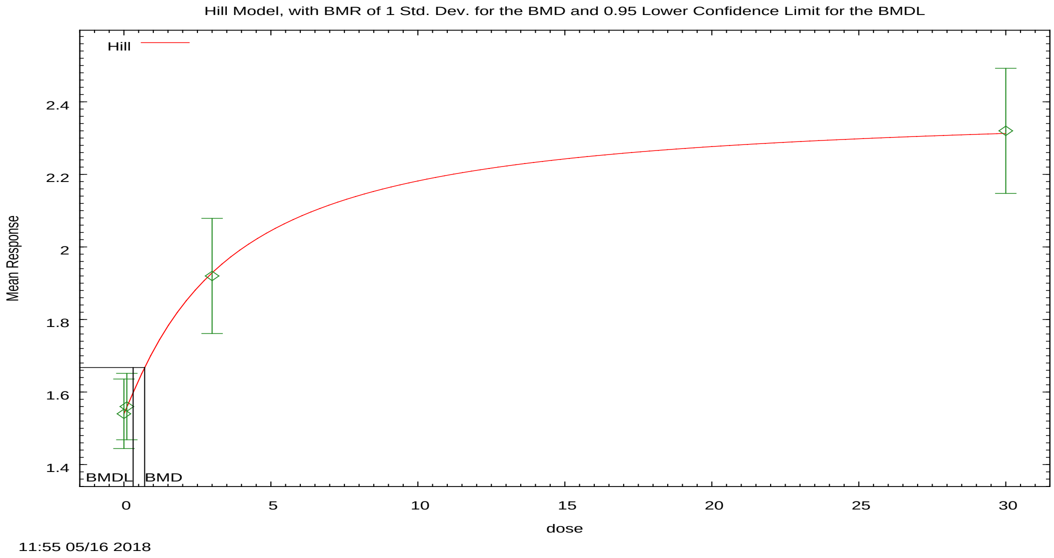

Figure 68. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Warning: Likelihood for fitted model larger than the Likelihood for model A3.

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.705233

BMDL at the 95% confidence level = 0.313181

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-5.54158	-3.3403
rho	3.29976	0
intercept	1.53986	1.54
v	0.849098	0.78

n	1.07989	0.295906
k	3.5068	56.325

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.54	0.13	0.13	0.00348
0.1	10	1.56	1.56	0.13	0.13	0.0559
3	10	1.92	1.93	0.22	0.18	-0.149
30	10	2.32	2.31	0.24	0.25	0.0907

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.913254	5	-87.826509
A2	52.043978	8	-88.087955
A3	51.725684	6	-91.451368
fitted	51.725684	6	-91.451368
R	20.324284	2	-36.648568

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.4394	6	<0.0001
Test 2	6.26145	3	0.09956
Test 3	0.636587	2	0.7274
Test 4	-1.7053E-13	0	N/A

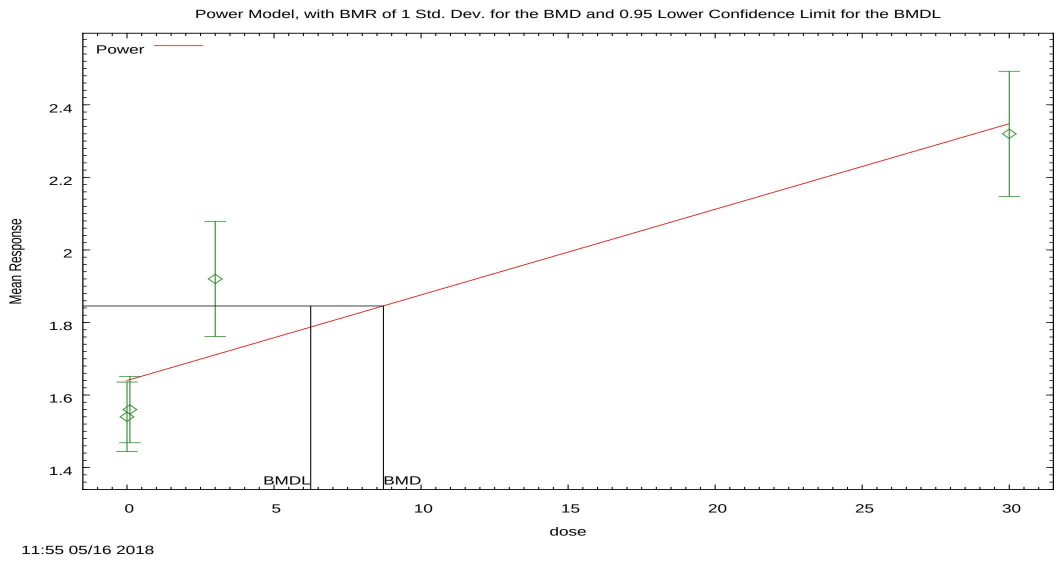

Figure 69. Plot of mean response by dose with fitted curve for Power model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 8.71976

BMDL at the 95% confidence level = 6.24707

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.63569	-3.3403
rho	0.96328	0
control	1.63947	1.54
slope	0.0236278	0.0828657
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.64	0.13	0.21	-1.53
0.1	10	1.56	1.64	0.13	0.21	-1.26
3	10	1.92	1.71	0.22	0.21	3.15
30	10	2.32	2.35	0.24	0.24	-0.365

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.913254	5	-87.826509
A2	52.043978	8	-88.087955
A3	51.725684	6	-91.451368
fitted	41.248063	4	-74.496127
R	20.324284	2	-36.648568

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.4394	6	<0.0001
Test 2	6.26145	3	0.09956
Test 3	0.636587	2	0.7274
Test 4	20.9552	2	<0.0001

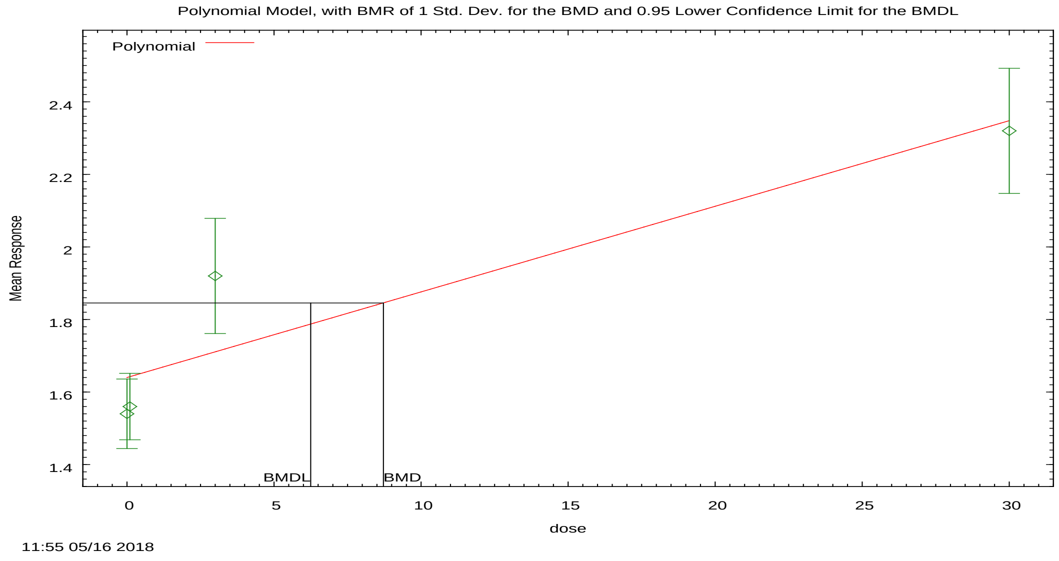

Figure 70. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 8.71975

BMDL at the 95% confidence level = 6.24707

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.6357	-3.3403
rho	0.963286	0
beta_0	1.63947	1.54
beta_1	0.0236279	0.202745
beta_2	0	0

beta_3	0	0.000721035

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.64	0.13	0.21	-1.53
0.1	10	1.56	1.64	0.13	0.21	-1.26
3	10	1.92	1.71	0.22	0.21	3.15
30	10	2.32	2.35	0.24	0.24	-0.365

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.913254	5	-87.826509
A2	52.043978	8	-88.087955
A3	51.725684	6	-91.451368
fitted	41.248063	4	-74.496127
R	20.324284	2	-36.648568

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.4394	6	<0.0001
Test 2	6.26145	3	0.09956
Test 3	0.636587	2	0.7274
Test 4	20.9552	2	<0.0001

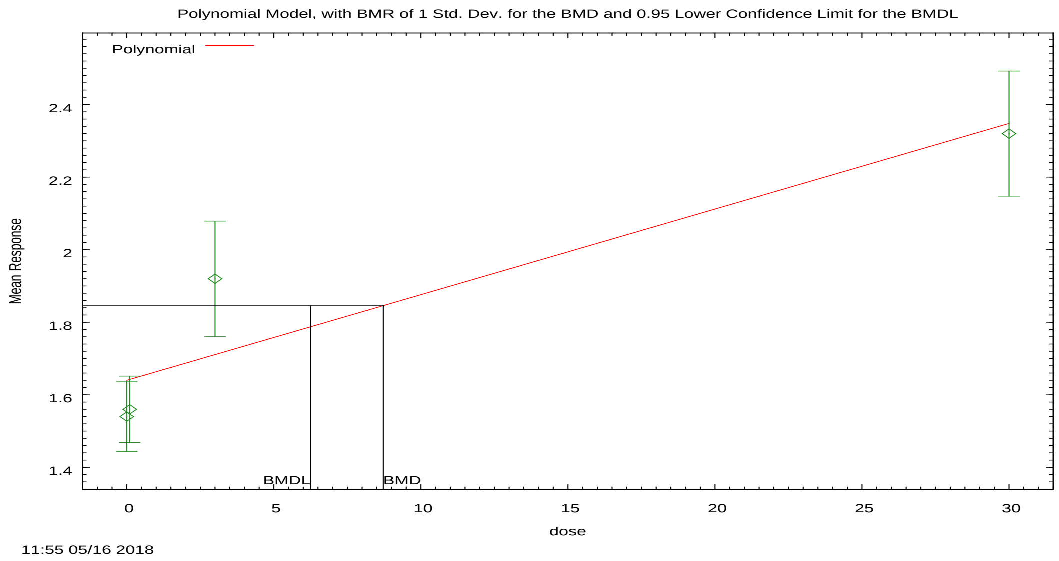

Figure 71. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 8.71976

BMDL at the 95% confidence level = 6.24707

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.63569	-3.3403
rho	0.96328	0
beta_0	1.63947	1.54312
beta_1	0.0236278	0.136752
beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.64	0.13	0.21	-1.53
0.1	10	1.56	1.64	0.13	0.21	-1.26
3	10	1.92	1.71	0.22	0.21	3.15
30	10	2.32	2.35	0.24	0.24	-0.365

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.913254	5	-87.826509
A2	52.043978	8	-88.087955
A3	51.725684	6	-91.451368
fitted	41.248063	4	-74.496127
R	20.324284	2	-36.648568

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.4394	6	<0.0001
Test 2	6.26145	3	0.09956
Test 3	0.636587	2	0.7274
Test 4	20.9552	2	<0.0001

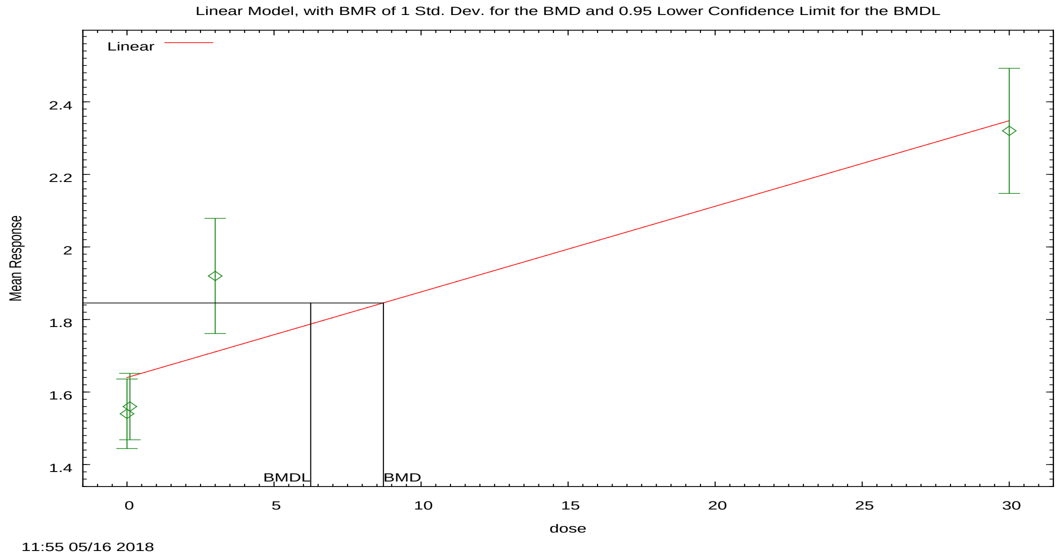

Figure 72. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Albumin to Globulin Ratio in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 8.71976

BMDL at the 95% confidence level = 6.24707

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.63569	-3.3403
rho	0.963279	0
beta_0	1.63947	1.64246
beta_1	0.0236278	0.0232677

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.54	1.64	0.13	0.21	-1.53
0.1	10	1.56	1.64	0.13	0.21	-1.26
3	10	1.92	1.71	0.22	0.21	3.15
30	10	2.32	2.35	0.24	0.24	-0.365

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	48.913254	5	-87.826509
A2	52.043978	8	-88.087955
A3	51.725684	6	-91.451368
fitted	41.248063	4	-74.496127
R	20.324284	2	-36.648568

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.4394	6	<0.0001
Test 2	6.26145	3	0.09956
Test 3	0.636587	2	0.7274
Test 4	20.9552	2	<0.0001

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Albumin to Globulin Ratio in Females

1.9. BMDS Summary of Albumin to Globulin Ratio Females (28 Day Mice GenX)

Table 9. Summary of BMD Modeling Results for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.00175	-98.689	11.6	9.13	1.27	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. Selected BMDL is from model with lowest AIC and lowest BMDL.
Exponential (M4) Exponential (M5)[c]	0.538	-109.00	1.42	0.863	1.64	
Hill	**0.573**	**-109.07**	**1.22**	**0.595**	**2.04**	
Power[d] Polynomial 3°[e] Polynomial 2°[f] Linear	0.00216	-99.106	10.7	8.29	1.29	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.119), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were -0.38, 0.41, -0.05, 0.01, respectively.
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.
[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[e] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[f] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

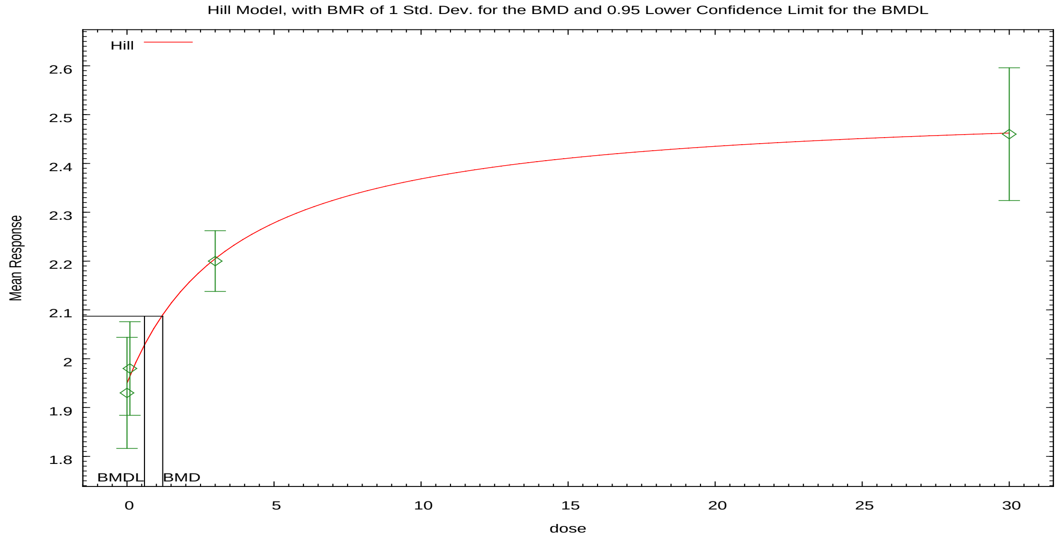

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Figure 73. Plot of mean response by dose with fitted curve for Hill model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.21611

BMDL at the 95% confidence level = 0.595276

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0197096	0.0217265
rho	n/a	0
intercept	1.94679	1.93
v	0.577417	0.53
n	1	0.330384
k	3.78567	3.06591

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	1.95	0.16	0.14	-0.378
0.1	10	1.98	1.96	0.13	0.14	0.413
3	10	2.2	2.2	0.09	0.14	-0.0465
30	10	2.46	2.46	0.19	0.14	0.0112

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC

A1	58.691662	5	-107.383323
A2	61.62066	8	-107.241319
A3	58.691662	5	-107.383323
fitted	58.532951	4	-109.065902
R	35.142939	2	-66.285878

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.9554	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 4	0.317422	1	0.5732

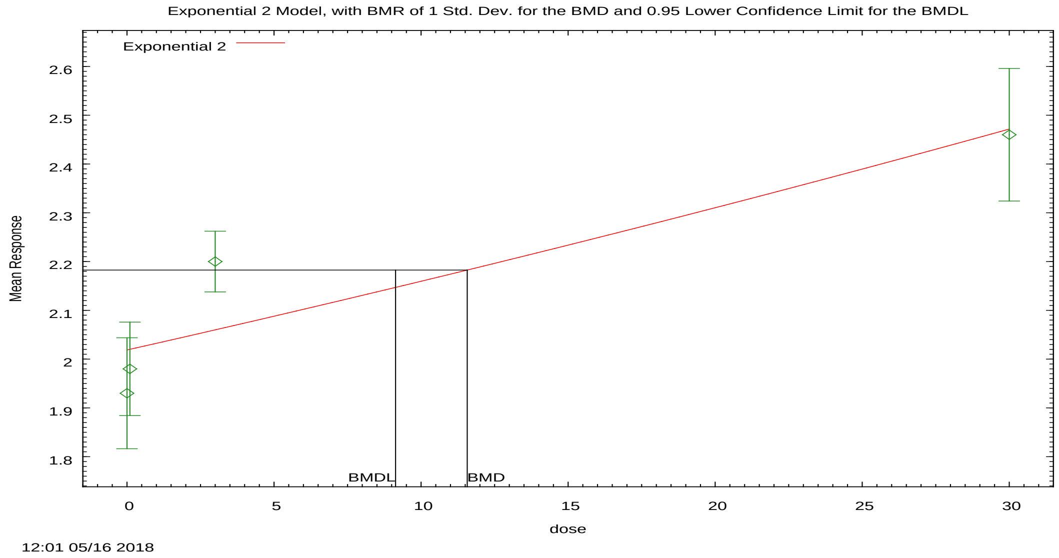

Figure 74. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 11.5691

BMDL at the 95% confidence level = 9.13206

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.61722	-3.93458
rho	n/a	0
a	2.01868	2.01446
b	0.00674689	0.00688324
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	2.02	0.16	0.16	-1.711
0.1	10	1.98	2.02	0.13	0.16	-0.7727
3	10	2.2	2.06	0.09	0.16	2.702
30	10	2.46	2.47	0.19	0.16	-0.2231

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	58.69166	5	-107.3833
A2	61.62066	8	-107.2413
A3	58.69166	5	-107.3833
R	35.14294	2	-66.28588
2	52.34439	3	-98.68877

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.96	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 4	12.69	2	0.001752

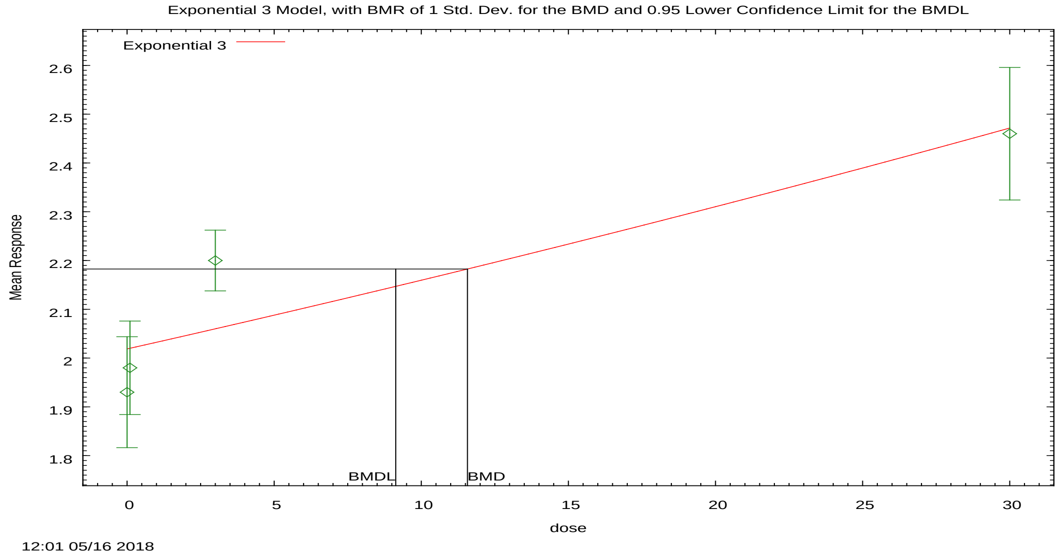

Figure 75. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 11.5691

BMDL at the 95% confidence level = 9.13206

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.61722	-3.93458
rho	n/a	0
a	2.01868	2.01446
b	0.00674689	0.00688324
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	2.02	0.16	0.16	-1.711
0.1	10	1.98	2.02	0.13	0.16	-0.7727
3	10	2.2	2.06	0.09	0.16	2.702
30	10	2.46	2.47	0.19	0.16	-0.2231

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	58.69166	5	-107.3833
A2	61.62066	8	-107.2413
A3	58.69166	5	-107.3833
R	35.14294	2	-66.28588
3	52.34439	3	-98.68877

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.96	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 5a	12.69	2	0.001752

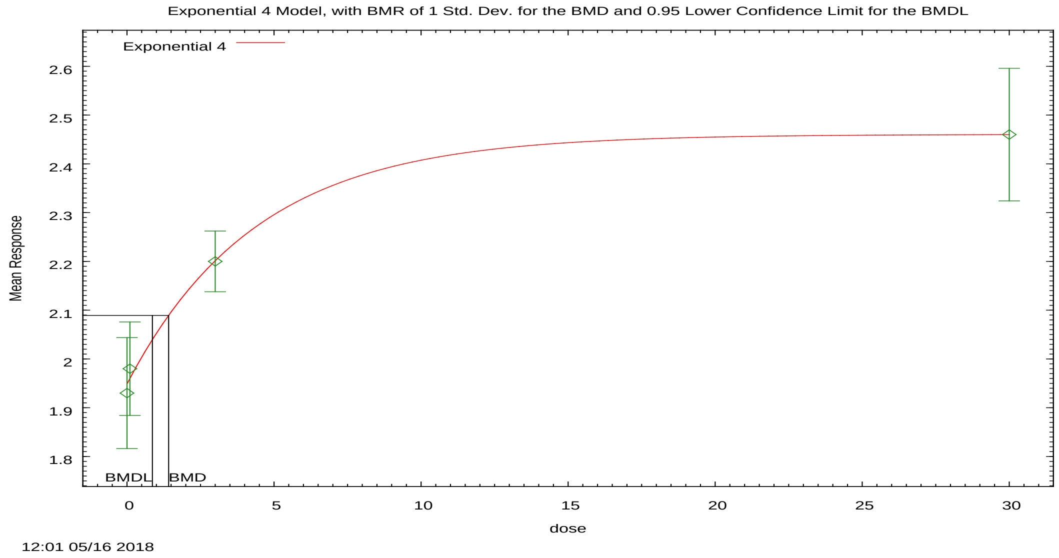

Figure 76. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.41534

BMDL at the 95% confidence level = 0.863474

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.92511	-3.93458
rho	n/a	0
a	1.94872	1.8335
b	0.226816	0.0618833

c	1.26256	1.40878
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	1.95	0.16	0.14	-0.4213
0.1	10	1.98	1.96	0.13	0.14	0.4458
3	10	2.2	2.2	0.09	0.14	-0.02878
30	10	2.46	2.46	0.19	0.14	0.004218

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	58.69166	5	-107.3833
A2	61.62066	8	-107.2413
A3	58.69166	5	-107.3833
R	35.14294	2	-66.28588
4	58.50222	4	-109.0044

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.96	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 6a	0.3789	1	0.5382

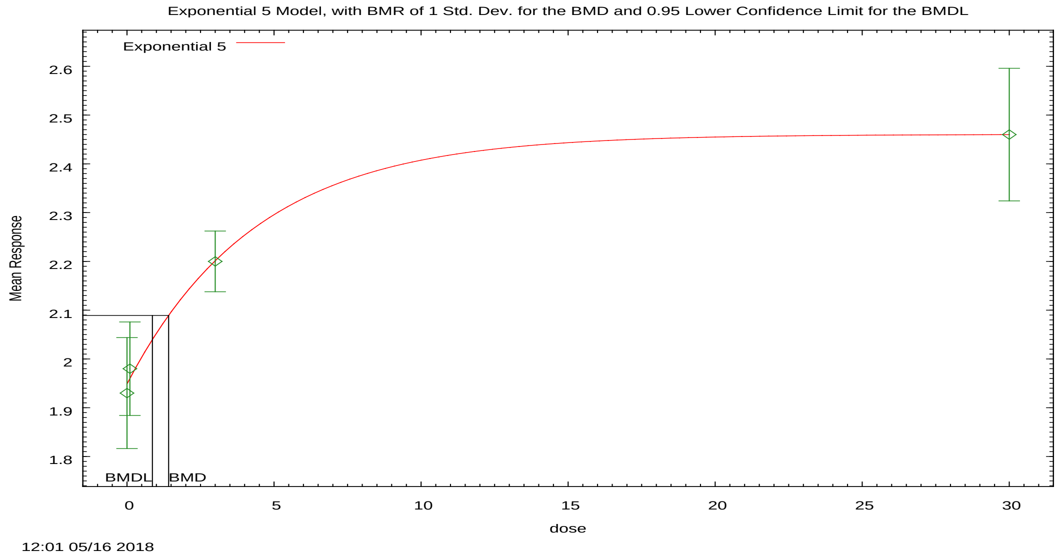

Figure 77. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.41534

BMDL at the 95% confidence level = 0.863474

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.92511	-3.93458
rho	n/a	0
a	1.94872	1.8335
b	0.226816	0.0618833

c	1.26256	1.40878
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	1.95	0.16	0.14	-0.4213
0.1	10	1.98	1.96	0.13	0.14	0.4458
3	10	2.2	2.2	0.09	0.14	-0.02878
30	10	2.46	2.46	0.19	0.14	0.004213

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	58.69166	5	-107.3833
A2	61.62066	8	-107.2413
A3	58.69166	5	-107.3833
R	35.14294	2	-66.28588
5	58.50222	4	-109.0044

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.96	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 7a	0.3789	1	0.5382

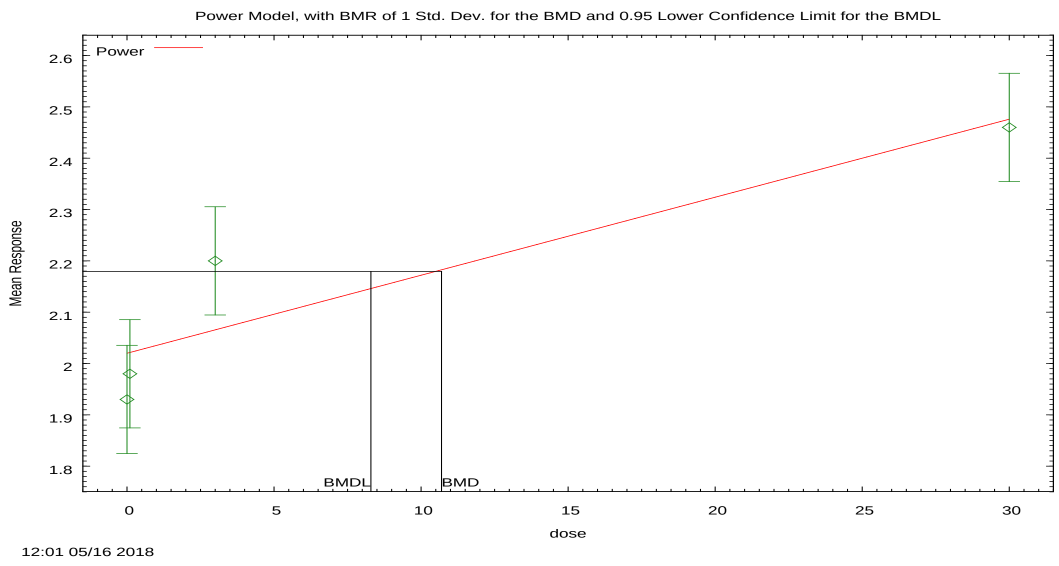

Figure 78. Plot of mean response by dose with fitted curve for Power model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 10.695

BMDL at the 95% confidence level = 8.29343

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0265786	0.0217265
rho	n/a	0
control	2.01636	1.93
slope	0.0152435	0.126978
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	2.02	0.16	0.16	-1.68
0.1	10	1.98	2.02	0.13	0.16	-0.735
3	10	2.2	2.06	0.09	0.16	2.68
30	10	2.46	2.47	0.19	0.16	-0.265

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	58.691662	5	-107.383323
A2	61.62066	8	-107.241319
A3	58.691662	5	-107.383323
fitted	52.552971	3	-99.105942
R	35.142939	2	-66.285878

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.9554	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 4	12.2774	2	0.002158

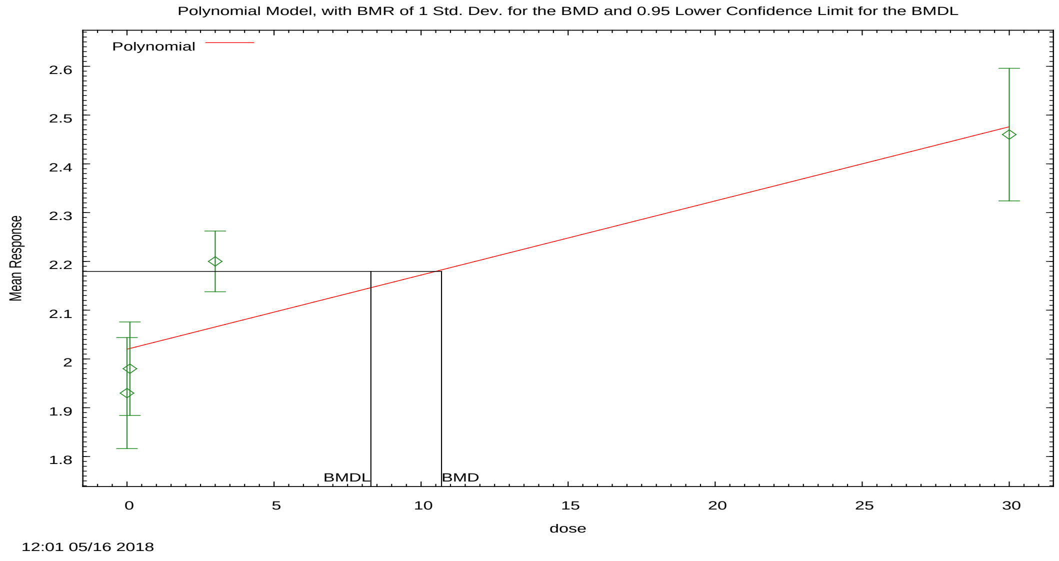

Figure 79. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 10.695

BMDL at the 95% confidence level = 8.29343

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0265786	0.0217265
rho	n/a	0
beta_0	2.01636	1.93
beta_1	0.0152435	0.51553

beta_2	5.74431E-29	0
beta_3	0	0.00463881

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	2.02	0.16	0.16	-1.68
0.1	10	1.98	2.02	0.13	0.16	-0.735
3	10	2.2	2.06	0.09	0.16	2.68
30	10	2.46	2.47	0.19	0.16	-0.265

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	58.691662	5	-107.383323
A2	61.62066	8	-107.241319
A3	58.691662	5	-107.383323
fitted	52.552971	3	-99.105942
R	35.142939	2	-66.285878

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.9554	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 4	12.2774	2	0.002158

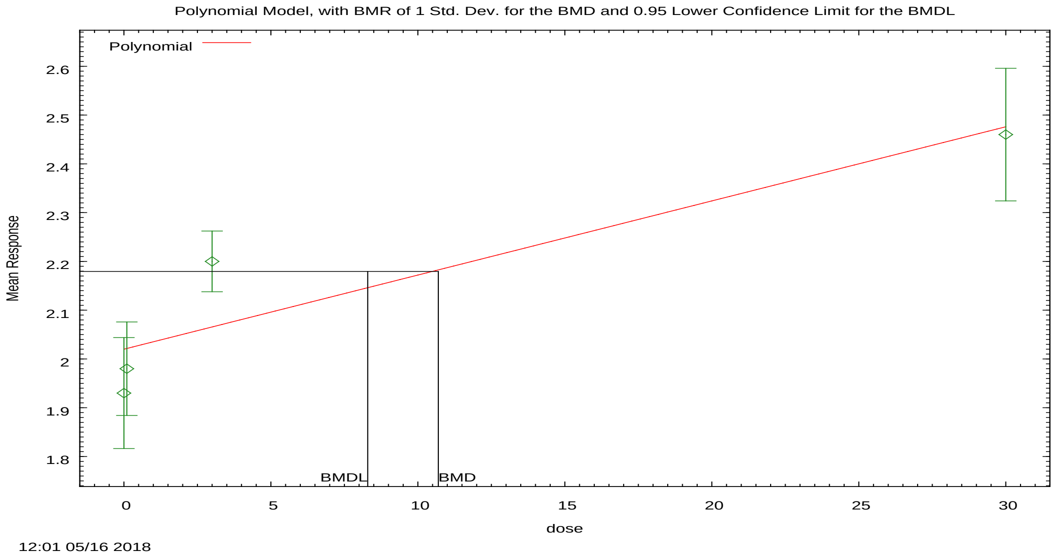

Figure 80. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 10.695

BMDL at the 95% confidence level = 8.29343

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0265786	0.0217265
rho	n/a	0
beta_0	2.01636	1.95008
beta_1	0.0152435	0.0909581

beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	2.02	0.16	0.16	-1.68
0.1	10	1.98	2.02	0.13	0.16	-0.735
3	10	2.2	2.06	0.09	0.16	2.68
30	10	2.46	2.47	0.19	0.16	-0.265

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	58.691662	5	-107.383323
A2	61.62066	8	-107.241319
A3	58.691662	5	-107.383323
fitted	52.552971	3	-99.105942
R	35.142939	2	-66.285878

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.9554	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 4	12.2774	2	0.002158

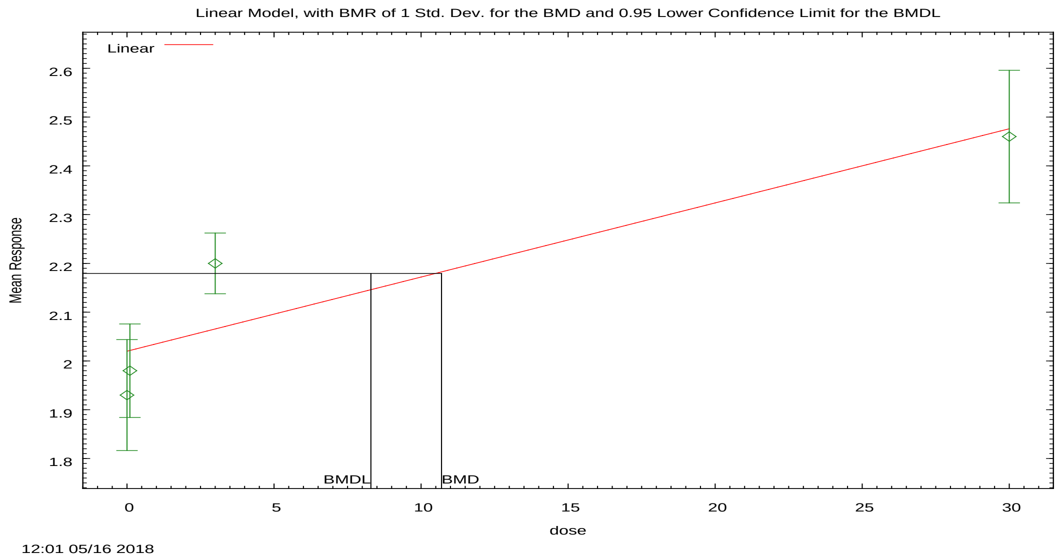

Figure 81. Plot of mean response by dose with fitted curve for Linear model with constant variance for Albumin to Globulin Ratio in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 10.695

BMDL at the 95% confidence level = 8.29343

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0265786	0.0217265
rho	n/a	0
beta_0	2.01636	2.01636
beta_1	0.0152435	0.0152435

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.93	2.02	0.16	0.16	-1.68
0.1	10	1.98	2.02	0.13	0.16	-0.735
3	10	2.2	2.06	0.09	0.16	2.68
30	10	2.46	2.47	0.19	0.16	-0.265

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	58.691662	5	-107.383323
A2	61.62066	8	-107.241319
A3	58.691662	5	-107.383323
fitted	52.552971	3	-99.105942
R	35.142939	2	-66.285878

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	52.9554	6	<0.0001
Test 2	5.858	3	0.1187
Test 3	5.858	3	0.1187
Test 4	12.2774	2	0.002158

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery – Albumin to Globulin Ratio in Males

1.10. BMDS Summary of Albumin to Globulin ratio Males (28 Day Rats GenX)

Table 10. Summary of BMD Modeling Results for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.0361	-77.595	10.7	8.62	1.24	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. Selected BMDL is from model with lowest AIC and lowest BMDL.
Exponential (M4) Exponential (M5)[c]	0.511	-81.804	2.07	1.17	1.76	
Hill	**0.544**	**-81.868**	**1.94**	**0.945**	**2.05**	
Power[d] Polynomial 3°[e] Polynomial 2°[f] Linear	0.0456	-78.061	9.58	7.53	1.27	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.764), selected model in bold; scaled residuals for selected model for doses 0, 0.3, 3, and 30 mg/kg/day were -0.38, 0.46, -0.1, 0.01, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[e] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[f] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

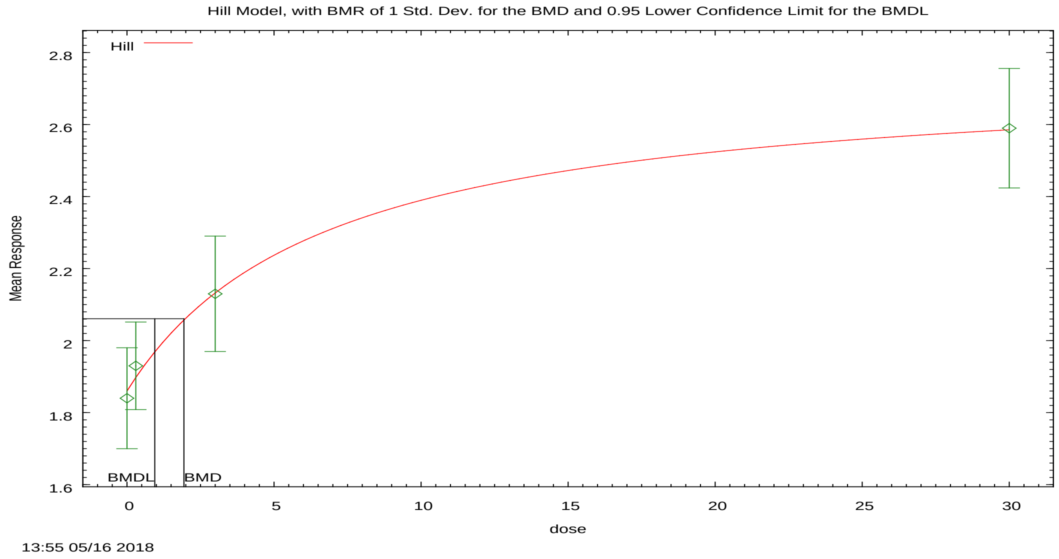

Figure 82. Plot of mean response by dose with fitted curve for Hill model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.93577

BMDL at the 95% confidence level = 0.944663

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0389019	0.042829
rho	n/a	0
intercept	1.86356	1.84
v	0.890165	0.75
n	1	0.274093
k	6.80075	52.0109

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.86	0.2	0.2	-0.378
0.3	10	1.93	1.9	0.17	0.2	0.462
3	10	2.13	2.14	0.22	0.2	-0.0969
30	10	2.59	2.59	0.23	0.2	0.0124

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.118007	5	-80.236014

A2	45.694456	8	-75.388913
A3	45.118007	5	-80.236014
fitted	44.934219	4	-81.868439
R	22.006792	2	-40.013584

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	47.3753	6	<0.0001
Test 2	1.1529	3	0.7643
Test 3	1.1529	3	0.7643
Test 4	0.367575	1	0.5443

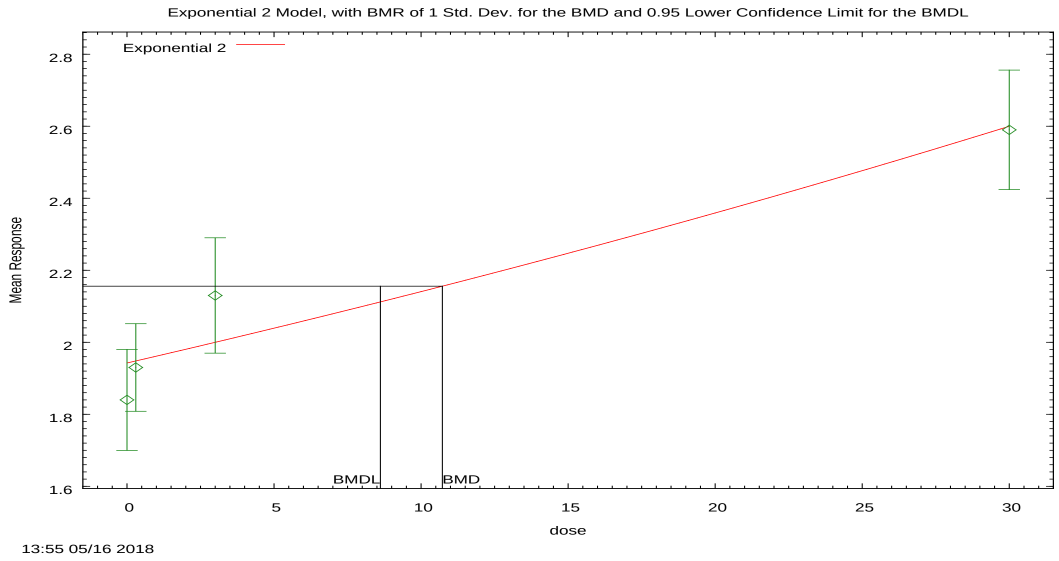

Figure 83. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 10.724

BMDL at the 95% confidence level = 8.61641

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.08988	-3.2559
rho	n/a	0
a	1.94249	1.9376
b	0.0097164	0.00988805
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.94	0.2	0.21	-1.519
0.3	10	1.93	1.95	0.17	0.21	-0.2692
3	10	2.13	2	0.22	0.21	1.928
30	10	2.59	2.6	0.23	0.21	-0.1463

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.11801	5	-80.23601
A2	45.69446	8	-75.38891
A3	45.11801	5	-80.23601
R	22.00679	2	-40.01358
2	41.79755	3	-77.5951

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	47.38	6	<0.0001
Test 2	1.153	3	0.7643
Test 3	1.153	3	0.7643
Test 4	6.641	2	0.03614

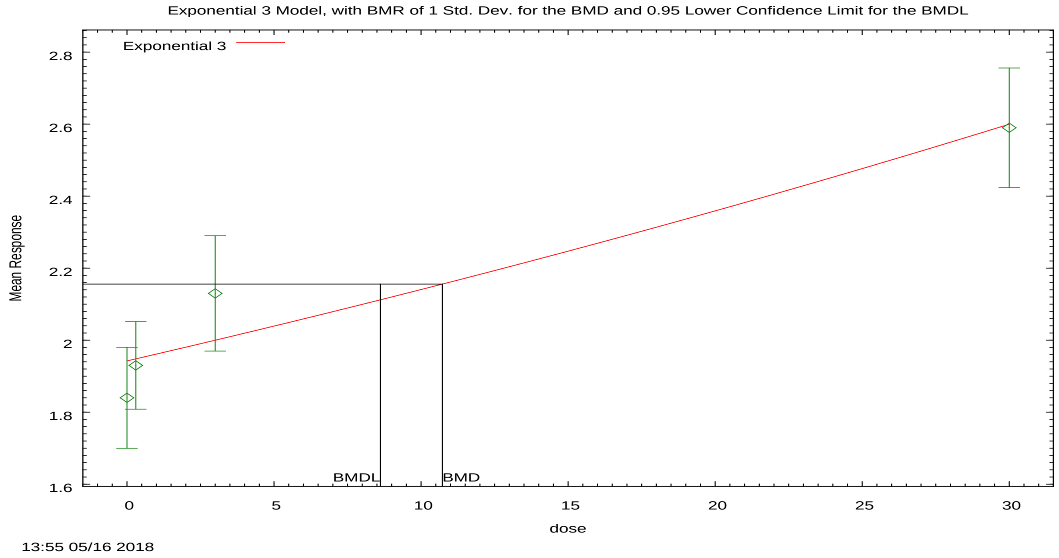

Figure 84. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 10.724

BMDL at the 95% confidence level = 8.61641

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.08988	-3.2559
rho	n/a	0
a	1.94249	1.9376
b	0.0097164	0.00988805
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.94	0.2	0.21	-1.519
0.3	10	1.93	1.95	0.17	0.21	-0.2692
3	10	2.13	2	0.22	0.21	1.928
30	10	2.59	2.6	0.23	0.21	-0.1463

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.11801	5	-80.23601
A2	45.69446	8	-75.38891
A3	45.11801	5	-80.23601
R	22.00679	2	-40.01358
3	41.79755	3	-77.5951

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	47.38	6	<0.0001
Test 2	1.153	3	0.7643
Test 3	1.153	3	0.7643
Test 5a	6.641	2	0.03614

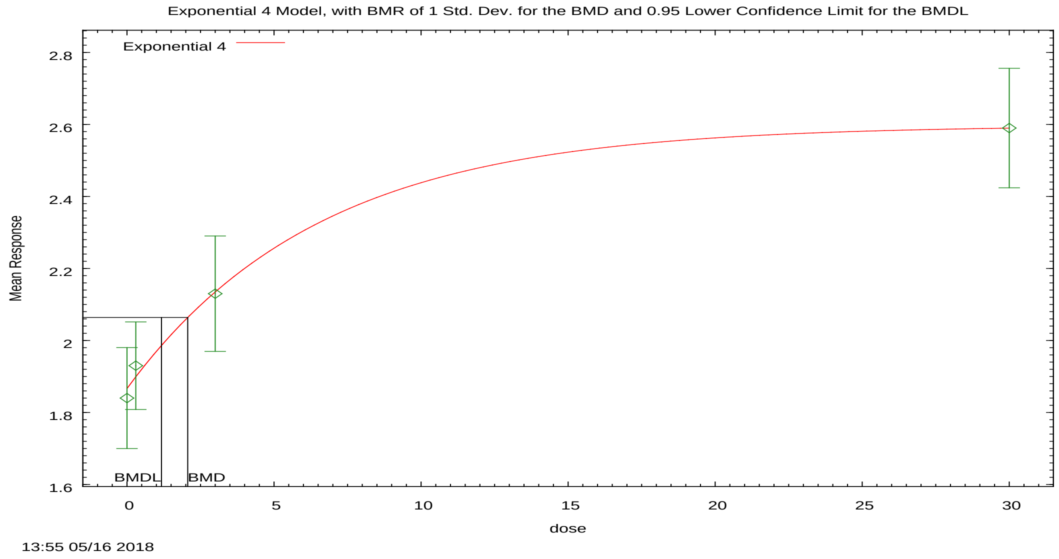

Figure 85. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.06536

BMDL at the 95% confidence level = 1.1729

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.24509	-3.2559
rho	n/a	0
a	1.86649	1.748
b	0.152473	0.0682174

c	1.39148	1.55578
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.87	0.2	0.2	-0.4243
0.3	10	1.93	1.9	0.17	0.2	0.4941
3	10	2.13	2.13	0.22	0.2	-0.07551
30	10	2.59	2.59	0.23	0.2	0.005683

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.11801	5	-80.23601
A2	45.69446	8	-75.38891
A3	45.11801	5	-80.23601
R	22.00679	2	-40.01358
4	44.90188	4	-81.80377

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	47.38	6	<0.0001
Test 2	1.153	3	0.7643
Test 3	1.153	3	0.7643
Test 6a	0.4322	1	0.5109

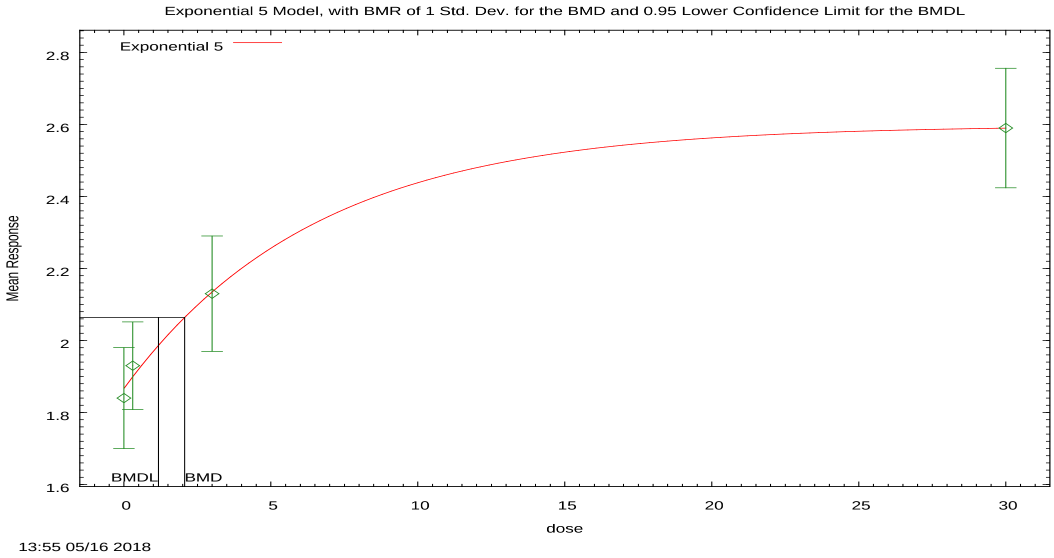

Figure 86. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.06536

BMDL at the 95% confidence level = 1.1729

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.24509	-3.2559
rho	n/a	0
a	1.86649	1.748
b	0.152473	0.0682174

c	1.39148	1.55578
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.87	0.2	0.2	-0.4243
0.3	10	1.93	1.9	0.17	0.2	0.4941
3	10	2.13	2.13	0.22	0.2	-0.07551
30	10	2.59	2.59	0.23	0.2	0.005683

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.11801	5	-80.23601
A2	45.69446	8	-75.38891
A3	45.11801	5	-80.23601
R	22.00679	2	-40.01358
5	44.90188	4	-81.80377

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	47.38	6	<0.0001
Test 2	1.153	3	0.7643
Test 3	1.153	3	0.7643
Test 7a	0.4322	1	0.5109

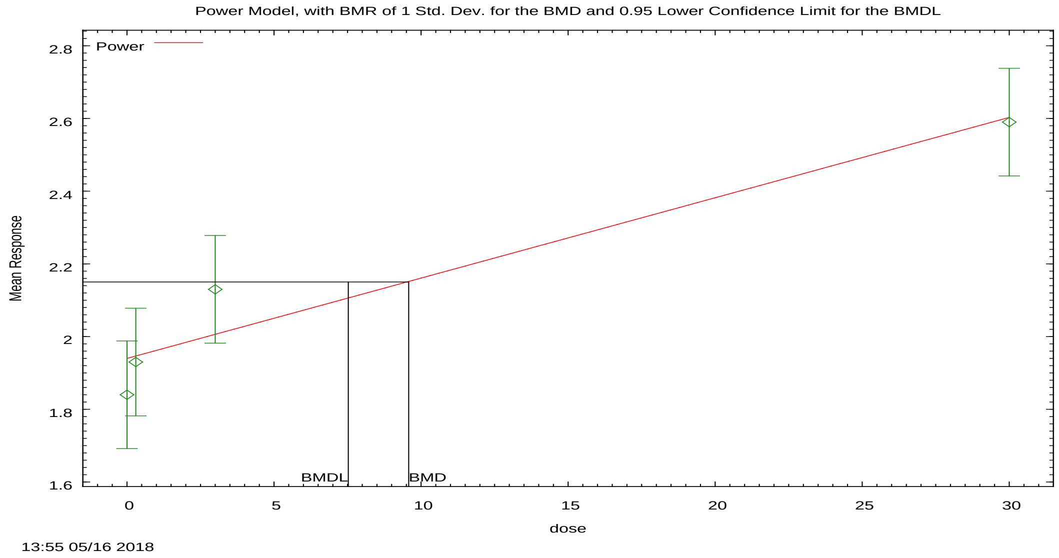

Figure 87. Plot of mean response by dose with fitted curve for Power model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 9.57917

BMDL at the 95% confidence level = 7.52523

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0449805	0.042829
rho	n/a	0
control	1.93818	1.84
slope	0.0221403	0.156668
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.94	0.2	0.21	-1.46
0.3	10	1.93	1.94	0.17	0.21	-0.221
3	10	2.13	2	0.22	0.21	1.87
30	10	2.59	2.6	0.23	0.21	-0.185

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.118007	5	-80.236014
A2	45.694456	8	-75.388913
A3	45.118007	5	-80.236014
fitted	42.030543	3	-78.061087
R	22.006792	2	-40.013584

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	47.3753	6	<0.0001
Test 2	1.1529	3	0.7643
Test 3	1.1529	3	0.7643
Test 4	6.17493	2	0.04562

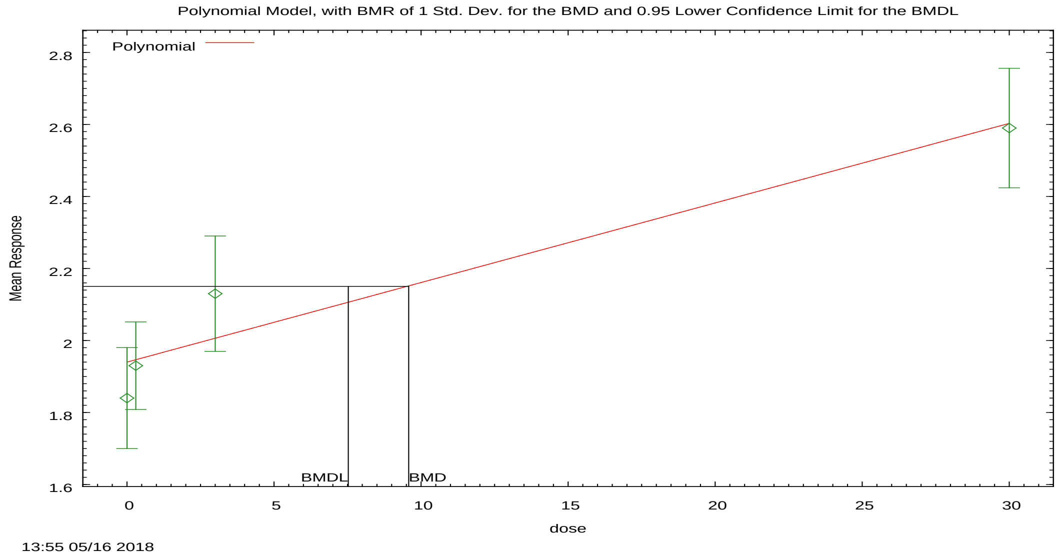

Figure 88. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 9.57917

BMDL at the 95% confidence level = 7.52523

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0449805	0.042829
rho	n/a	0
beta_0	1.93818	1.84
beta_1	0.0221403	0.324794
beta_2	0	0

beta_3	0	0.00244627

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.94	0.2	0.21	-1.46
0.3	10	1.93	1.94	0.17	0.21	-0.221
3	10	2.13	2	0.22	0.21	1.87
30	10	2.59	2.6	0.23	0.21	-0.185

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.118007	5	-80.236014
A2	45.694456	8	-75.388913
A3	45.118007	5	-80.236014
fitted	42.030543	3	-78.061087
R	22.006792	2	-40.013584

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	47.3753	6	<0.0001
Test 2	1.1529	3	0.7643
Test 3	1.1529	3	0.7643
Test 4	6.17493	2	0.04562

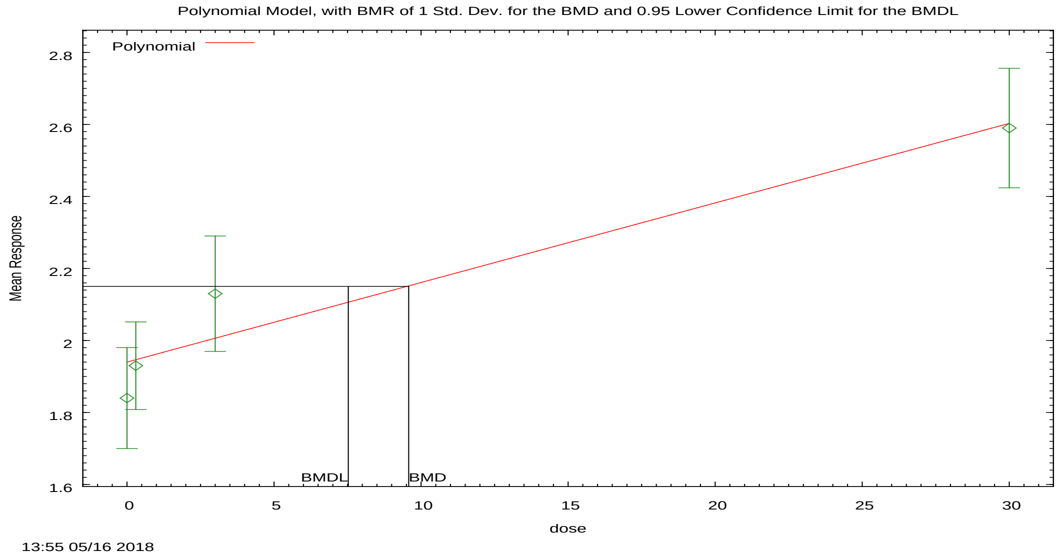

Figure 89. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 9.57917

BMDL at the 95% confidence level = 7.52523

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0449805	0.042829
rho	n/a	0
beta_0	1.93818	1.86903
beta_1	0.0221403	0.0953114
beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.94	0.2	0.21	-1.46
0.3	10	1.93	1.94	0.17	0.21	-0.221
3	10	2.13	2	0.22	0.21	1.87
30	10	2.59	2.6	0.23	0.21	-0.185

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.118007	5	-80.236014
A2	45.694456	8	-75.388913
A3	45.118007	5	-80.236014
fitted	42.030543	3	-78.061087
R	22.006792	2	-40.013584

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	47.3753	6	<0.0001
Test 2	1.1529	3	0.7643
Test 3	1.1529	3	0.7643
Test 4	6.17493	2	0.04562

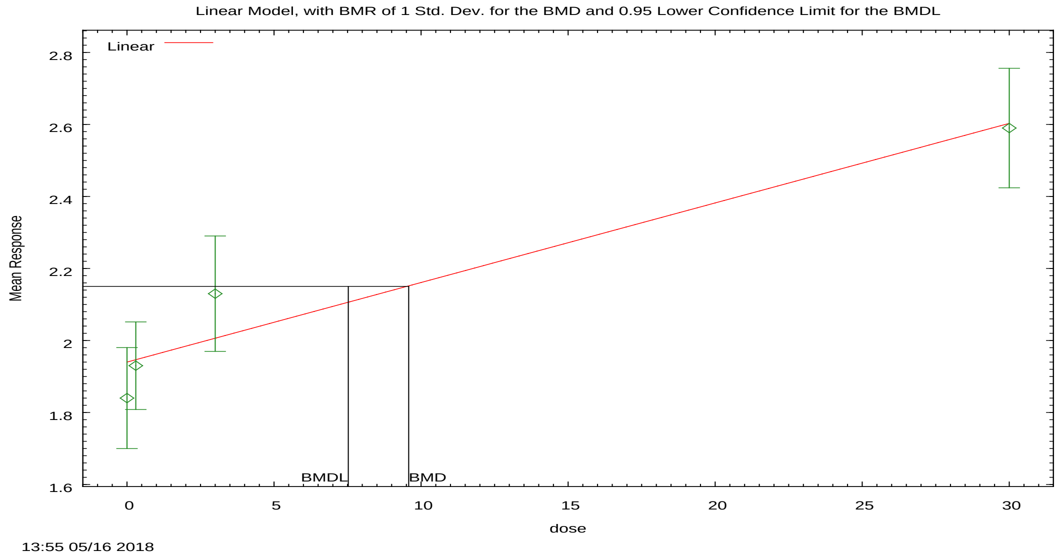

Figure 90. Plot of mean response by dose with fitted curve for Linear model with constant variance for Albumin to Globulin Ratio in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 9.57917

BMDL at the 95% confidence level = 7.52523

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0449805	0.042829
rho	n/a	0
beta_0	1.93818	1.93818
beta_1	0.0221403	0.0221403

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.84	1.94	0.2	0.21	-1.46
0.3	10	1.93	1.94	0.17	0.21	-0.221
3	10	2.13	2	0.22	0.21	1.87
30	10	2.59	2.6	0.23	0.21	-0.185

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	45.118007	5	-80.236014
A2	45.694456	8	-75.388913
A3	45.118007	5	-80.236014
fitted	42.030543	3	-78.061087
R	22.006792	2	-40.013584

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	47.3753	6	<0.0001
Test 2	1.1529	3	0.7643
Test 3	1.1529	3	0.7643
Test 4	6.17493	2	0.04562

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery – Albumin to Globulin Ratio in Males

1.11. BMDS Summary of Albumin to globulin ration Males (90 Day Rats GenX)

Table 11. Summary of BMD Modeling Results for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	3.57E-04	-52.840	58.6	38.3	1.53	Only one model met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from this model.
Exponential (M4) **Exponential (M5)[c]**	**0.287**	**-65.584**	**3.39**	**0.0741**	**45.8**	
Hill	0.317	-65.718	2.10	error[d]	error	
Power[e] Polynomial 3°[f] Polynomial 2°[g] Linear	4.29E-04	-53.210	53.6	32.6	1.64	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0976), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 10, and 100 mg/kg/day were -0.72, 0.73, 0.01, -0.02, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[d] BMD or BMDL computation failed for this model.

[e] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[g] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

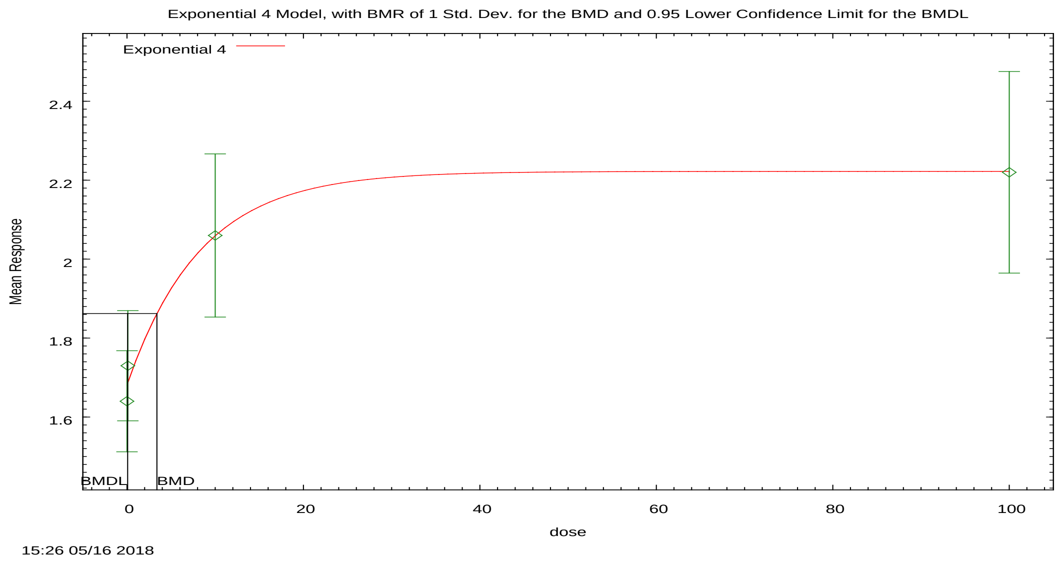

Figure 91. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 3.39438

BMDL at the 95% confidence level = 0.0740762

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.68779	-5.73506
rho	4.36573	4.55995
a	1.68125	1.558
b	0.119894	0.0202556
c	1.32183	1.49615
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.68	0.18	0.18	-0.7212
0.1	10	1.73	1.69	0.2	0.18	0.7332
10	10	2.06	2.06	0.29	0.28	0.0091
100	10	2.22	2.22	0.36	0.33	-0.02215

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.21855	5	-60.4371
A2	38.37194	8	-60.74389
A3	38.35916	6	-64.71831
R	22.53874	2	-41.07748
4	37.79209	5	-65.58419

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.67	6	<0.0001
Test 2	6.307	3	0.0976
Test 3	0.02558	2	0.9873
Test 6a	1.134	1	0.2869

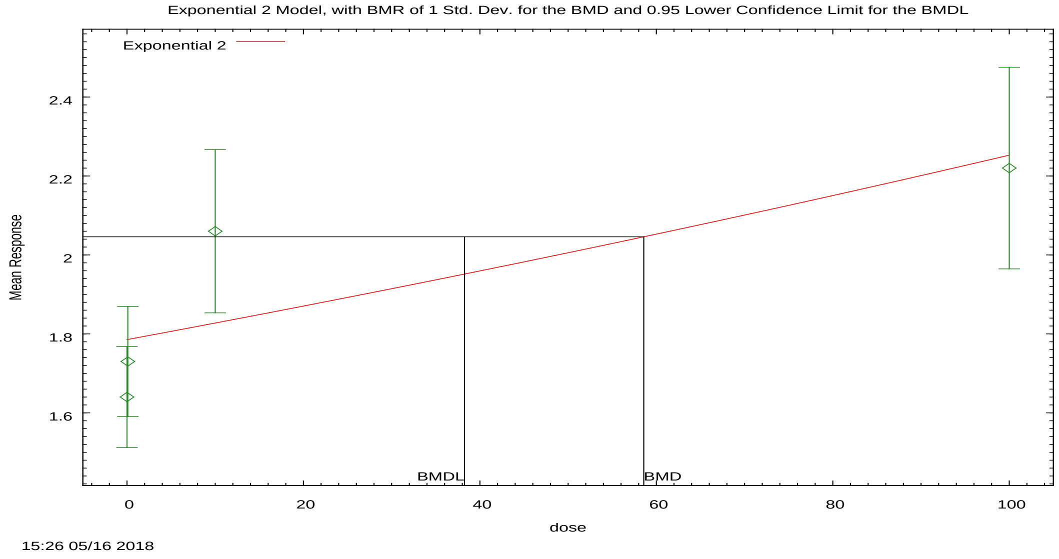

Figure 92. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 58.5756

BMDL at the 95% confidence level = 38.2584

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.22829	-5.73506
rho	2.65236	4.55995
a	1.78551	1.77993
b	0.00232455	0.00233187
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.79	0.18	0.26	-1.767
0.1	10	1.73	1.79	0.2	0.26	-0.6788
10	10	2.06	1.83	0.29	0.27	2.737
100	10	2.22	2.25	0.36	0.35	-0.2923

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.21855	5	-60.4371
A2	38.37194	8	-60.74389
A3	38.35916	6	-64.71831
R	22.53874	2	-41.07748
2	30.42	4	-52.84

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.67	6	<0.0001
Test 2	6.307	3	0.0976
Test 3	0.02558	2	0.9873
Test 4	15.88	2	0.0003565

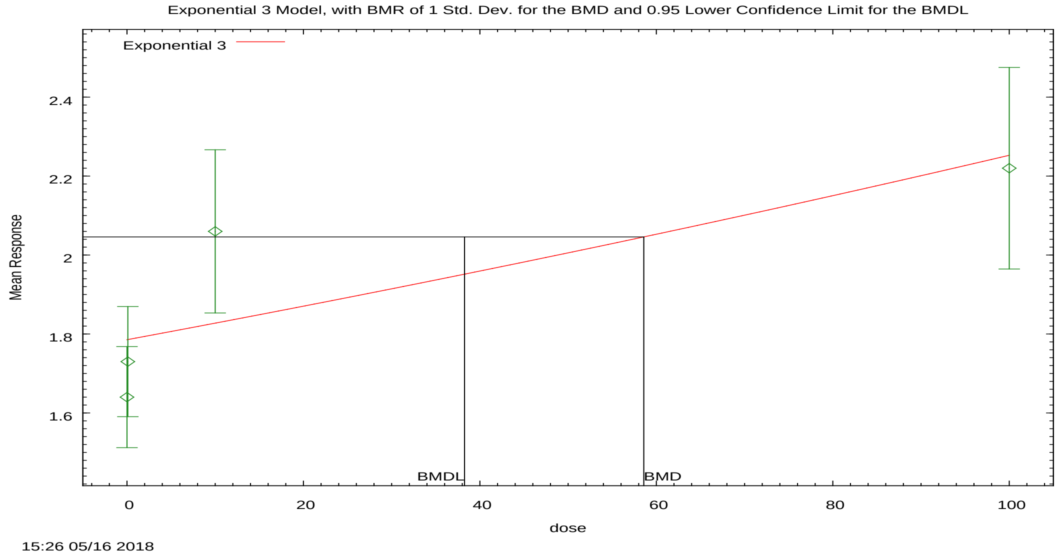

Figure 93. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 58.5756

BMDL at the 95% confidence level = 38.2584

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.22829	-5.73506
rho	2.65236	4.55995
a	1.78551	1.77993
b	0.00232455	0.00233187
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.79	0.18	0.26	-1.767
0.1	10	1.73	1.79	0.2	0.26	-0.6788
10	10	2.06	1.83	0.29	0.27	2.737
100	10	2.22	2.25	0.36	0.35	-0.2923

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.21855	5	-60.4371
A2	38.37194	8	-60.74389
A3	38.35916	6	-64.71831
R	22.53874	2	-41.07748
3	30.42	4	-52.84

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.67	6	<0.0001
Test 2	6.307	3	0.0976
Test 3	0.02558	2	0.9873
Test 5a	15.88	2	0.0003565

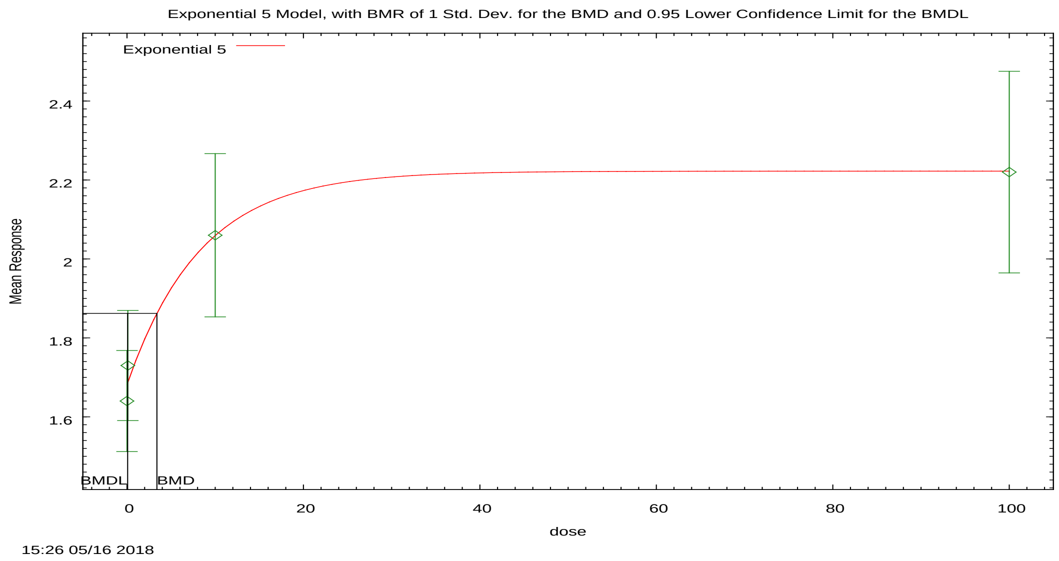

Figure 94. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 3.39438

BMDL at the 95% confidence level = 0.0740762

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.68779	-5.73506
rho	4.36573	4.55995
a	1.68125	1.558
b	0.119894	0.0202556

c	1.32183	1.49615
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.68	0.18	0.18	-0.7212
0.1	10	1.73	1.69	0.2	0.18	0.7332
10	10	2.06	2.06	0.29	0.28	0.0091
100	10	2.22	2.22	0.36	0.33	-0.02215

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.21855	5	-60.4371
A2	38.37194	8	-60.74389
A3	38.35916	6	-64.71831
R	22.53874	2	-41.07748
5	37.79209	5	-65.58419

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.67	6	<0.0001
Test 2	6.307	3	0.0976
Test 3	0.02558	2	0.9873
Test 7a	1.134	1	0.2869

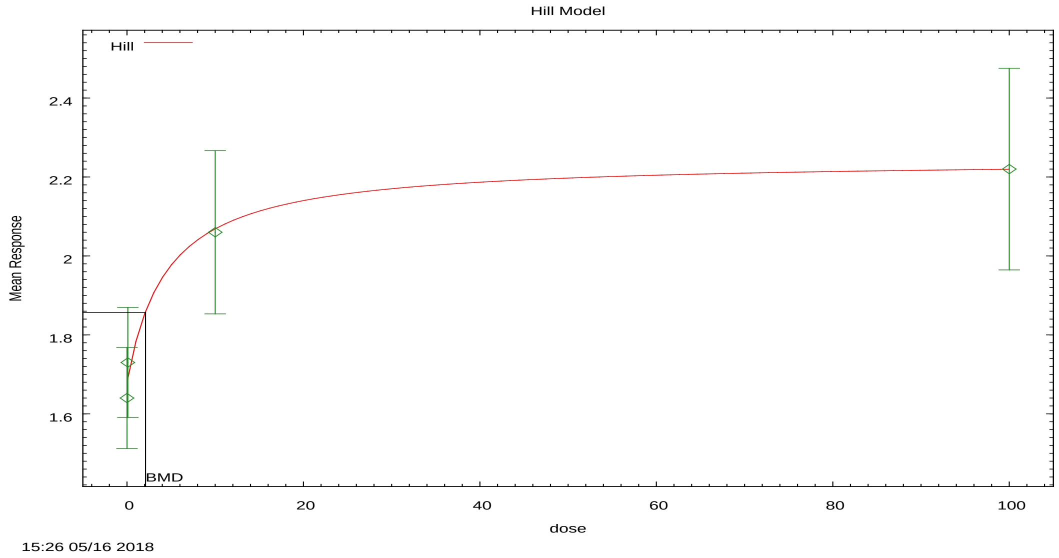

Figure 95. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.10363

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-5.71034	-2.65557
rho	4.39592	0
intercept	1.67749	1.64
v	0.563704	0.58
n	1	0.17171

k	4.50647	13.9

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.68	0.18	0.18	-0.661
0.1	10	1.73	1.69	0.2	0.18	0.699
10	10	2.06	2.07	0.29	0.28	-0.0678
100	10	2.22	2.22	0.36	0.33	0.0297

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.218548	5	-60.437095
A2	38.371943	8	-60.743886
A3	38.359155	6	-64.718311
fitted	37.859149	5	-65.718297
R	22.53874	2	-41.07748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.6664	6	<0.0001
Test 2	6.30679	3	0.0976
Test 3	0.0255757	2	0.9873
Test 4	1.00001	1	0.3173

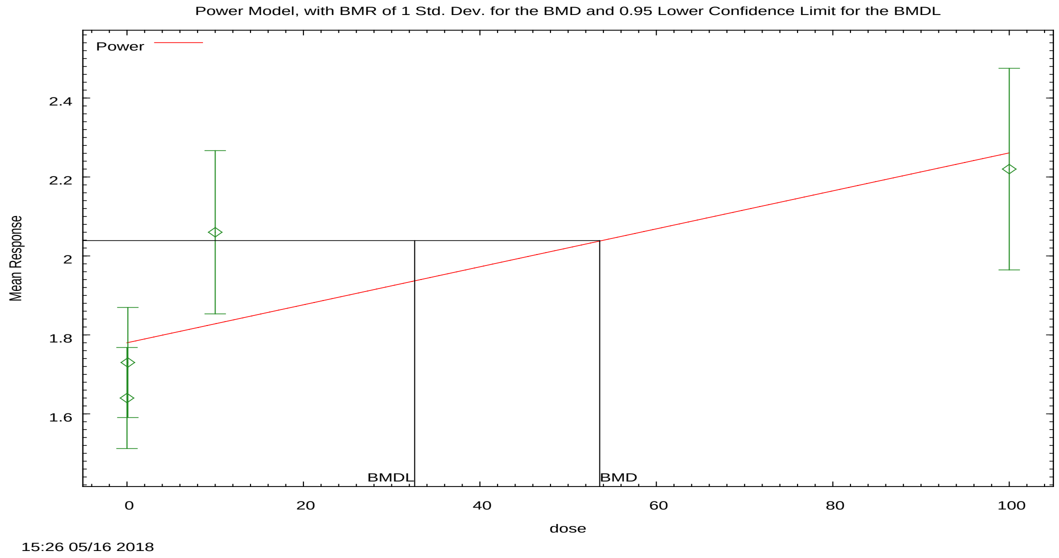

Figure 96. Plot of mean response by dose with fitted curve for Power model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 53.5795

BMDL at the 95% confidence level = 32.6083

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.29434	-2.65557
rho	2.7405	0
control	1.78111	1.64
slope	0.00480846	0.160496
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.78	0.18	0.26	-1.73
0.1	10	1.73	1.78	0.2	0.26	-0.633
10	10	2.06	1.83	0.29	0.27	2.73
100	10	2.22	2.26	0.36	0.36	-0.371

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.218548	5	-60.437095
A2	38.371943	8	-60.743886
A3	38.359155	6	-64.718311
fitted	30.605013	4	-53.210026
R	22.53874	2	-41.07748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.6664	6	<0.0001
Test 2	6.30679	3	0.0976
Test 3	0.0255757	2	0.9873
Test 4	15.5083	2	0.000429

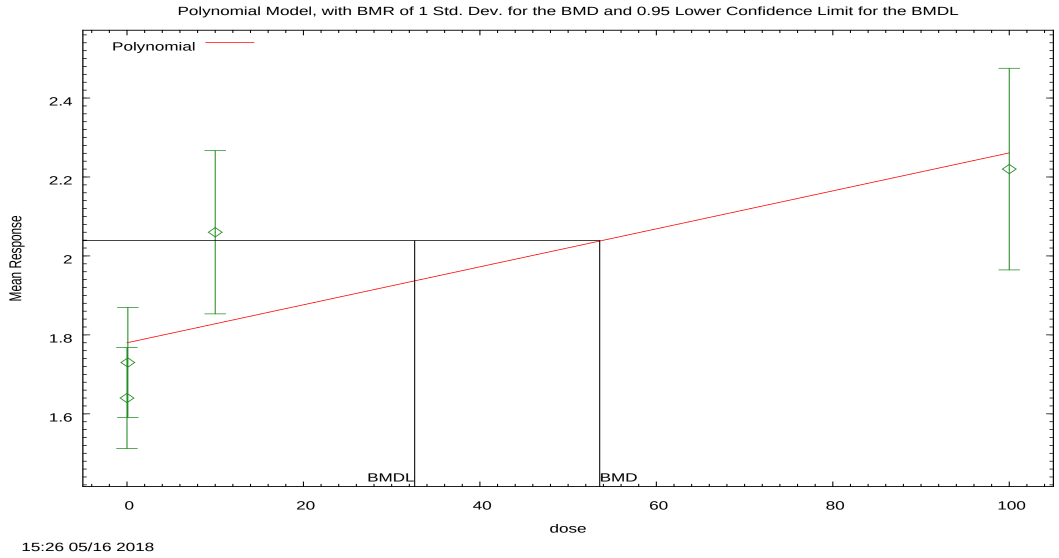

Figure 97. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 53.5795

BMDL at the 95% confidence level = 32.6083

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.29434	-2.65557
rho	2.7405	0
beta_0	1.78111	1.64
beta_1	0.00480846	0.90953
beta_2	0	0

beta_3	0	0.000863508

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.78	0.18	0.26	-1.73
0.1	10	1.73	1.78	0.2	0.26	-0.633
10	10	2.06	1.83	0.29	0.27	2.73
100	10	2.22	2.26	0.36	0.36	-0.371

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.218548	5	-60.437095
A2	38.371943	8	-60.743886
A3	38.359155	6	-64.718311
fitted	30.605013	4	-53.210026
R	22.53874	2	-41.07748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.6664	6	<0.0001
Test 2	6.30679	3	0.0976
Test 3	0.0255757	2	0.9873
Test 4	15.5083	2	0.000429

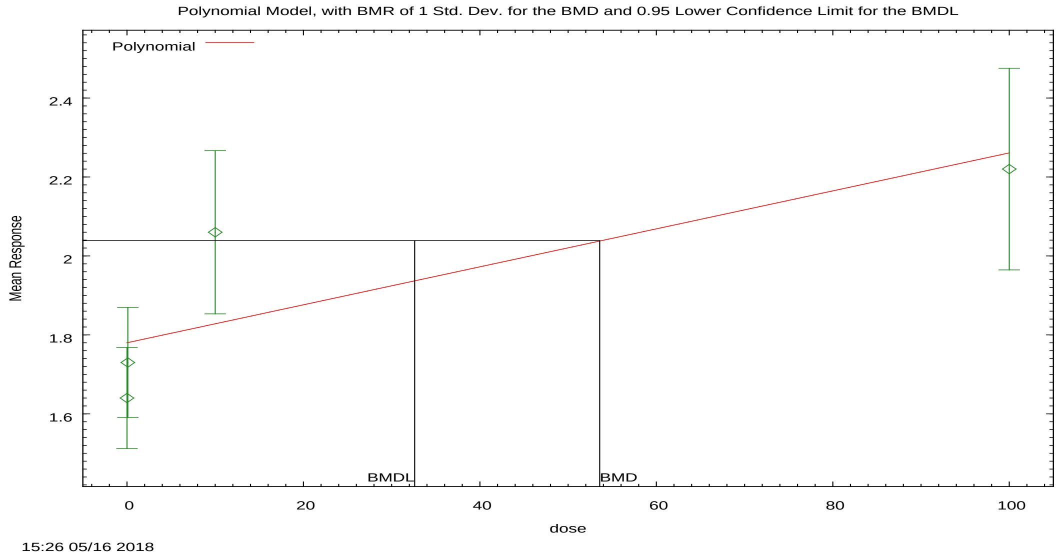

Figure 98. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 53.5795

BMDL at the 95% confidence level = 32.6083

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.29434	-2.65557
rho	2.74049	0
beta_0	1.78111	1.6827
beta_1	0.00480845	0.041379
beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.78	0.18	0.26	-1.73
0.1	10	1.73	1.78	0.2	0.26	-0.633
10	10	2.06	1.83	0.29	0.27	2.73
100	10	2.22	2.26	0.36	0.36	-0.371

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.218548	5	-60.437095
A2	38.371943	8	-60.743886
A3	38.359155	6	-64.718311
fitted	30.605013	4	-53.210026
R	22.53874	2	-41.07748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.6664	6	<0.0001
Test 2	6.30679	3	0.0976
Test 3	0.0255757	2	0.9873
Test 4	15.5083	2	0.000429

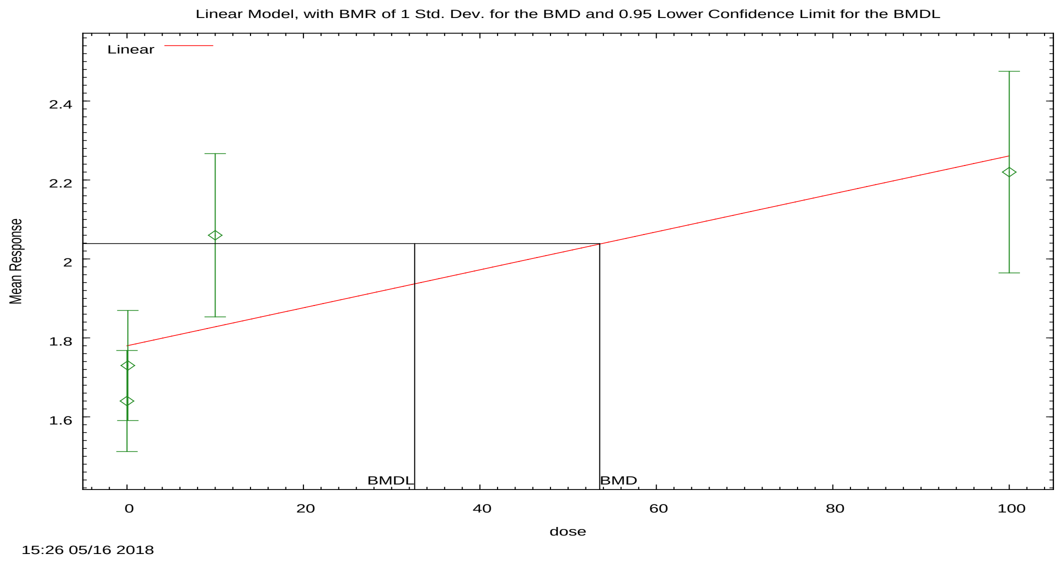

Figure 99. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Albumin to Globulin Ratio in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 53.5795

BMDL at the 95% confidence level = 32.6083

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.29434	-2.65557
rho	2.7405	0
beta_0	1.78111	1.7871
beta_1	0.00480846	0.00455573

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	1.64	1.78	0.18	0.26	-1.73
0.1	10	1.73	1.78	0.2	0.26	-0.633
10	10	2.06	1.83	0.29	0.27	2.73
100	10	2.22	2.26	0.36	0.36	-0.371

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	35.218548	5	-60.437095
A2	38.371943	8	-60.743886
A3	38.359155	6	-64.718311
fitted	30.605013	4	-53.210026
R	22.53874	2	-41.07748

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	31.6664	6	<0.0001
Test 2	6.30679	3	0.0976
Test 3	0.0255757	2	0.9873
Test 4	15.5083	2	0.000429

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Alkaline Phosphatase (U/L) in Males

1.12. BMDS Summary of Alkaline Phosphatase (U/L) Males (28 Day Mice GenX)

Table 12. Summary of BMD Modeling Results for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.00187	391.80	3.47	2.78	1.25	No models met all model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). No BMDL was selected.
Exponential (M4)	0.00390	389.57	0.862	0.606	1.42	
Exponential (M5)	N/A[c]	387.31	1.43	0.862	1.66	
Hill	N/A[c]	386.96	2.48	error[d]	error	
Power	0.0435	385.31	1.43	0.862	1.66	
Polynomial 3°[e]	0.0344	385.71	1.25	0.774	1.62	
Polynomial 2°[f]	0.0344	385.71	1.25	0.774	1.62	
Linear	0.0155	387.57	0.862	0.606	1.42	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001, BMDS Test 3 *p*-value = 0.776), no model was selected as a best-fitting model.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] No available degrees of freedom to calculate a goodness of fit value.

[d] BMD or BMDL computation failed for this model.

[e] The Polynomial 3° model may appear equivalent to the Polynomial 2° model, however differences exist in digits not displayed in the table.

[f] The Polynomial 2° model may appear equivalent to the Polynomial 3° model, however differences exist in digits not displayed in the table.

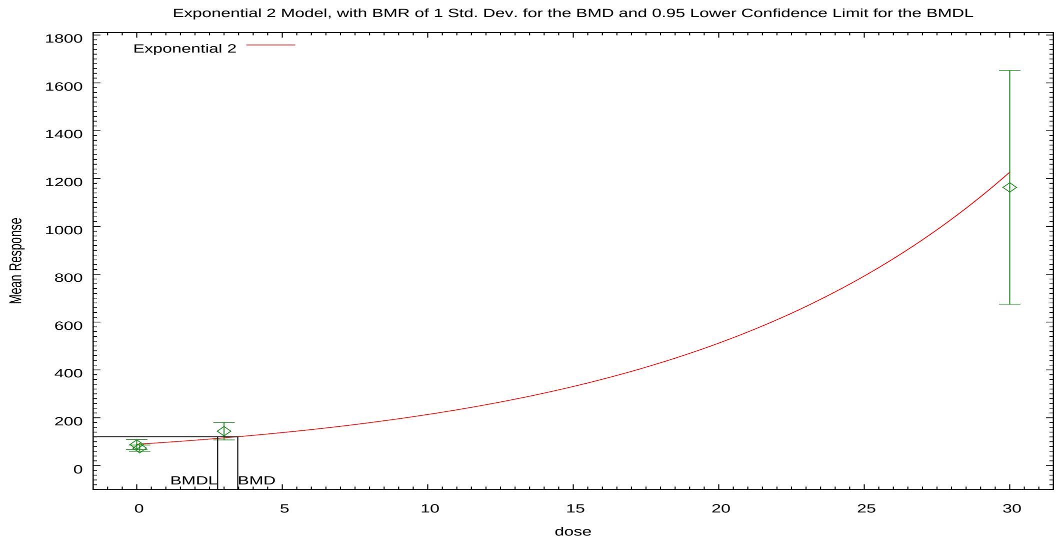

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Figure 100. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 3.47188

BMDL at the 95% confidence level = 2.78094

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.5774	-4.80015
rho	2.33475	2.53385
a	89.1533	88.4408
b	0.0873921	0.0866173
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	88	89.15	29.5	31.6	-0.1154
0.1	10	73	89.94	18.2	31.93	-1.677
3	10	144	115.9	51.2	42.92	2.072
30	10	1163	1227	682.4	674.4	-0.2989

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC

A1	-251.3551	5	512.7101
A2	-185.3645	8	386.7289
A3	-185.6179	6	383.2357
R	-273.3673	2	550.7345
2	-191.8982	4	391.7964

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	176	6	<0.0001
Test 2	132	3	<0.0001
Test 3	0.5068	2	0.7761
Test 4	12.56	2	0.001873

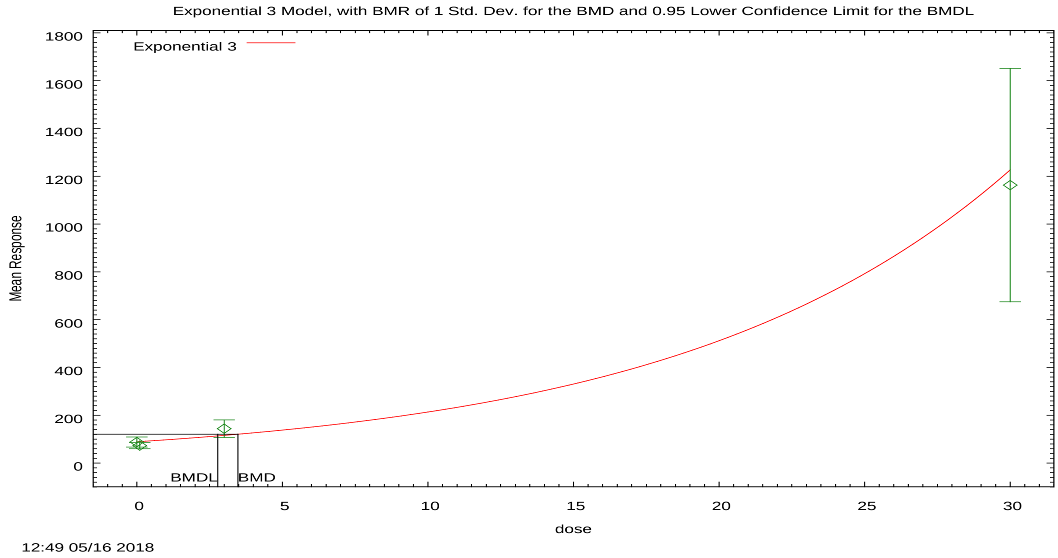

Figure 101. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 3.47188

BMDL at the 95% confidence level = 2.78094

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.57739	-4.80015
rho	2.33475	2.53385
a	89.1533	88.4408
b	0.0873921	0.0866173
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	88	89.15	29.5	31.6	-0.1154
0.1	10	73	89.94	18.2	31.93	-1.677
3	10	144	115.9	51.2	42.92	2.072
30	10	1163	1227	682.4	674.4	-0.2989

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-251.3551	5	512.7101
A2	-185.3645	8	386.7289
A3	-185.6179	6	383.2357
R	-273.3673	2	550.7345
3	-191.8982	4	391.7964

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	176	6	<0.0001
Test 2	132	3	<0.0001
Test 3	0.5068	2	0.7761
Test 5a	12.56	2	0.001873

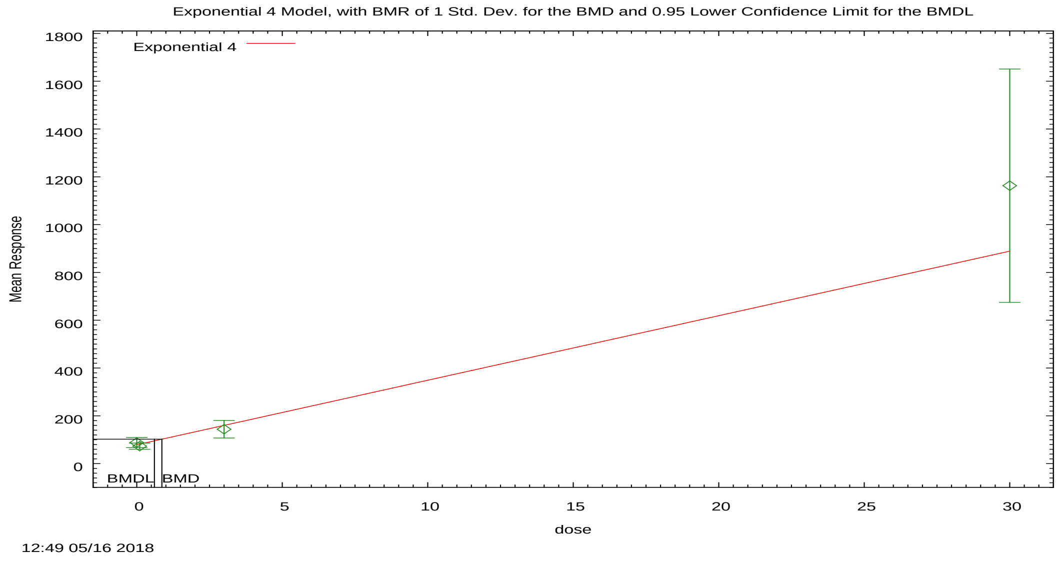

Figure 102. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.862411

BMDL at the 95% confidence level = 0.606488

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values

lnalpha	-5.83404	-4.80015
rho	2.7762	2.53385
a	78.9796	69.35
b	0.000000651607	0.0000312636
c	524659	16770
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	88	78.98	29.5	23.29	1.225
0.1	10	73	81.68	18.2	24.4	-1.125
3	10	144	160	51.2	62.03	-0.8147
30	10	1163	889	682.4	670.7	1.292

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-251.3551	5	512.7101
A2	-185.3645	8	386.7289
A3	-185.6179	6	383.2357
R	-273.3673	2	550.7345
4	-189.7831	5	389.5662

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	176	6	<0.0001
Test 2	132	3	<0.0001
Test 3	0.5068	2	0.7761
Test 6a	8.33	1	0.003899

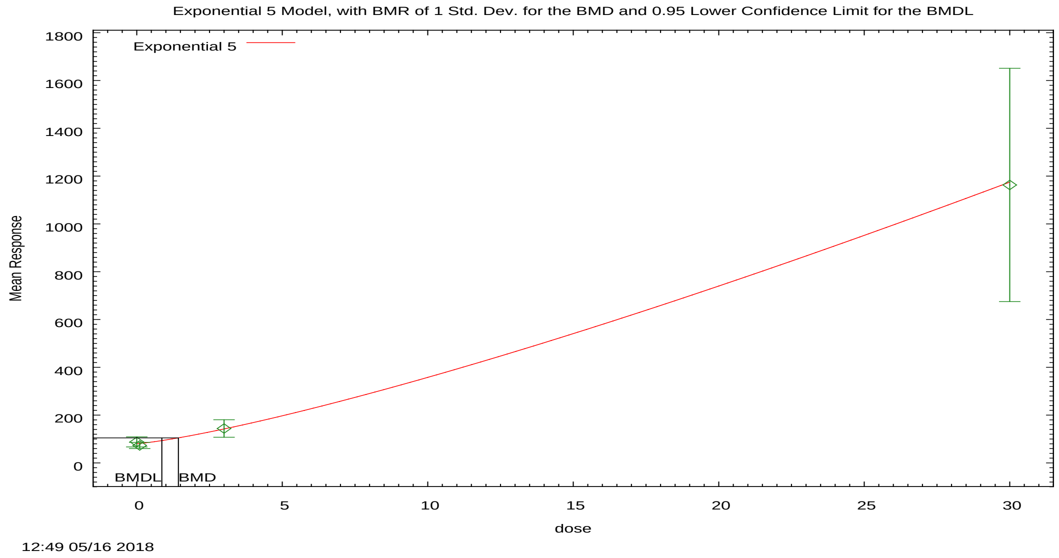

Figure 103. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.42988

BMDL at the 95% confidence level = 0.861795

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.32796	-4.80015
rho	2.44313	2.53385
a	80.4279	69.35
b	0.000198274	0.0000312636
c	8224.2	16770

d	1.24954	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	88	80.43	29.5	24.42	0.9805
0.1	10	73	81.31	18.2	24.75	-1.061
3	10	144	142.1	51.2	48.94	0.1246
30	10	1163	1175	682.4	646.1	-0.05686

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-251.3551	5	512.7101
A2	-185.3645	8	386.7289
A3	-185.6179	6	383.2357
R	-273.3673	2	550.7345
5	-187.656	6	387.312

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	176	6	<0.0001
Test 2	132	3	<0.0001
Test 3	0.5068	2	0.7761
Test 7a	4.076	0	N/A

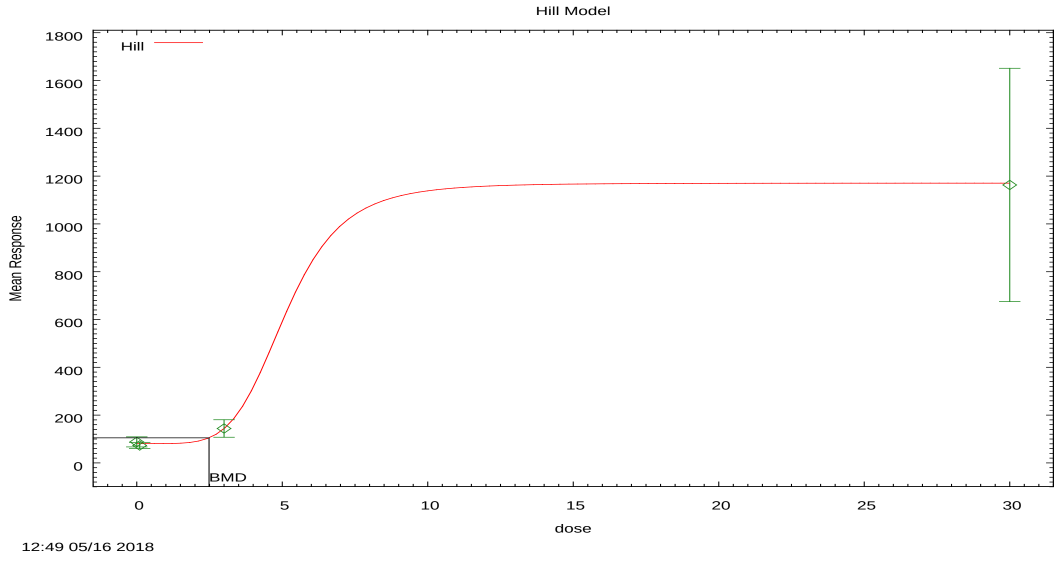

Figure 104. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.48314

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.3962	11.6731
rho	2.45514	0
intercept	80.6007	88
v	1085.21	1075
n	5.21813	1.0781

k	5.12055	44.2419

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	88	80.6	29.5	24.3	0.963
0.1	10	73	80.6	18.2	24.3	-0.989
3	10	144	143	51.2	49.3	0.0381
30	10	1160	1170	682	645	-0.0132

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-251.355063	5	512.710125
A2	-185.364464	8	386.728927
A3	-185.617874	6	383.235747
fitted	-187.481591	6	386.963182
R	-273.367267	2	550.734534

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	176.006	6	<0.0001
Test 2	131.981	3	<0.0001
Test 3	0.50682	2	0.7761
Test 4	3.72743	0	N/A

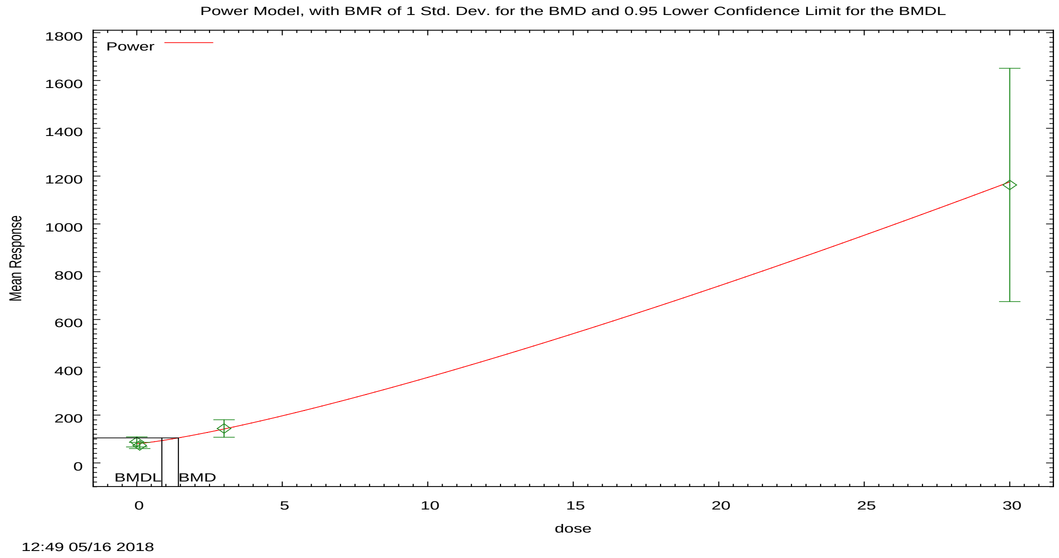

Figure 105. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.42969

BMDL at the 95% confidence level = 0.861719

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.32785	11.6731
rho	2.44311	0
control	80.4278	73
slope	15.6259	19.2891
power	1.24922	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	88	80.4	29.5	24.4	0.98
0.1	10	73	81.3	18.2	24.7	-1.06
3	10	144	142	51.2	48.9	0.125
30	10	1160	1170	682	646	-0.0569

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-251.355063	5	512.710125
A2	-185.364464	8	386.728927
A3	-185.617874	6	383.235747
fitted	-187.656196	5	385.312392
R	-273.367267	2	550.734534

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	176.006	6	<0.0001
Test 2	131.981	3	<0.0001
Test 3	0.50682	2	0.7761
Test 4	4.07664	1	0.04348

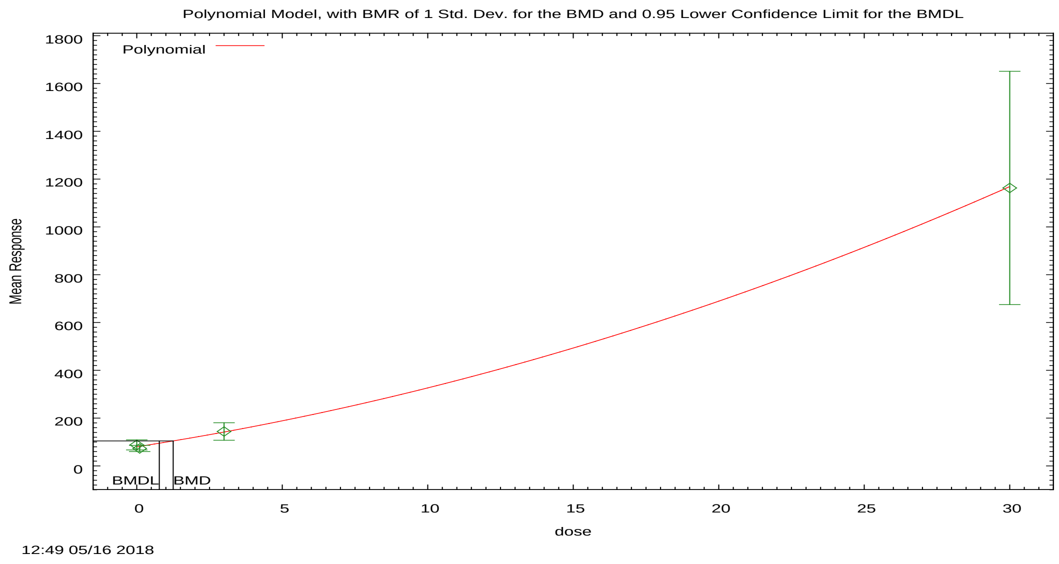

Figure 106. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.2518

BMDL at the 95% confidence level = 0.773778

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.3077	11.6731
rho	2.44135	0
beta_0	80.122	88
beta_1	18.8097	0
beta_2	0.583222	0

beta_3	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	88	80.1	29.5	24.5	1.02
0.1	10	73	82	18.2	25.2	-1.13
3	10	144	142	51.2	49.1	0.142
30	10	1160	1170	682	645	-0.031

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-251.355063	5	512.710125
A2	-185.364464	8	386.728927
A3	-185.617874	6	383.235747
fitted	-187.855409	5	385.710818
R	-273.367267	2	550.734534

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	176.006	6	<0.0001
Test 2	131.981	3	<0.0001
Test 3	0.50682	2	0.7761
Test 4	4.47507	1	0.03439

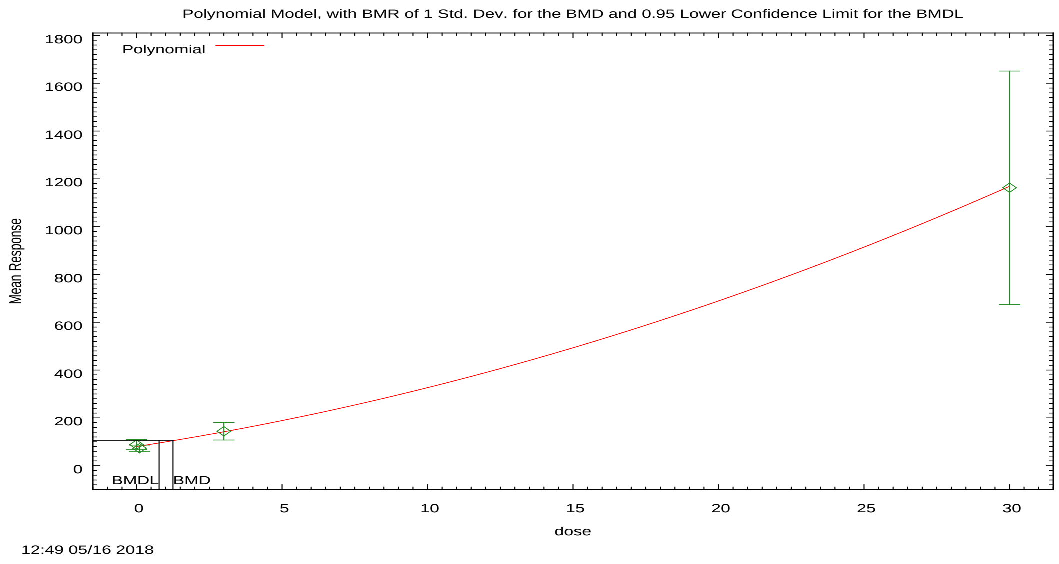

Figure 107. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.25179

BMDL at the 95% confidence level = 0.773789

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.3077	11.6731
rho	2.44134	0
beta_0	80.122	79.6705
beta_1	18.8097	0
beta_2	0.583221	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	88	80.1	29.5	24.5	1.02
0.1	10	73	82	18.2	25.2	-1.13
3	10	144	142	51.2	49.1	0.142
30	10	1160	1170	682	645	-0.031

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-251.355063	5	512.710125
A2	-185.364464	8	386.728927
A3	-185.617874	6	383.235747
fitted	-187.855409	5	385.710818
R	-273.367267	2	550.734534

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	176.006	6	<0.0001
Test 2	131.981	3	<0.0001
Test 3	0.50682	2	0.7761
Test 4	4.47507	1	0.03439

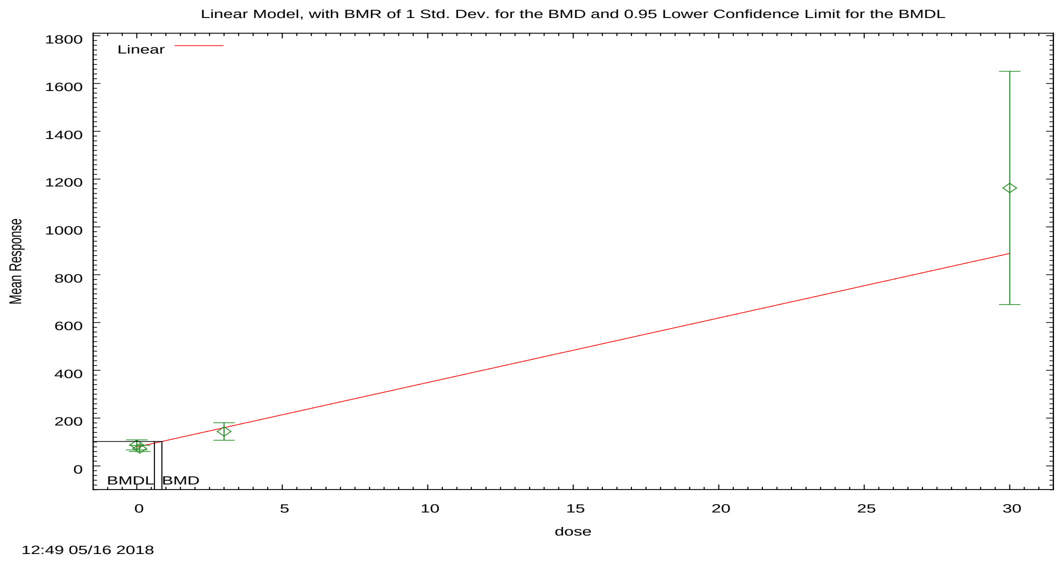

Figure 108. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alkaline Phosphatase in Males (28-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.862413

BMDL at the 95% confidence level = 0.606491

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-5.83399	11.6731
rho	2.77619	0
beta_0	78.9795	64.9602
beta_1	27.0008	36.5003

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	88	79	29.5	23.3	1.23
0.1	10	73	81.7	18.2	24.4	-1.12
3	10	144	160	51.2	62	-0.815
30	10	1160	889	682	671	1.29

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-251.355063	5	512.710125
A2	-185.364464	8	386.728927
A3	-185.617874	6	383.235747
fitted	-189.783063	4	387.566127
R	-273.367267	2	550.734534

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	176.006	6	<0.0001
Test 2	131.981	3	<0.0001
Test 3	0.50682	2	0.7761
Test 4	8.33038	2	0.01553

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Alkaline Phosphatase (U/L) in Females

1.13. BMDS Summary of Alkaline Phosphatase (U/L) (28 Day Mice GenX)

Table 13. Summary of BMD Modeling Results for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	**0.535**	**307.32**	**6.97**	**5.55**	1.26	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.458	308.62	13.3	5.72	2.32	
Exponential (M4)	0.128	310.38	4.97	3.73	1.33	
Exponential (M5)	N/A[b]	310.62	12.1	error[c]	error	
Hill	N/A[b]	310.62	9.70	error[c]	error	
Power	0.458	308.62	12.1	4.18	2.89	
Polynomial 3°	0.461	308.61	15.0	4.18	3.58	
Polynomial 2°	0.458	308.62	12.0	4.18	2.88	
Linear	0.315	308.38	4.97	3.73	1.33	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.00267), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were -0.27, 0.78, -0.56, 0.05, respectively.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

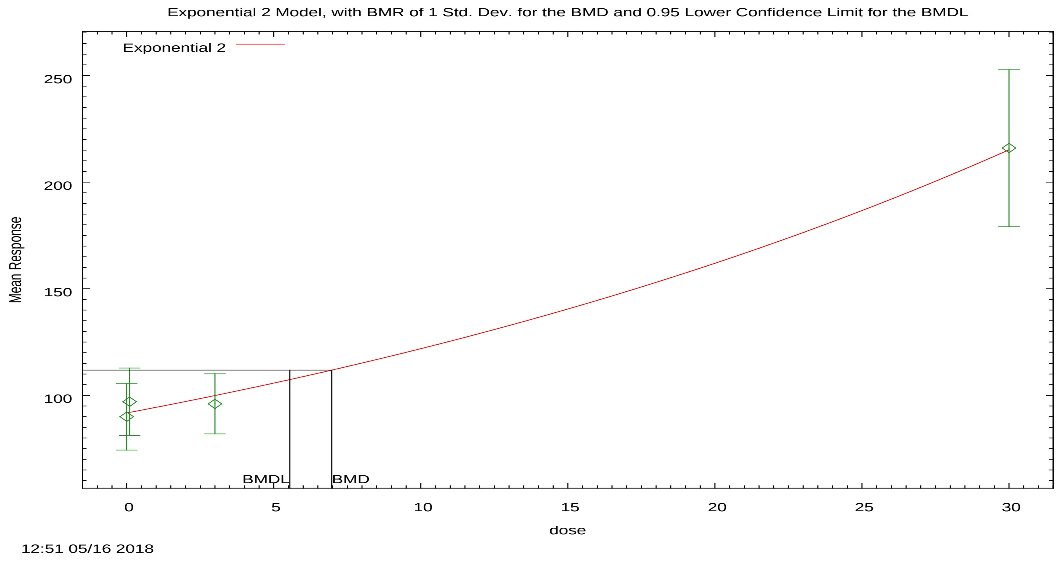

Figure 109. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alkaline Phosphatase in Females (28-

Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 6.97274

BMDL at the 95% confidence level = 5.54681

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.25046	-3.48696
rho	2.04737	2.11151
a	91.7451	91.6649
b	0.0284134	0.0284468
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	91.75	21.9	20.1	-0.2745
0.1	10	97	92.01	22.1	20.16	0.7833
3	10	96	99.91	19.7	21.94	-0.5635
30	10	216	215.2	51.3	48.11	0.05472

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.9868	5	321.9736

A2	-148.8965	8	313.7931
A3	-149.0341	6	310.0682
R	-184.213	2	372.4261
2	-149.6606	4	307.3212

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.63	6	<0.0001
Test 2	14.18	3	0.002669
Test 3	0.2752	2	0.8715
Test 4	1.253	2	0.5345

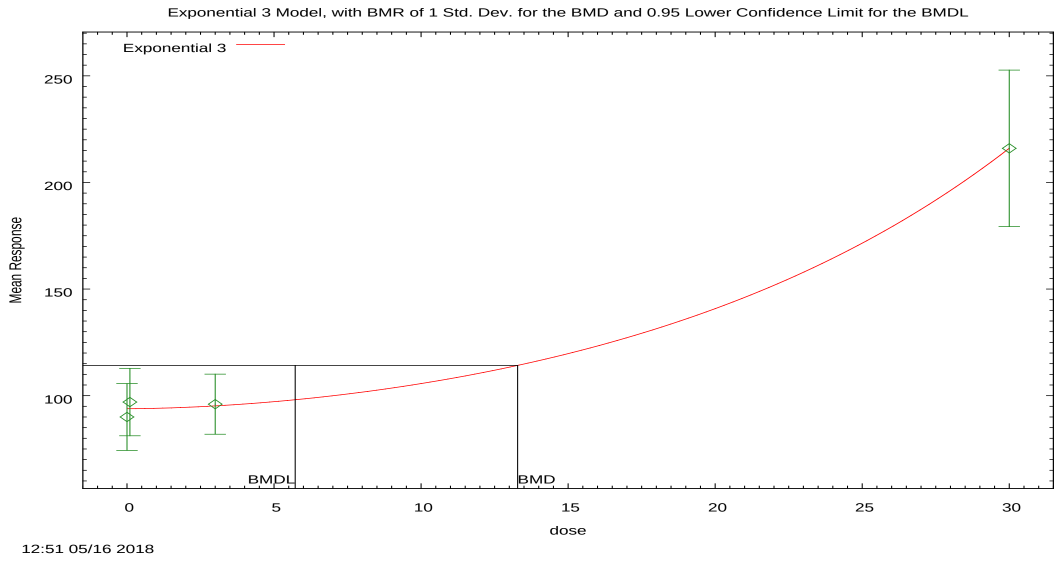

Figure 110. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 13.2823

BMDL at the 95% confidence level = 5.72002

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.49022	-3.48696
rho	2.09422	2.11151
a	93.8856	91.6649
b	0.0300844	0.0284468
c	n/a	0
d	1.77762	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	93.89	21.9	20.31	-0.6051
0.1	10	97	93.89	22.1	20.31	0.4845
3	10	96	95.2	19.7	20.6	0.1227
30	10	216	216	51.3	48.6	-0.002149

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.9868	5	321.9736
A2	-148.8965	8	313.7931
A3	-149.0341	6	310.0682
R	-184.213	2	372.4261
3	-149.3095	5	308.6191

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	70.63	6	<0.0001
Test 2	14.18	3	0.002669
Test 3	0.2752	2	0.8715
Test 5a	0.5508	1	0.458

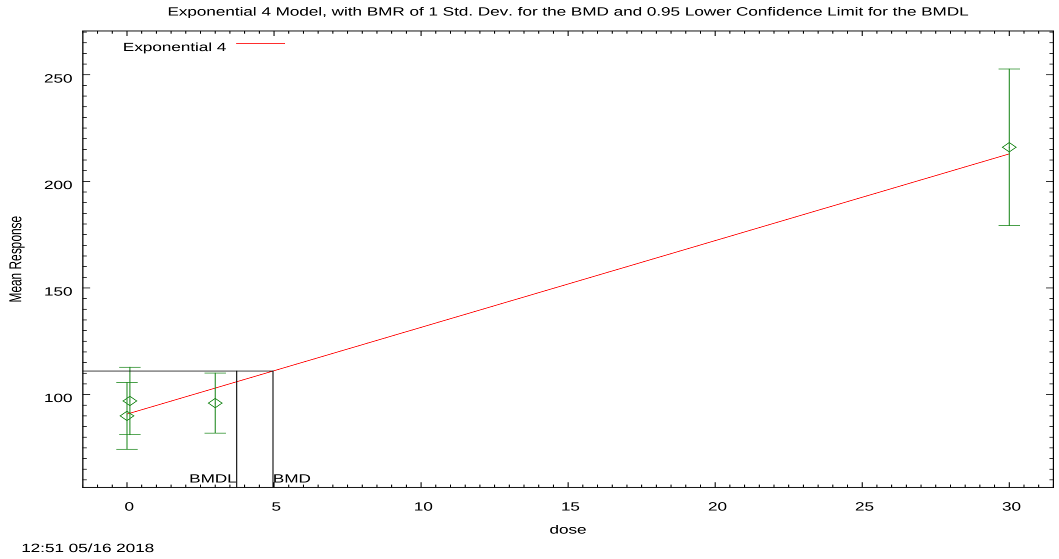

Figure 111. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.96504

BMDL at the 95% confidence level = 3.73159

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.13899	-3.48696
rho	2.02929	2.11151
a	90.8386	85.5
b	0.000000267161	0.0000201196
c	167634	2526.32
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	90.84	21.9	20.2	-0.1313
0.1	10	97	91.25	22.1	20.29	0.8968
3	10	96	103	19.7	22.95	-0.9703
30	10	216	212.9	51.3	47.93	0.2055

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.9868	5	321.9736
A2	-148.8965	8	313.7931
A3	-149.0341	6	310.0682
R	-184.213	2	372.4261
4	-150.1908	5	310.3816

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.63	6	<0.0001
Test 2	14.18	3	0.002669
Test 3	0.2752	2	0.8715
Test 6a	2.313	1	0.1283

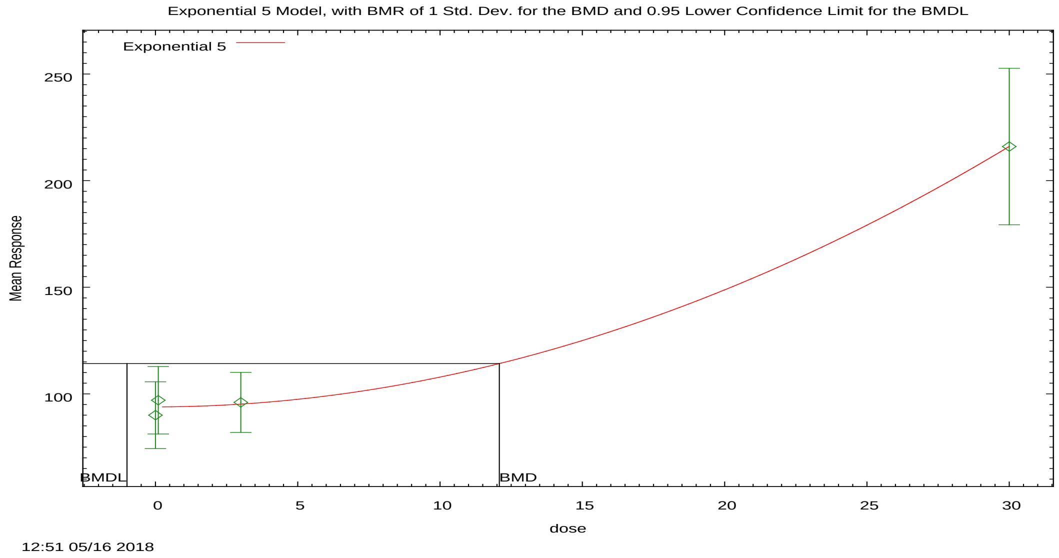

Figure 112. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 12.0822

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.49045	-3.48696
rho	2.09427	2.11151
a	93.8909	85.5
b	0.000236033	0.0000201196

c	22680.7	2526.32
d	1.97282	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	93.89	21.9	20.31	-0.6059
0.1	10	97	93.89	22.1	20.31	0.4839
3	10	96	95.19	19.7	20.6	0.1241
30	10	216	216	51.3	48.6	-0.002132

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.9868	5	321.9736
A2	-148.8965	8	313.7931
A3	-149.0341	6	310.0682
R	-184.213	2	372.4261
5	-149.3096	6	310.6193

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.63	6	<0.0001
Test 2	14.18	3	0.002669
Test 3	0.2752	2	0.8715
Test 7a	0.5511	0	N/A

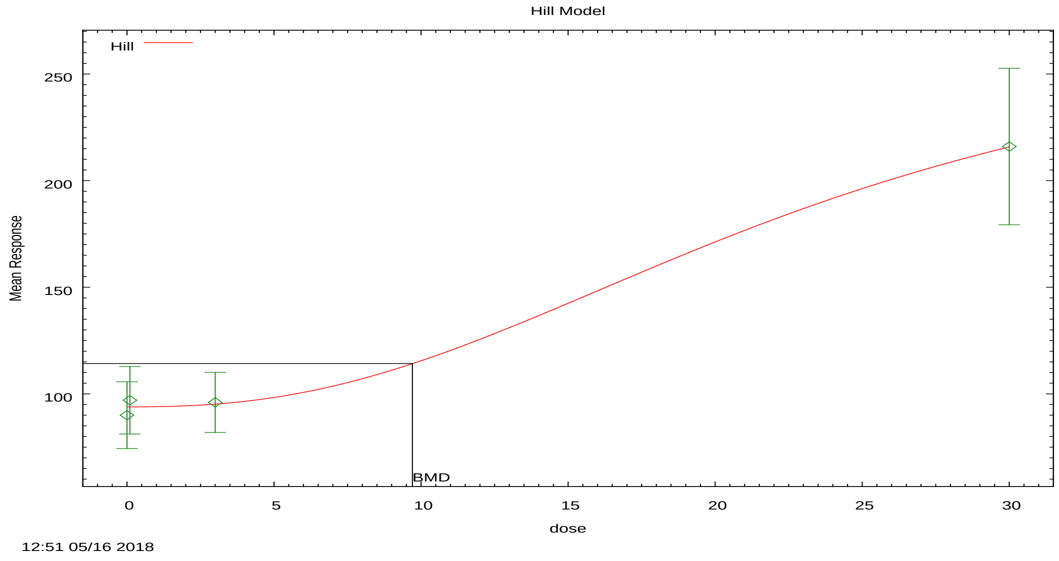

Figure 113. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 9.70479

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.49065	6.9047
rho	2.09431	0
intercept	93.8955	90
v	185.095	126
n	2.44226	0.789505

k	22.8708	44.175

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	93.9	21.9	20.3	-0.607
0.1	10	97	93.9	22.1	20.3	0.483
3	10	96	95.2	19.7	20.6	0.125
30	10	216	216	51.3	48.6	-0.00212

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.986802	5	321.973604
A2	-148.896526	8	313.793052
A3	-149.034119	6	310.068237
fitted	-149.309756	6	310.619511
R	-184.213048	2	372.426096

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.633	6	<0.0001
Test 2	14.1806	3	0.002669
Test 3	0.275185	2	0.8715
Test 4	0.551274	0	N/A

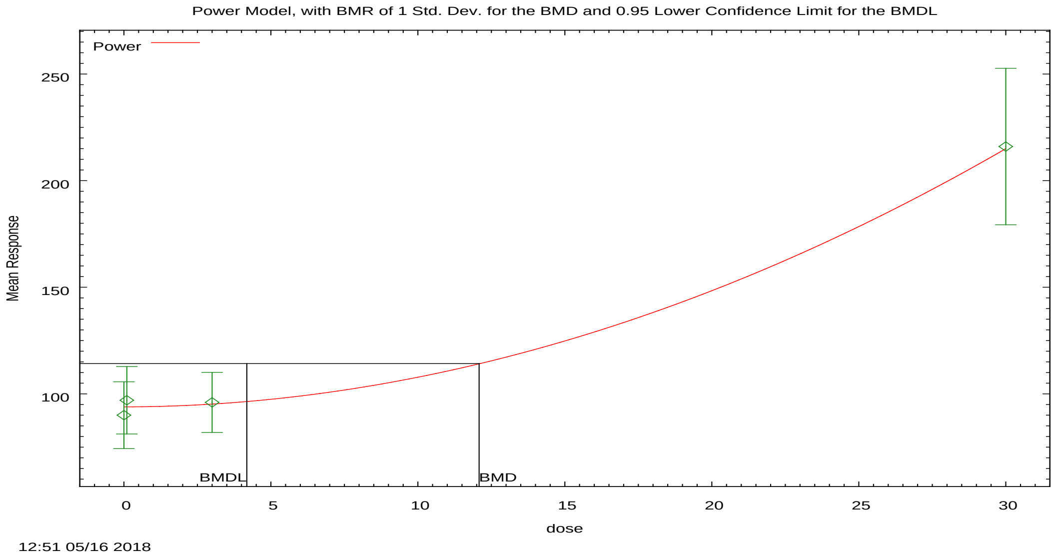

Figure 114. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 12.0822

BMDL at the 95% confidence level = 4.181

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.49043	6.9047
rho	2.09426	0
control	93.8909	90
slope	0.148867	12.3966
power	1.9728	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	93.9	21.9	20.3	-0.606
0.1	10	97	93.9	22.1	20.3	0.484
3	10	96	95.2	19.7	20.6	0.124
30	10	216	216	51.3	48.6	-0.00214

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.986802	5	321.973604
A2	-148.896526	8	313.793052
A3	-149.034119	6	310.068237
fitted	-149.30965	5	308.619299
R	-184.213048	2	372.426096

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.633	6	<0.0001
Test 2	14.1806	3	0.002669
Test 3	0.275185	2	0.8715
Test 4	0.551062	1	0.4579

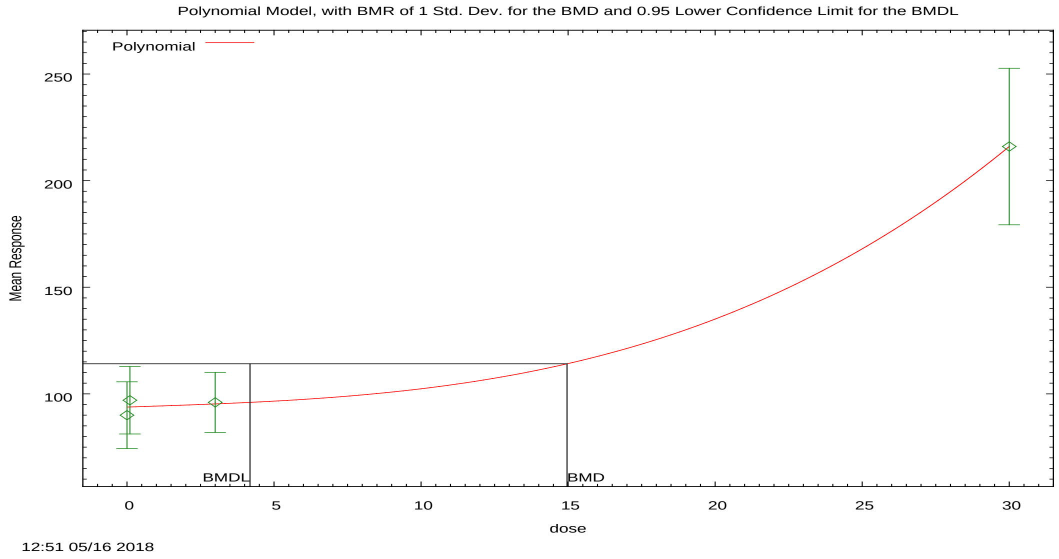

Figure 115. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 14.9627

BMDL at the 95% confidence level = 4.18359

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.48864	6.9047
rho	2.09385	0
beta_0	93.8164	90
beta_1	0.456035	0
beta_2	2.21944E-13	0

beta_3	0.00401997	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	93.8	21.9	20.3	-0.595
0.1	10	97	93.9	22.1	20.3	0.489
3	10	96	95.3	19.7	20.6	0.108
30	10	216	216	51.3	48.6	-0.00239

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.986802	5	321.973604
A2	-148.896526	8	313.793052
A3	-149.034119	6	310.068237
fitted	-149.306152	5	308.612304
R	-184.213048	2	372.426096

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.633	6	<0.0001
Test 2	14.1806	3	0.002669
Test 3	0.275185	2	0.8715
Test 4	0.544067	1	0.4608

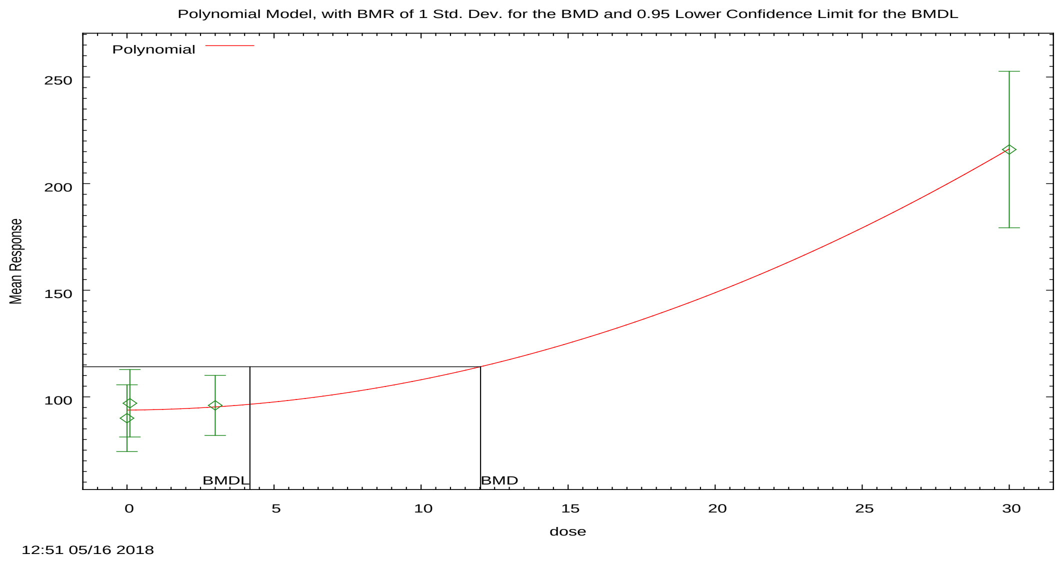

Figure 116. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 12.022

BMDL at the 95% confidence level = 4.18135

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.48753	6.9047
rho	2.09365	0
beta_0	93.8305	93.407
beta_1	0.0931736	0
beta_2	0.132672	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	93.8	21.9	20.3	-0.597
0.1	10	97	93.8	22.1	20.3	0.492
3	10	96	95.3	19.7	20.6	0.107
30	10	216	216	51.3	48.6	-0.00199

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.986802	5	321.973604
A2	-148.896526	8	313.793052
A3	-149.034119	6	310.068237
fitted	-149.309169	5	308.618338
R	-184.213048	2	372.426096

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.633	6	<0.0001
Test 2	14.1806	3	0.002669
Test 3	0.275185	2	0.8715
Test 4	0.550101	1	0.4583

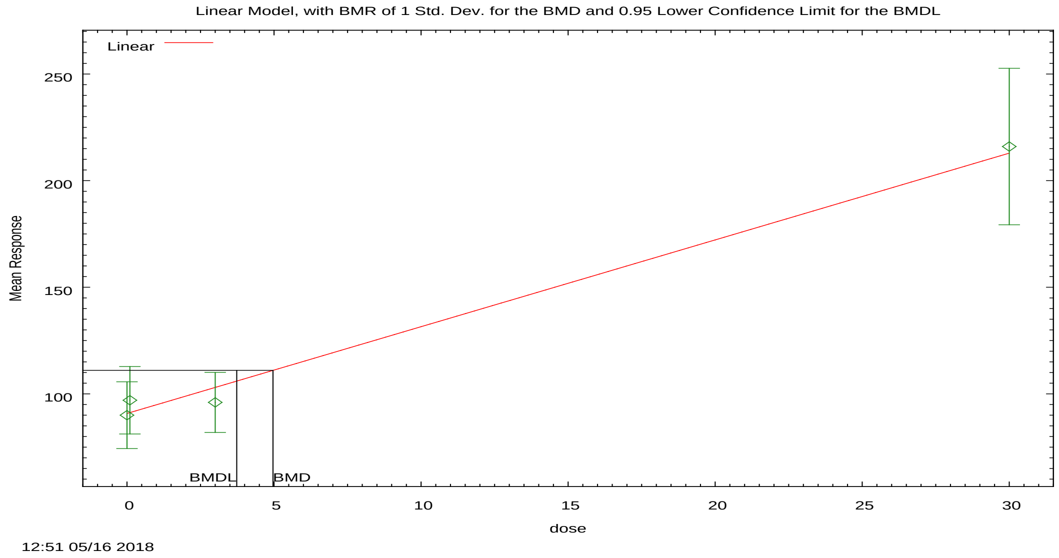

Figure 117. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alkaline Phosphatase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.96506

BMDL at the 95% confidence level = 3.7316

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.13897	6.9047
rho	2.02929	0
beta_0	90.8386	90.2423
beta_1	4.0682	4.17012

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	90	90.8	21.9	20.2	-0.131
0.1	10	97	91.2	22.1	20.3	0.897
3	10	96	103	19.7	23	-0.97
30	10	216	213	51.3	47.9	0.206

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-155.986802	5	321.973604
A2	-148.896526	8	313.793052
A3	-149.034119	6	310.068237
fitted	-150.190806	4	308.381612
R	-184.213048	2	372.426096

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	70.633	6	<0.0001
Test 2	14.1806	3	0.002669
Test 3	0.275185	2	0.8715
Test 4	2.31338	2	0.3145

BMDS WIZARD OUTPUT REPORT

Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Alkaline Phosphatase (U/L) in Males

1.14. BMDS Summary of Alkaline Phosphatase (U/L) Males (90 Day Mice GenX)

Table 14. Summary of BMD Modeling Results for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	BMDL_{1SD} (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) **Exponential (M3)[b]**	**0.384**	**344.14**	**0.596**	**0.480**	1.24	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M4)	0.0253	349.23	0.183	0.122	1.50	
Exponential (M5)	N/A[c]	347.24	0.383	0.190	2.02	
Hill	N/A[c]	347.24	0.383	error[d]	error	
Power	0.314	345.24	0.383	0.190	2.02	
Polynomial 3°	0.502	344.68	0.329	0.173	1.90	
Polynomial 2°	0.452	344.79	0.343	0.176	1.95	
Linear	0.0820	347.23	0.183	0.122	1.50	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.38, 0.03, 0.41, -0.06, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] No available degrees of freedom to calculate a goodness of fit value.

[d] BMD or BMDL computation failed for this model.

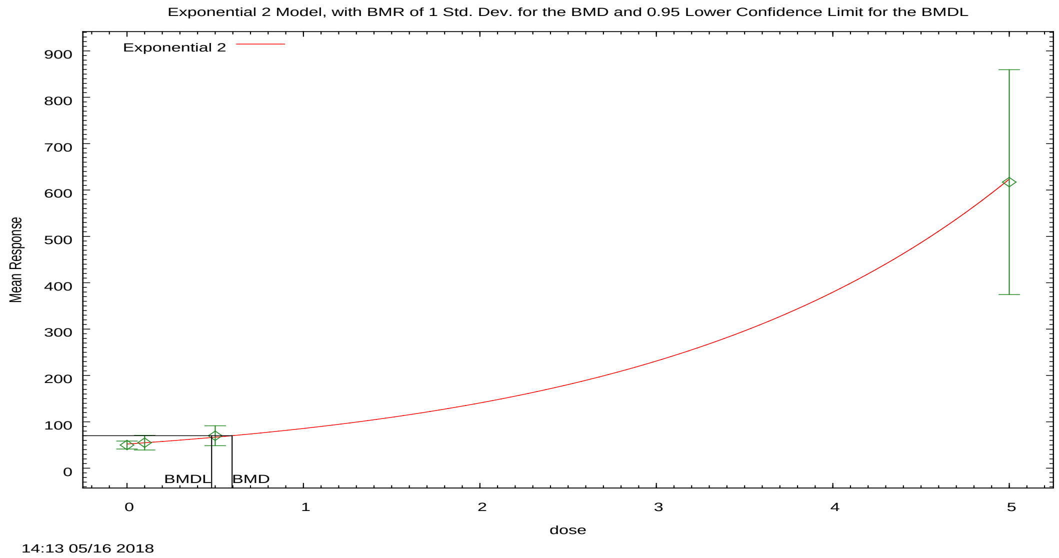

Figure 118. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.595588

BMDL at the 95% confidence level = 0.479579

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.50607	-3.88175
rho	2.34657	2.42747
a	52.176	52.2193
b	0.496121	0.494806
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	52.18	12	17.94	-0.3836
0.1	10	55	54.83	22	19.01	0.02831
0.5	10	70	66.87	30	24	0.4131
5	10	617	623.4	339	329.4	-0.06168

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC

A1	-223.4711	5	456.9422
A2	-165.9243	8	347.8485
A3	-167.1141	6	346.2282
R	-246.9552	2	497.9105
2	-168.0715	4	344.143

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.1	6	<0.0001
Test 2	115.1	3	<0.0001
Test 3	2.38	2	0.3043
Test 4	1.915	2	0.3839

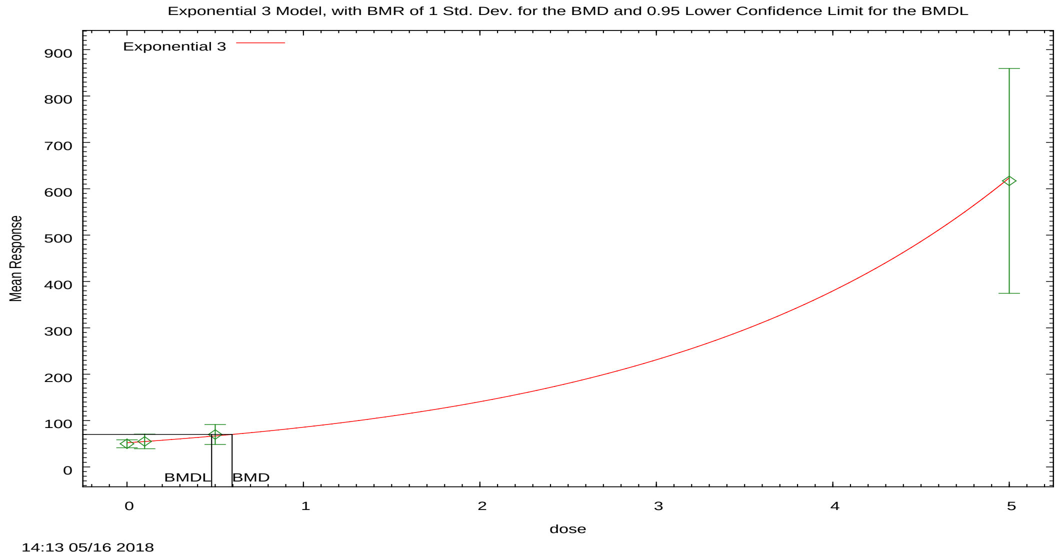

Figure 119. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.595588

BMDL at the 95% confidence level = 0.479579

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.50607	-3.88175
rho	2.34657	2.42747
a	52.176	52.2193
b	0.496121	0.494806
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	52.18	12	17.94	-0.3836
0.1	10	55	54.83	22	19.01	0.02831
0.5	10	70	66.87	30	24	0.4131
5	10	617	623.4	339	329.4	-0.06168

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.4711	5	456.9422
A2	-165.9243	8	347.8485
A3	-167.1141	6	346.2282
R	-246.9552	2	497.9105
3	-168.0715	4	344.143

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	162.1	6	<0.0001
Test 2	115.1	3	<0.0001
Test 3	2.38	2	0.3043
Test 5a	1.915	2	0.3839

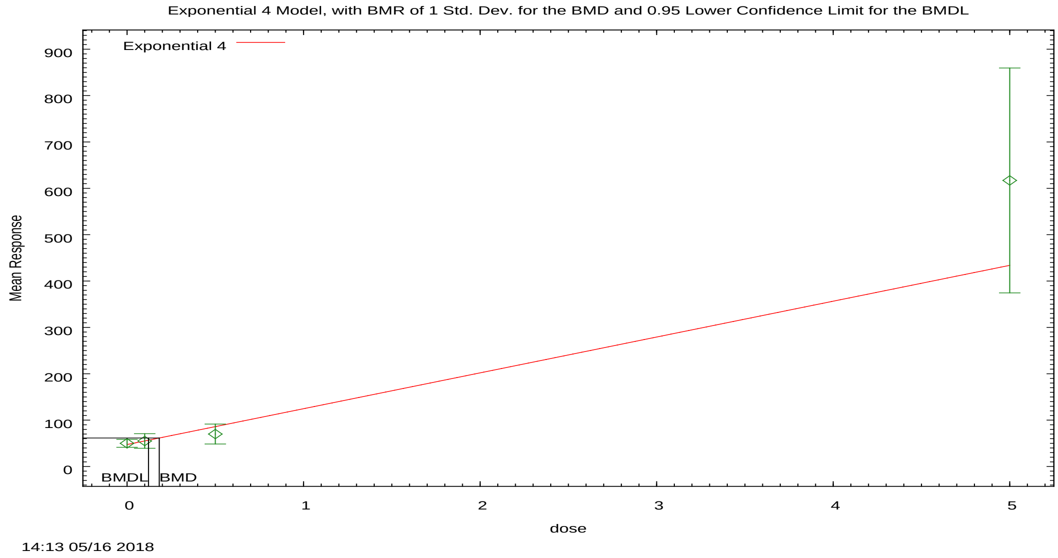

Figure 120. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.182554

BMDL at the 95% confidence level = 0.121505

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values

lnalpha	-6.0962	-3.88175
rho	2.95247	2.42747
a	47.3623	47.5
b	0.00000281194	0.000183571
c	580402	12989.5
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	47.36	12	14.11	0.5911
0.1	10	55	55.09	22	17.64	-0.0165
0.5	10	70	86.01	30	34.05	-1.487
5	10	617	433.8	339	371.2	1.56

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.4711	5	456.9422
A2	-165.9243	8	347.8485
A3	-167.1141	6	346.2282
R	-246.9552	2	497.9105
4	-169.6147	5	349.2294

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.1	6	<0.0001
Test 2	115.1	3	<0.0001
Test 3	2.38	2	0.3043
Test 6a	5.001	1	0.02533

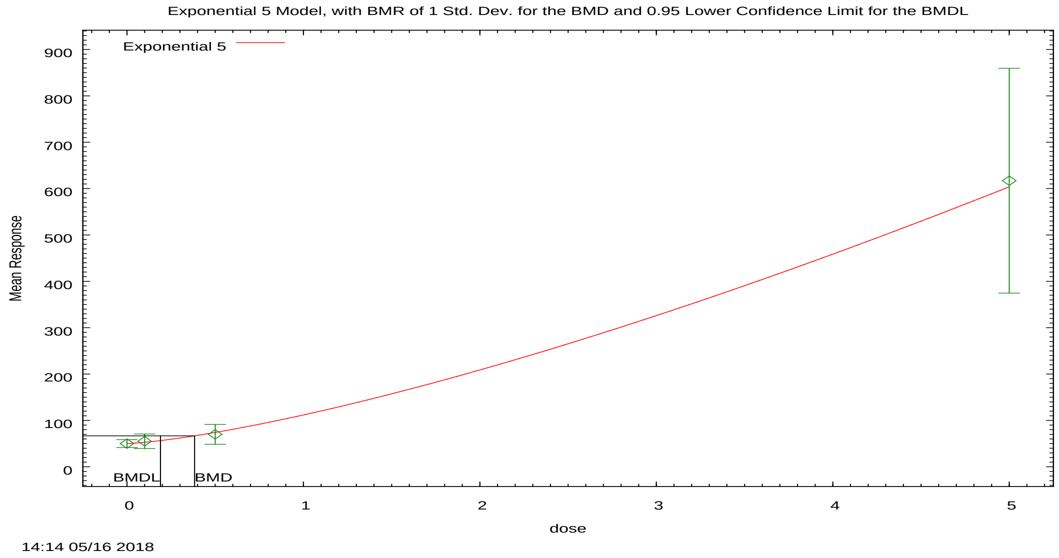

Figure 121. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.383064

BMDL at the 95% confidence level = 0.189841

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-3.74074	-3.88175
rho	2.39323	2.42747
a	50.1106	47.5
b	0.0000952421	0.000183571
c	374606	12989.5

d	1.36363	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	50.11	12	16.67	-0.02099
0.1	10	55	52.78	22	17.74	0.3957
0.5	10	70	74.08	30	26.61	-0.4848
5	10	617	603.8	339	327.6	0.1275

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.4711	5	456.9422
A2	-165.9243	8	347.8485
A3	-167.1141	6	346.2282
R	-246.9552	2	497.9105
5	-167.6203	6	347.2407

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.1	6	<0.0001
Test 2	115.1	3	<0.0001
Test 3	2.38	2	0.3043
Test 7a	1.012	0	N/A

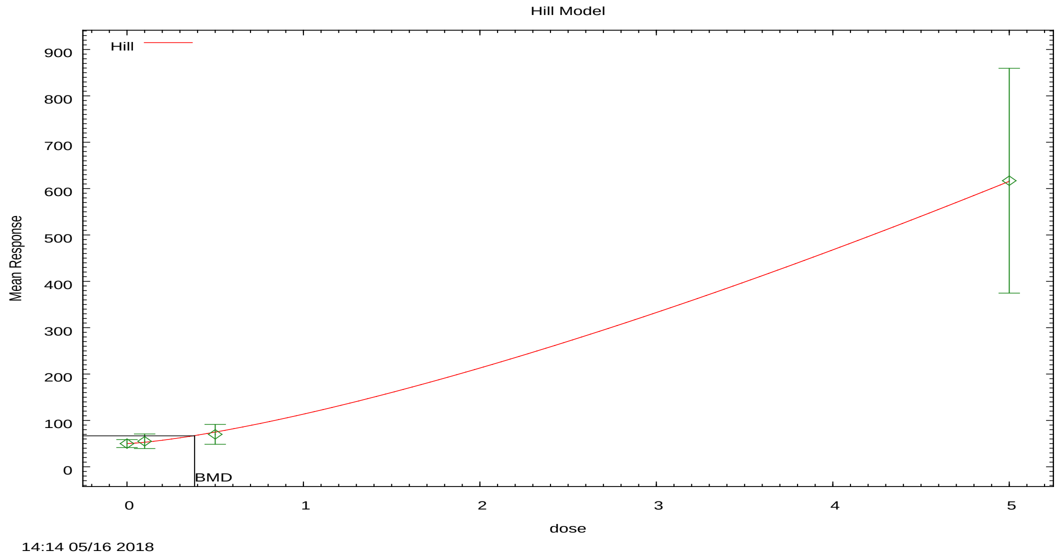

Figure 122. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.383177

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.74061	10.2789
rho	2.3932	0
intercept	50.1127	50
v	335963	567
n	1.36437	1.16578

k	547.321	7.33227

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	50.1	12	16.7	-0.0214
0.1	10	55	52.8	22	17.7	0.396
0.5	10	70	74.1	30	26.6	-0.485
5	10	617	604	339	328	0.128

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.471076	5	456.942152
A2	-165.924256	8	347.848511
A3	-167.114116	6	346.228232
fitted	-167.620788	6	347.241575
R	-246.955243	2	497.910486

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.062	6	<0.0001
Test 2	115.094	3	<0.0001
Test 3	2.37972	2	0.3043
Test 4	1.01334	0	N/A

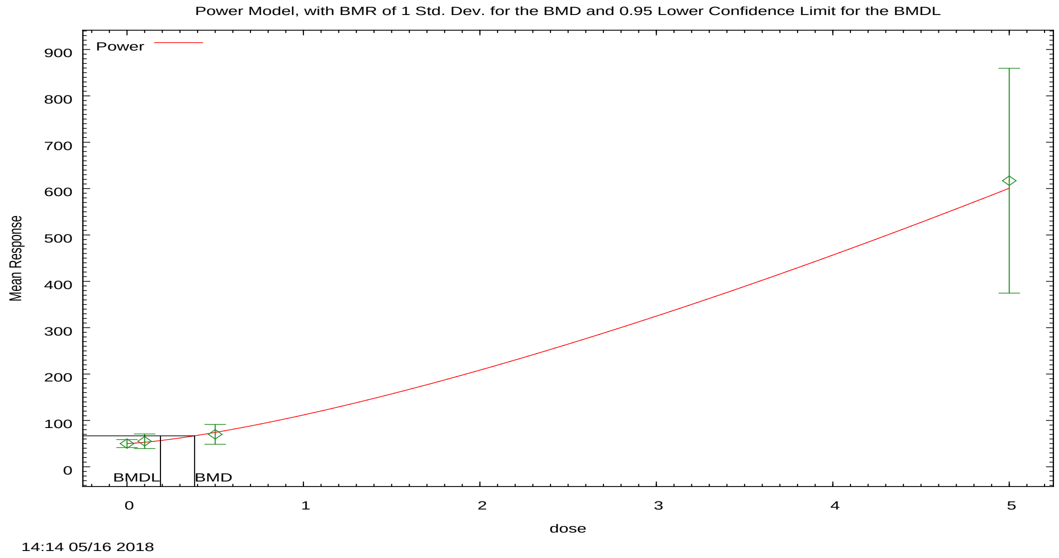

Figure 123. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.383064

BMDL at the 95% confidence level = 0.189838

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.74074	10.2789
rho	2.39323	0
control	50.1106	50
slope	61.6774	78.8136
power	1.36362	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	50.1	12	16.7	-0.021
0.1	10	55	52.8	22	17.7	0.396
0.5	10	70	74.1	30	26.6	-0.485
5	10	617	604	339	328	0.128

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.471076	5	456.942152
A2	-165.924256	8	347.848511
A3	-167.114116	6	346.228232
fitted	-167.62034	5	345.24068
R	-246.955243	2	497.910486

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.062	6	<0.0001
Test 2	115.094	3	<0.0001
Test 3	2.37972	2	0.3043
Test 4	1.01245	1	0.3143

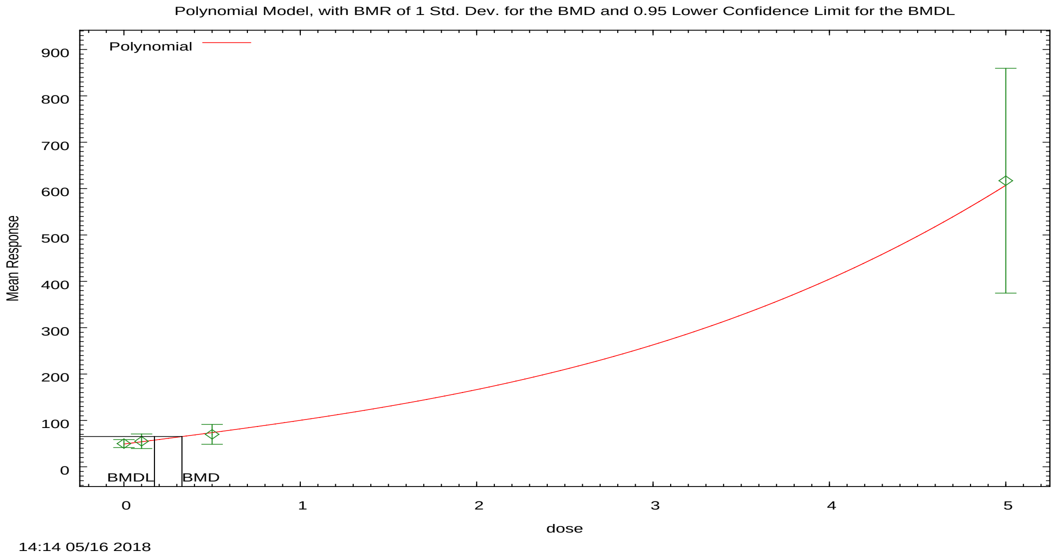

Figure 124. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.329181

BMDL at the 95% confidence level = 0.172959

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.78821	10.2789
rho	2.40012	0
beta_0	49.095	50
beta_1	48.6274	52.9215
beta_2	0	0

beta_3	2.51926	8.43084

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	49.1	12	16.1	0.178
0.1	10	55	54	22	18	0.182
0.5	10	70	73.7	30	26.2	-0.449
5	10	617	607	339	329	0.0947

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.471076	5	456.942152
A2	-165.924256	8	347.848511
A3	-167.114116	6	346.228232
fitted	-167.340021	5	344.680042
R	-246.955243	2	497.910486

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.062	6	<0.0001
Test 2	115.094	3	<0.0001
Test 3	2.37972	2	0.3043
Test 4	0.45181	1	0.5015

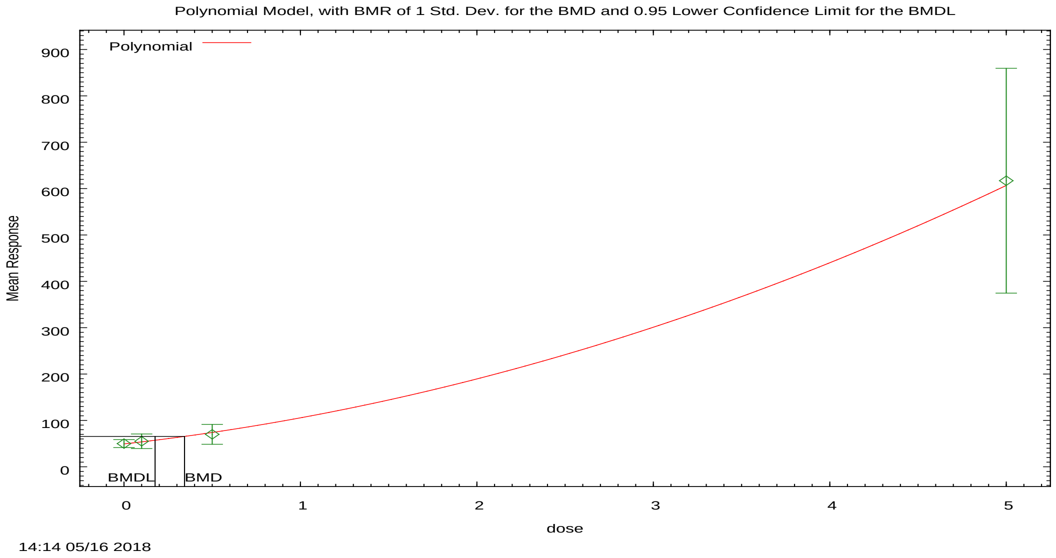

Figure 125. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.343149

BMDL at the 95% confidence level = 0.176227

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.78664	10.2789
rho	2.40053	0
beta_0	49.2818	50.7795
beta_1	42.4794	30.6108
beta_2	13.7541	16.5266

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	49.3	12	16.2	0.14
0.1	10	55	53.7	22	17.9	0.235
0.5	10	70	74	30	26.4	-0.475
5	10	617	606	339	329	0.11

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.471076	5	456.942152
A2	-165.924256	8	347.848511
A3	-167.114116	6	346.228232
fitted	-167.396602	5	344.793204
R	-246.955243	2	497.910486

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.062	6	<0.0001
Test 2	115.094	3	<0.0001
Test 3	2.37972	2	0.3043
Test 4	0.564972	1	0.4523

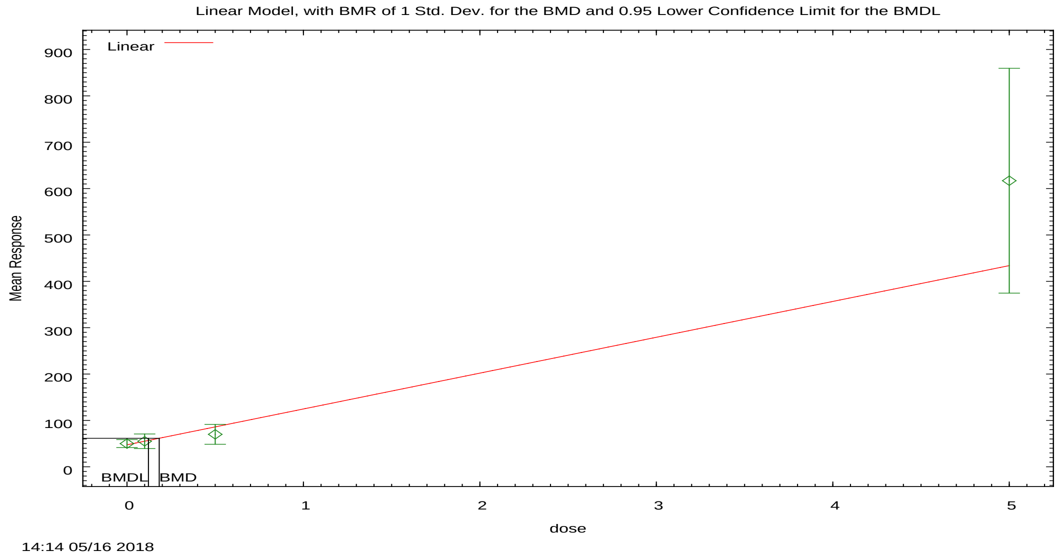

Figure 126. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alkaline Phosphatase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.182565

BMDL at the 95% confidence level = 0.121506

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-6.09677	10.2789
rho	2.95261	0
beta_0	47.3627	35.9231
beta_1	77.2924	115.769

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	50	47.4	12	14.1	0.591
0.1	10	55	55.1	22	17.6	-0.0165
0.5	10	70	86	30	34	-1.49
5	10	617	434	339	371	1.56

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-223.471076	5	456.942152
A2	-165.924256	8	347.848511
A3	-167.114116	6	346.228232
fitted	-169.614675	4	347.22935
R	-246.955243	2	497.910486

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	162.062	6	<0.0001
Test 2	115.094	3	<0.0001
Test 3	2.37972	2	0.3043
Test 4	5.00112	2	0.08204

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Alkaline Phosphatase (U/L) in Females

1.15. BMDS Summary of Alkaline Phosphatase (U/L) Females (90 Day Mice GenX)

Table 15. Summary of BMD Modeling Results for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.279	285.79	1.55	1.23	1.27	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.123	287.61	4.29	1.24	3.48	
Exponential (M4)	0.0877	288.15	1.13	0.833	1.36	
Exponential (M5)	N/A[b]	289.61	4.12	0.538	7.67	
Hill	N/A[b]	289.61	4.09	error[c]	error	
Power	**0.305**	**285.61**	**4.62**	**0.859**	**5.37**	
Polynomial 3°	0.126	287.58	2.69	0.861	3.13	
Polynomial 2°	0.123	287.62	2.22	0.859	2.59	
Linear	0.233	286.15	1.13	0.833	1.36	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0751), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.97, 0.88, 0.1, 0, respectively.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

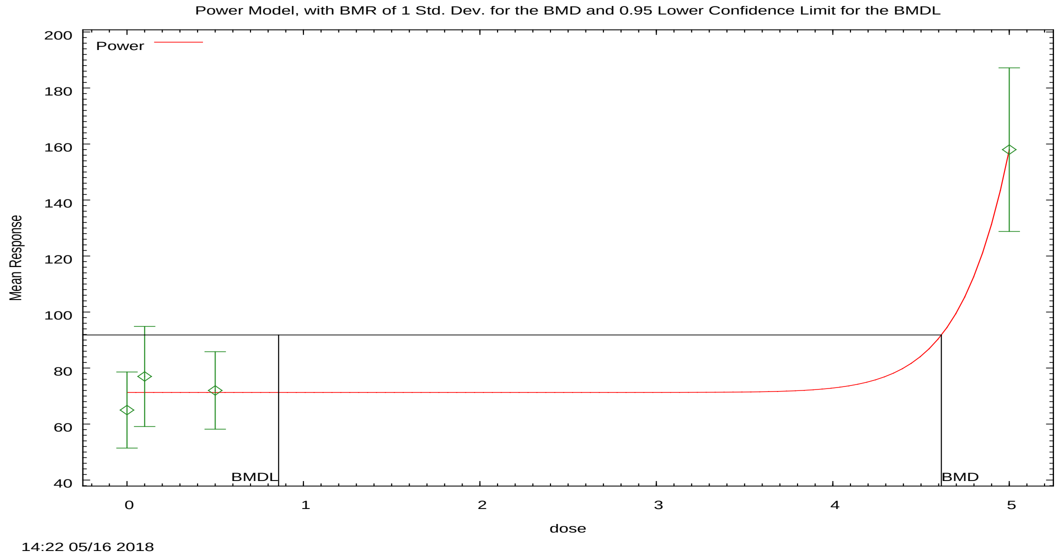

Figure 127. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.61514

BMDL at the 95% confidence level = 0.85933

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.0547528	6.51767
rho	1.40296	0
control	71.3103	65
slope	2.27252E-11	25.7584
power	18	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	71.3	19	20.5	-0.973
0.1	10	77	71.3	25	20.5	0.877
0.5	9	72	71.3	18	20.5	0.101
5	9	158	158	38	35.8	-0.0000000501

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.722467	5	291.444934
A2	-137.271117	8	290.542234
A3	-137.618003	6	287.236006
fitted	-138.80647	4	285.61294

R	-163.256735	2	330.513469

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.9712	6	<0.0001
Test 2	6.9027	3	0.07506
Test 3	0.693772	2	0.7069
Test 4	2.37693	2	0.3047

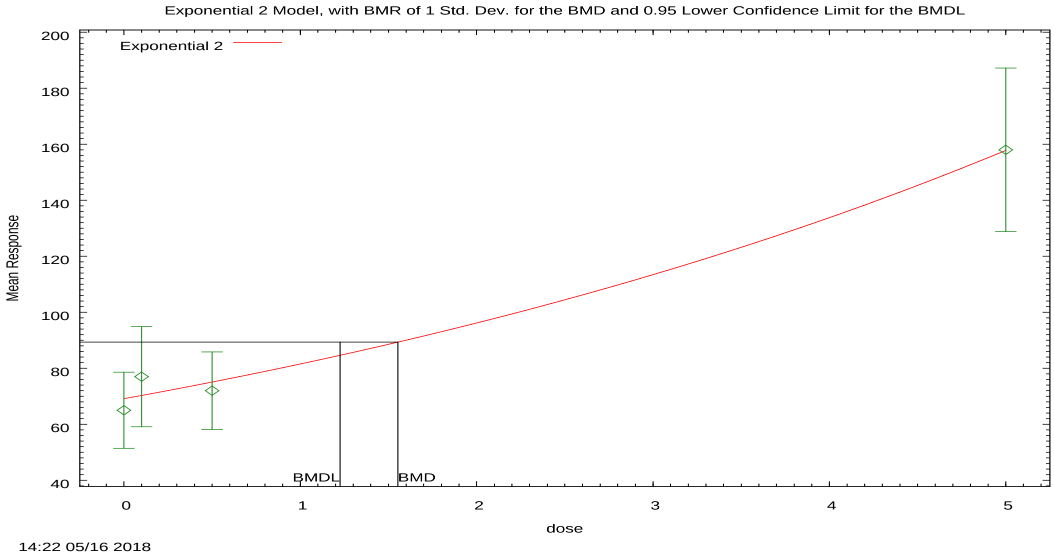

Figure 128. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.55374

BMDL at the 95% confidence level = 1.22565

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.261796	-0.767201
rho	1.35758	1.59325
a	69.1285	68.977
b	0.16507	0.165384
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	69.13	19	20.21	-0.646
0.1	10	77	70.28	25	20.44	1.04
0.5	9	72	75.08	18	21.38	-0.4317
5	9	158	157.8	38	35.39	0.0171

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.7225	5	291.4449
A2	-137.2711	8	290.5422
A3	-137.618	6	287.236
R	-163.2567	2	330.5135
2	-138.895	4	285.79

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.97	6	<0.0001
Test 2	6.903	3	0.07506
Test 3	0.6938	2	0.7069
Test 4	2.554	2	0.2789

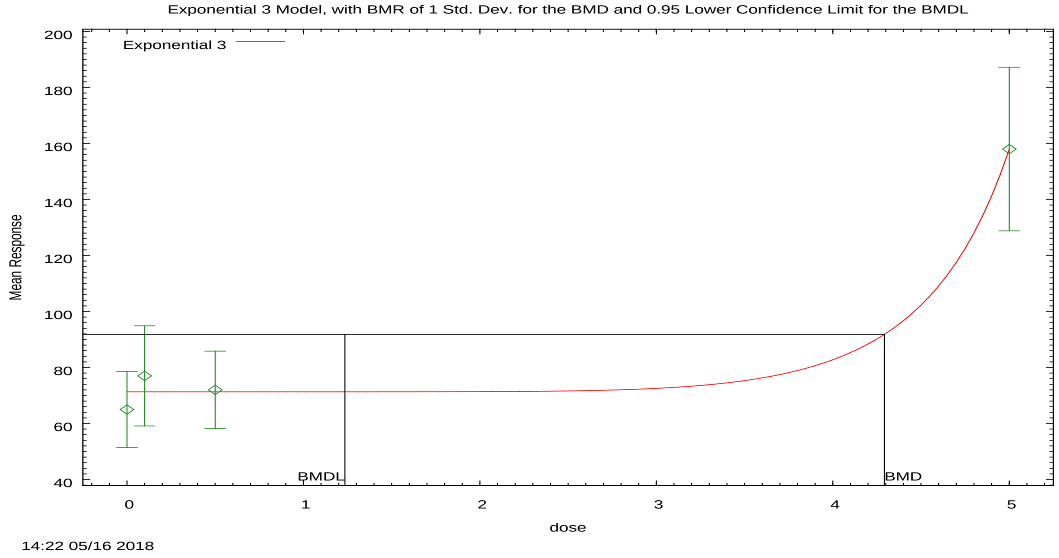

Figure 129. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.29214

BMDL at the 95% confidence level = 1.23501

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.0547497	-0.767201
rho	1.40296	1.59325
a	71.3103	68.977

b	0.194002	0.165384
c	n/a	0
d	7.51202	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	71.31	19	20.5	-0.9732
0.1	10	77	71.31	25	20.5	0.8775
0.5	9	72	71.31	18	20.5	0.1009
5	9	158	158	38	35.83	0.00000007256

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.7225	5	291.4449
A2	-137.2711	8	290.5422
A3	-137.618	6	287.236
R	-163.2567	2	330.5135
3	-138.8065	5	287.6129

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.97	6	<0.0001
Test 2	6.903	3	0.07506
Test 3	0.6938	2	0.7069
Test 5a	2.377	1	0.1231

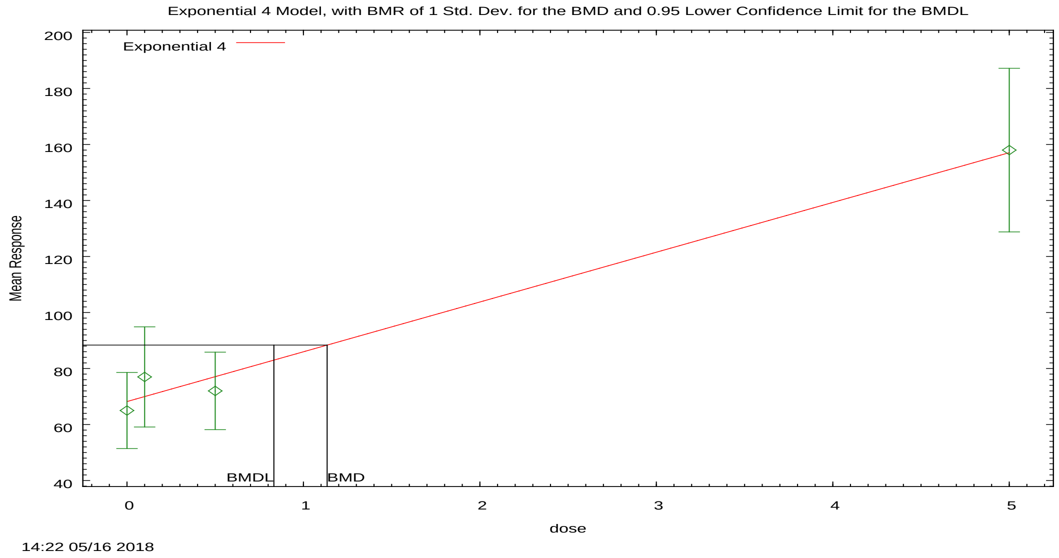

Figure 130. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.13417

BMDL at the 95% confidence level = 0.832528

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.359445	-0.767201
rho	1.33766	1.59325
a	68.1982	61.75
b	0.0000374361	0.0952247

c	6964.05	5.11741
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	68.2	19	20.16	-0.5016
0.1	10	77	69.98	25	20.51	1.083
0.5	9	72	77.09	18	21.88	-0.6973
5	9	158	157.1	38	35.23	0.0787

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.7225	5	291.4449
A2	-137.2711	8	290.5422
A3	-137.618	6	287.236
R	-163.2567	2	330.5135
4	-139.0761	5	288.1521

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.97	6	<0.0001
Test 2	6.903	3	0.07506
Test 3	0.6938	2	0.7069
Test 6a	2.916	1	0.0877

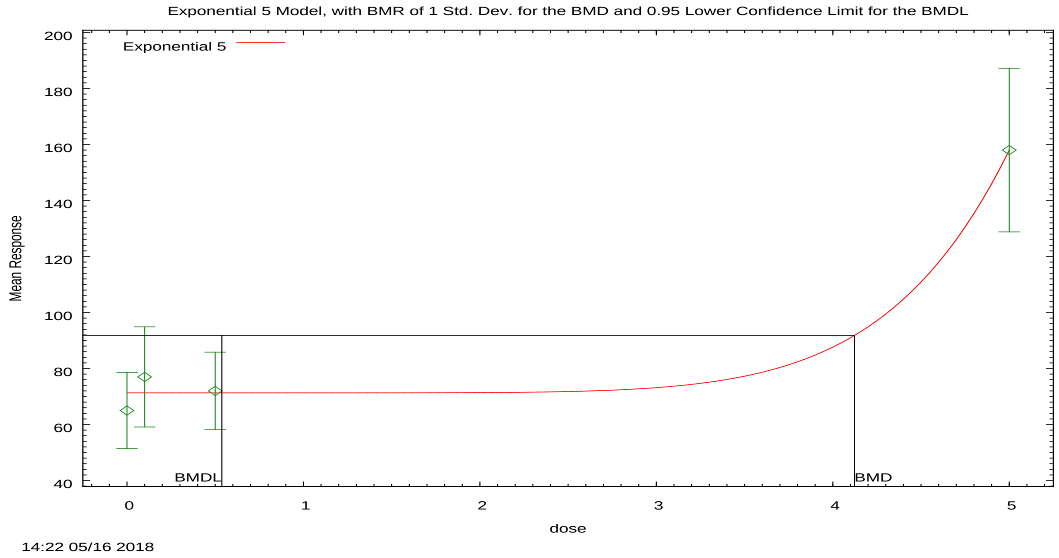

Figure 131. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.12265

BMDL at the 95% confidence level = 0.537501

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.0547522	-0.767201
rho	1.40296	1.59325
a	71.3103	61.75
b	0.136575	0.0952247

c	23.5345	5.11741
d	7.58207	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	71.31	19	20.5	-0.9732
0.1	10	77	71.31	25	20.5	0.8775
0.5	9	72	71.31	18	20.5	0.1009
5	9	158	158	38	35.83	0.00000005944

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.7225	5	291.4449
A2	-137.2711	8	290.5422
A3	-137.618	6	287.236
R	-163.2567	2	330.5135
5	-138.8065	6	289.6129

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.97	6	<0.0001
Test 2	6.903	3	0.07506
Test 3	0.6938	2	0.7069
Test 7a	2.377	0	N/A

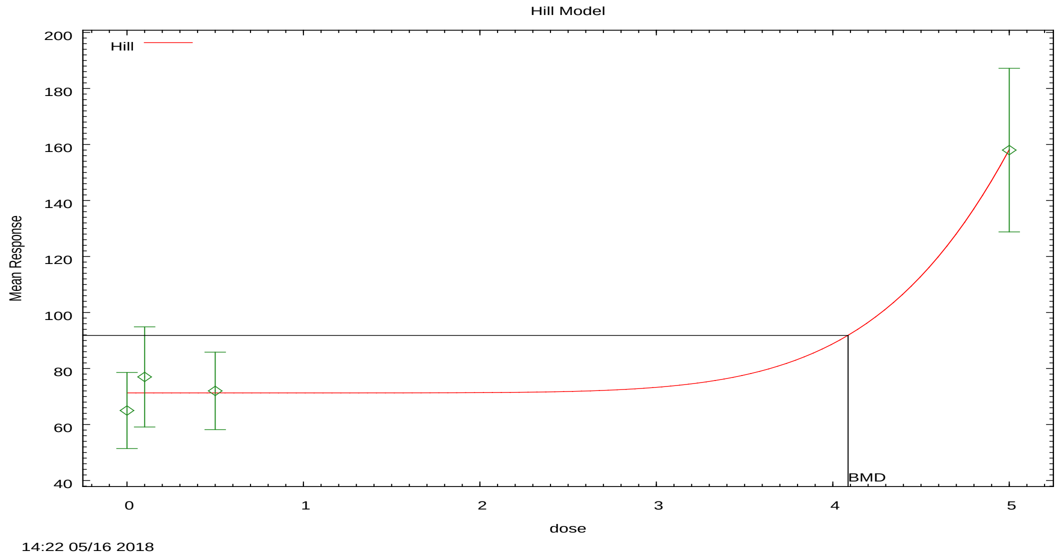

Figure 132. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.08647

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.0547498	6.51767
rho	1.40296	0
intercept	71.3104	65
v	677.844	93
n	7.67176	0.686281

k	6.42163	7.43314

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	71.3	19	20.5	-0.973
0.1	10	77	71.3	25	20.5	0.877
0.5	9	72	71.3	18	20.5	0.101
5	9	158	158	38	35.8	-0.00000112

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.722467	5	291.444934
A2	-137.271117	8	290.542234
A3	-137.618003	6	287.236006
fitted	-138.80647	6	289.61294
R	-163.256735	2	330.513469

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.9712	6	<0.0001
Test 2	6.9027	3	0.07506
Test 3	0.693772	2	0.7069
Test 4	2.37693	0	N/A

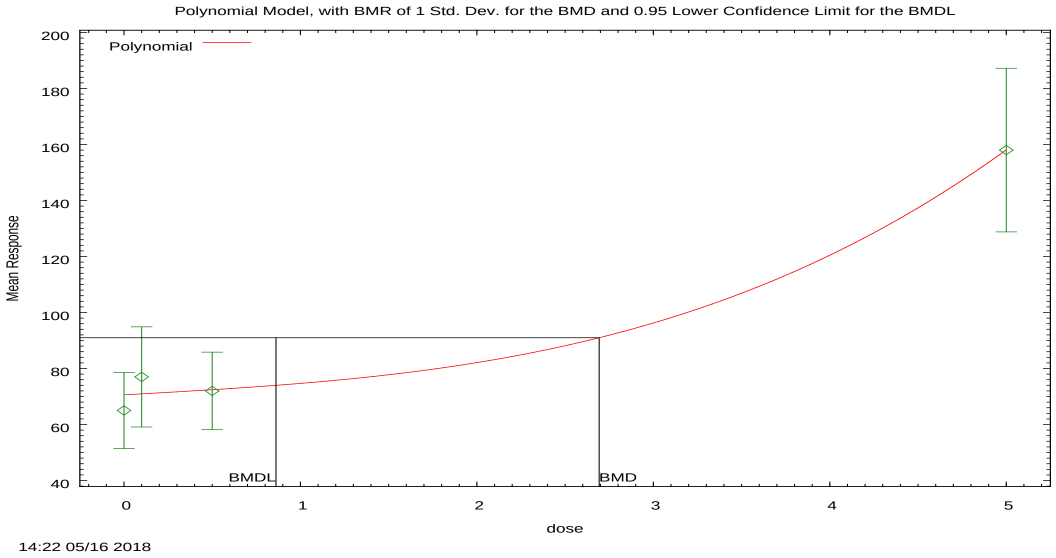

Figure 133. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.69286

BMDL at the 95% confidence level = 0.861199

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.10566	6.51767
rho	1.39137	0
beta_0	70.6107	65
beta_1	3.51553	0
beta_2	1.95415E-22	0

beta_3	0.55879	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	70.6	19	20.4	-0.871
0.1	10	77	71	25	20.4	0.934
0.5	9	72	72.4	18	20.7	-0.0634
5	9	158	158	38	35.7	-0.00311

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.722467	5	291.444934
A2	-137.271117	8	290.542234
A3	-137.618003	6	287.236006
fitted	-138.789061	5	287.578122
R	-163.256735	2	330.513469

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.9712	6	<0.0001
Test 2	6.9027	3	0.07506
Test 3	0.693772	2	0.7069
Test 4	2.34212	1	0.1259

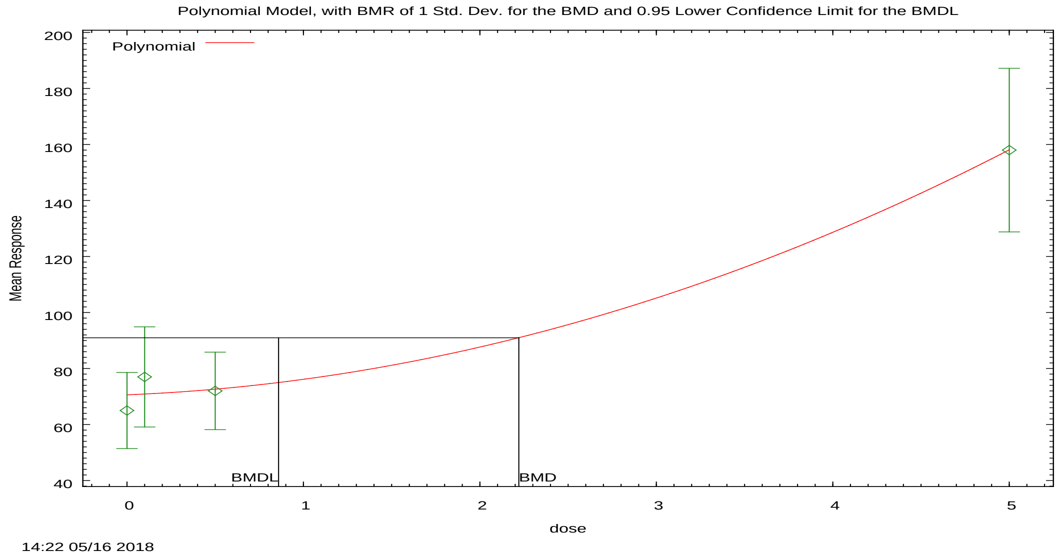

Figure 134. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.22069

BMDL at the 95% confidence level = 0.859021

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.124773	6.51767
rho	1.38731	0
beta_0	70.5826	70.0193
beta_1	2.54926	0
beta_2	2.98701	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	70.6	19	20.4	-0.866
0.1	10	77	70.9	25	20.4	0.948
0.5	9	72	72.6	18	20.8	-0.0871
5	9	158	158	38	35.7	-0.000349

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.722467	5	291.444934
A2	-137.271117	8	290.542234
A3	-137.618003	6	287.236006
fitted	-138.809366	5	287.618731
R	-163.256735	2	330.513469

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.9712	6	<0.0001
Test 2	6.9027	3	0.07506
Test 3	0.693772	2	0.7069
Test 4	2.38273	1	0.1227

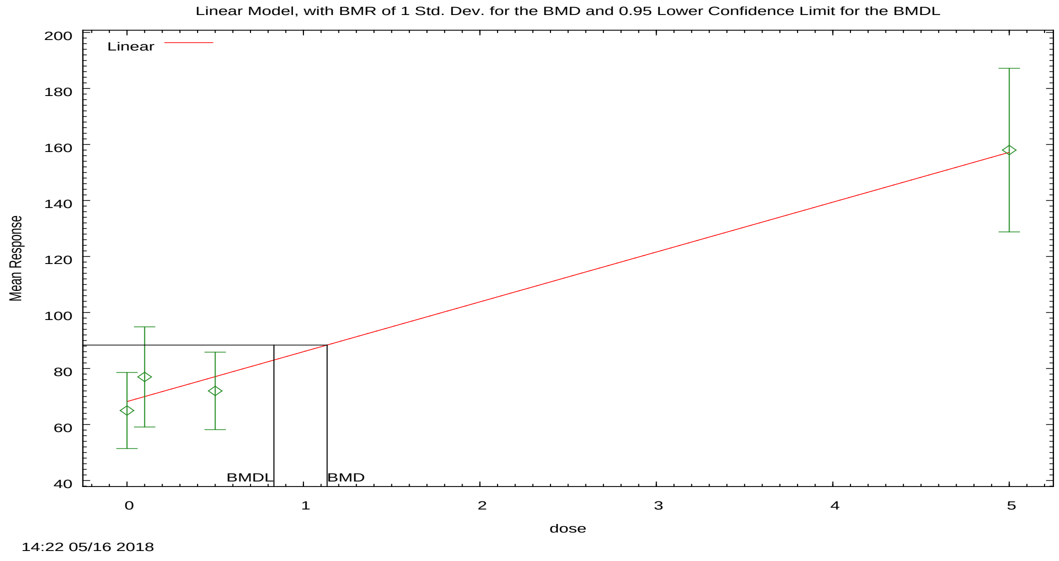

Figure 135. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alkaline Phosphatase in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.13426

BMDL at the 95% confidence level = 0.8326

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.359446	6.51767
rho	1.33766	0
beta_0	68.1984	67.853
beta_1	17.7756	17.9621

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	65	68.2	19	20.2	-0.502
0.1	10	77	70	25	20.5	1.08
0.5	9	72	77.1	18	21.9	-0.697
5	9	158	157	38	35.2	0.0787

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.722467	5	291.444934
A2	-137.271117	8	290.542234
A3	-137.618003	6	287.236006
fitted	-139.076002	4	286.152004
R	-163.256735	2	330.513469

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	51.9712	6	<0.0001
Test 2	6.9027	3	0.07506
Test 3	0.693772	2	0.7069
Test 4	2.916	2	0.2327

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery – Alkaline Phosphatase (U/L) in Males

1.16. BMDS Summary of Alkaline Phosphatase (U/L) Males (90 Day Rats GenX)

Table 16. Summary of BMD Modeling Results for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	**Goodness of fit**		**BMD_{1SD} (mg/kg/day)**	**BMDL_{1SD} (mg/kg/day)**	**BMD/BMDL**	**Basis for model selection**
	***p*-value**	**AIC**				
Exponential (M2) Exponential (M3)[b]	<0.0001	314.53	37.5	27.8	1.35	Only one model met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from this model.
Exponential (M4)	**0.952**	**295.55**	**2.66**	**1.43**	**1.86**	
Exponential (M5)	N/A[c]	297.54	3.37	1.43	2.35	
Hill	N/A[c]	297.54	3.00	error[d]	error	
Power[e] Polynomial 3°[f] Polynomial 2°[g] Linear	<0.0001	312.47	26.6	17.0	1.56	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 7.40E-04), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 10, and 100 mg/kg/day were 0.22, -0.14, -0.25, 0.18, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] No available degrees of freedom to calculate a goodness of fit value.

[d] BMD or BMDL computation failed for this model.

[e] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[g] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

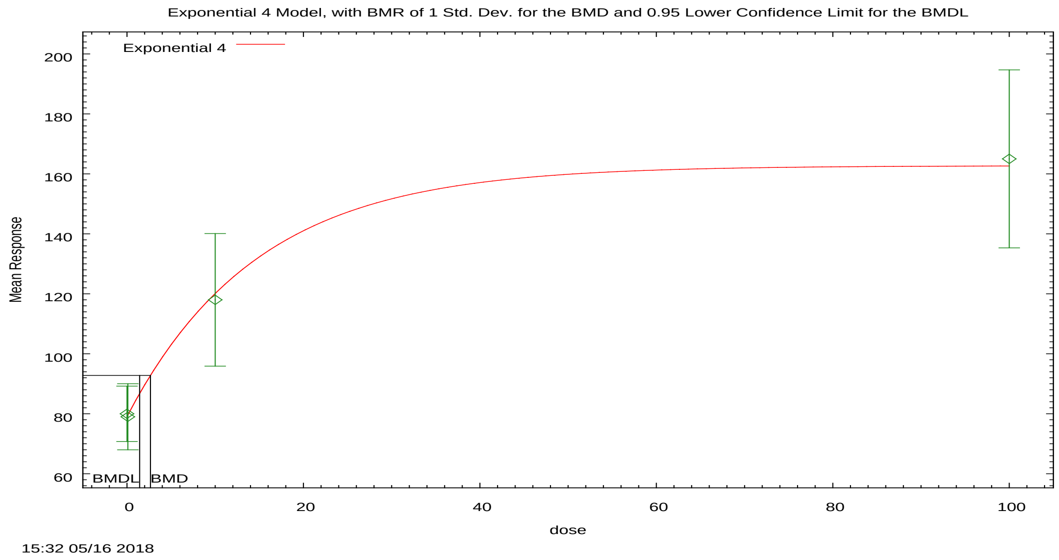

Figure 136. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.65934

BMDL at the 95% confidence level = 1.43235

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-8.41546	-8.09011
rho	3.12538	3.07366
a	79.043	75.05
b	0.0675108	0.0250925
c	2.05869	2.30846
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	80	79.04	12.9	13.75	0.2201
0.1	10	79	79.61	15.4	13.91	-0.1378
10	10	118	120.1	30.9	26.45	-0.2538
100	10	165	162.6	41.5	42.46	0.1767

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC

A1	-150.8247	5	311.6494
A2	-142.3732	8	300.7465
A3	-142.7721	6	297.5442
R	-171.3096	2	346.6191
4	-142.7739	5	295.5478

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.87	6	<0.0001
Test 2	16.9	3	0.00074
Test 3	0.7977	2	0.6711
Test 6a	0.003674	1	0.9517

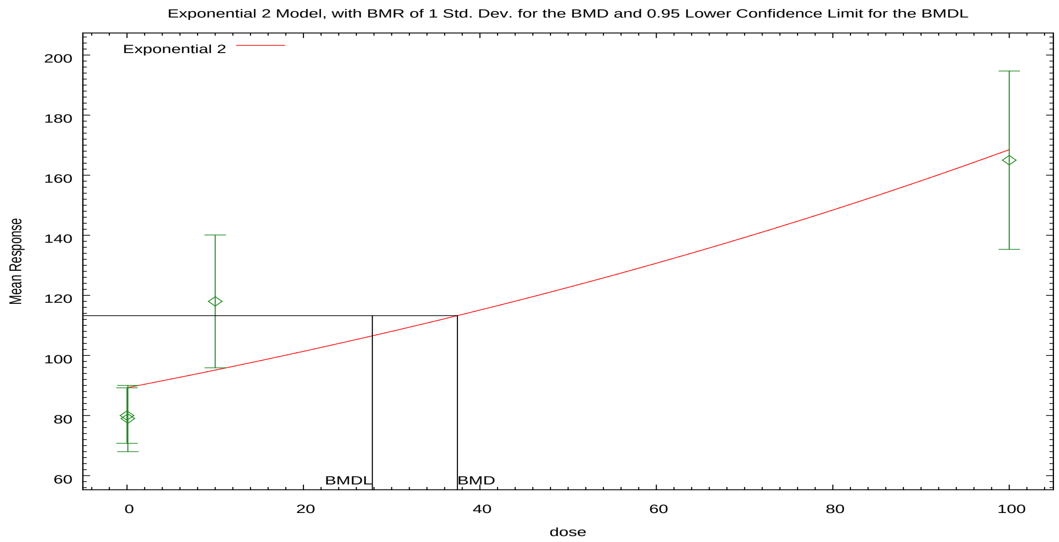

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Figure 137. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 37.4536

BMDL at the 95% confidence level = 27.8113

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.56933	-8.09011
rho	1.76412	3.07366
a	89.2804	88.0519
b	0.00635285	0.00650678
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	80	89.28	12.9	23.98	-1.224
0.1	10	79	89.34	15.4	24	-1.362
10	10	118	95.14	30.9	25.37	2.85
100	10	165	168.5	41.5	42	-0.2652

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-150.8247	5	311.6494
A2	-142.3732	8	300.7465
A3	-142.7721	6	297.5442
R	-171.3096	2	346.6191
2	-153.264	4	314.528

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	57.87	6	<0.0001
Test 2	16.9	3	0.00074
Test 3	0.7977	2	0.6711
Test 4	20.98	2	<0.0001

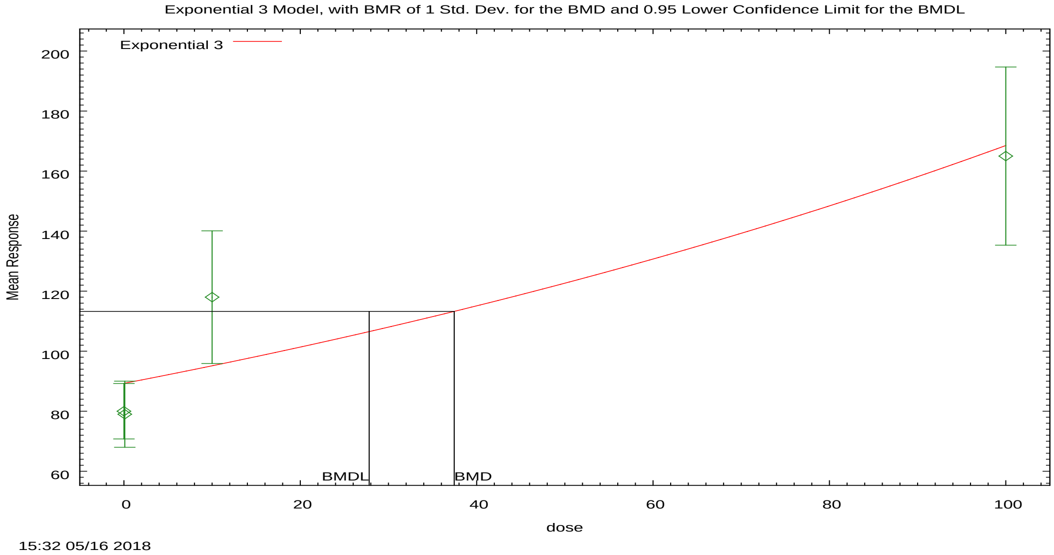


Figure 138. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 37.4536

BMDL at the 95% confidence level = 27.8113

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values

lnalpha	-1.56932	-8.09011
rho	1.76412	3.07366
a	89.2804	88.0519
b	0.00635285	0.00650678
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	80	89.28	12.9	23.98	-1.224
0.1	10	79	89.34	15.4	24	-1.362
10	10	118	95.14	30.9	25.37	2.85
100	10	165	168.5	41.5	42	-0.2652

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-150.8247	5	311.6494
A2	-142.3732	8	300.7465
A3	-142.7721	6	297.5442
R	-171.3096	2	346.6191
3	-153.264	4	314.528

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.87	6	<0.0001
Test 2	16.9	3	0.00074
Test 3	0.7977	2	0.6711
Test 5a	20.98	2	<0.0001

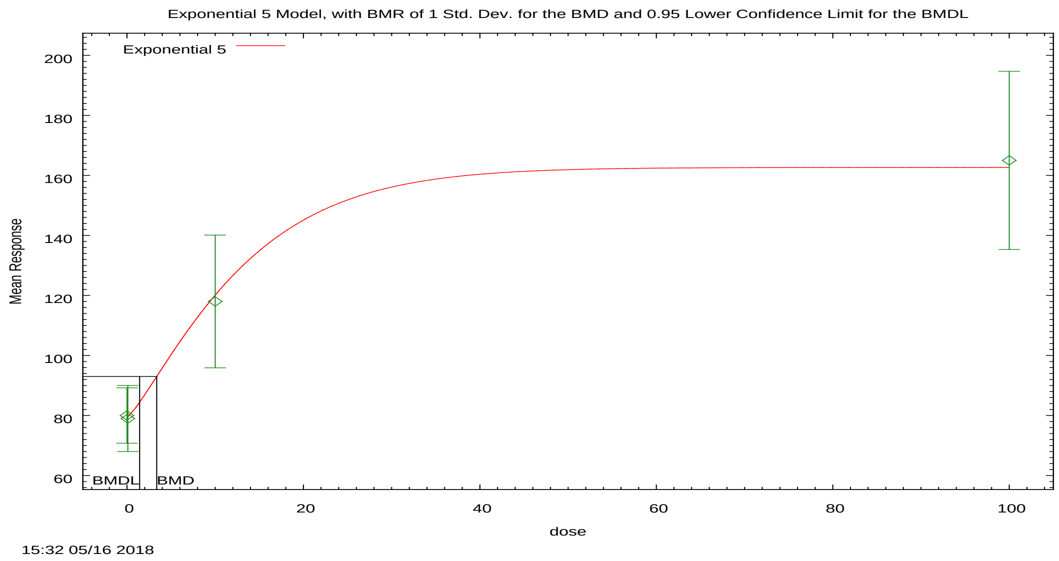


Figure 139. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 3.36987

BMDL at the 95% confidence level = 1.43304

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-8.40364	-8.09011
rho	3.12282	3.07366
a	79.2095	75.05
b	0.0722146	0.0250925
c	2.05331	2.30846

d	1.2101	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	80	79.21	12.9	13.8	0.1811
0.1	10	79	79.42	15.4	13.86	-0.09651
10	10	118	120.1	30.9	26.45	-0.2554
100	10	165	162.6	41.5	42.44	0.1758

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-150.8247	5	311.6494
A2	-142.3732	8	300.7465
A3	-142.7721	6	297.5442
R	-171.3096	2	346.6191
5	-142.7721	6	297.5442

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.87	6	<0.0001
Test 2	16.9	3	0.00074
Test 3	0.7977	2	0.6711
Test 7a	-0.000000000005002	0	N/A

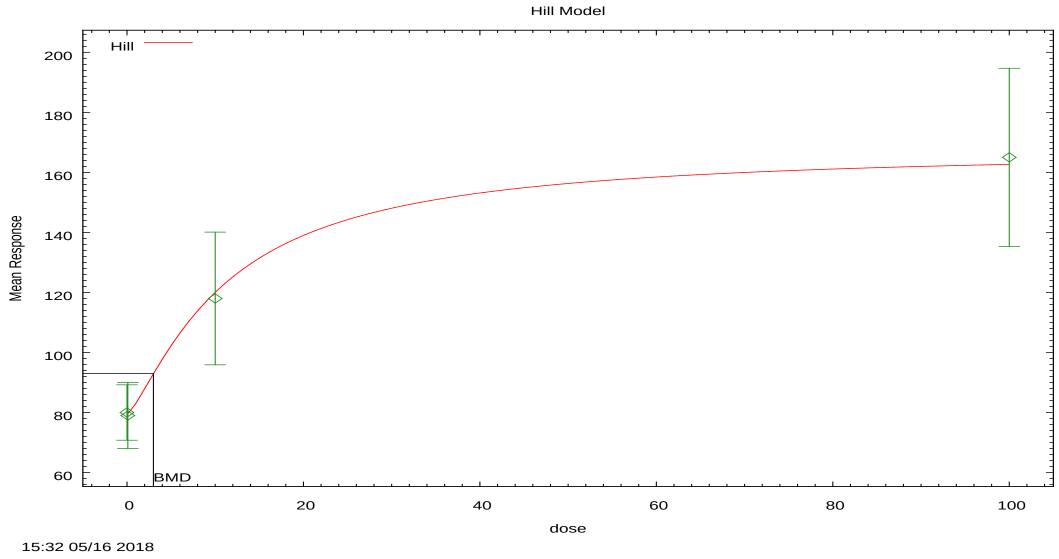


Figure 140. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.99517

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-8.40365	6.6466
rho	3.12283	0
intercept	79.2094	80
v	88.5842	85
n	1.27533	0.073347

k	11.268	181.383

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	80	79.2	12.9	13.8	0.181
0.1	10	79	79.4	15.4	13.9	-0.0965
10	10	118	120	30.9	26.4	-0.255
100	10	165	163	41.5	42.4	0.176

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-150.82469	5	311.649381
A2	-142.373234	8	300.746468
A3	-142.772075	6	297.544151
fitted	-142.772075	6	297.544151
R	-171.309565	2	346.61913

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.8727	6	<0.0001
Test 2	16.9029	3	0.00074
Test 3	0.797683	2	0.6711
Test 4	2.58638E-11	0	N/A

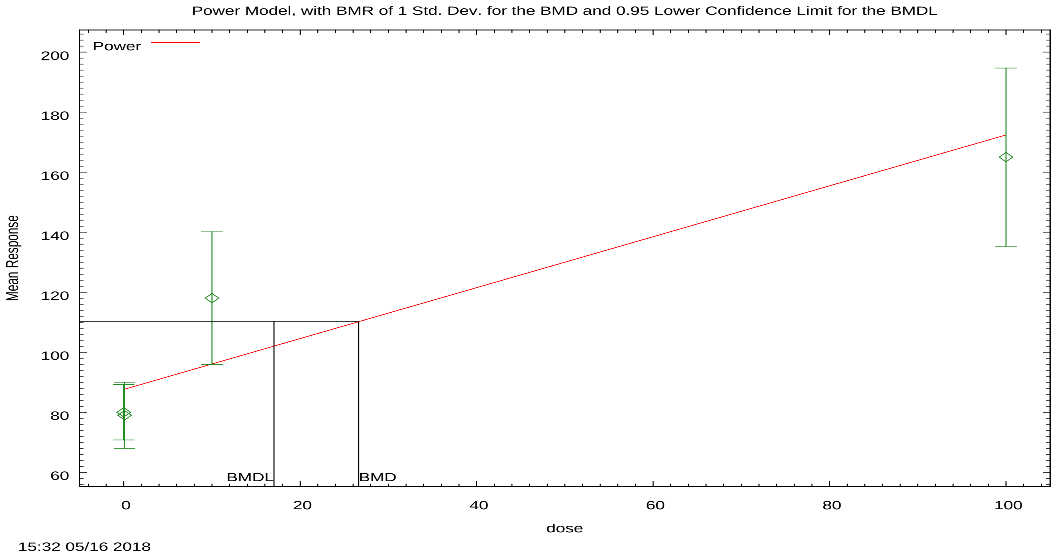


Figure 141. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 26.6376

BMDL at the 95% confidence level = 17.0313

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.49476	6.6466
rho	1.95201	0
control	87.5703	79
slope	0.848249	17.686
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	80	87.6	12.9	22.6	-1.06
0.1	10	79	87.7	15.4	22.6	-1.21
10	10	118	96.1	30.9	24.7	2.81
100	10	165	172	41.5	43.8	-0.534

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-150.82469	5	311.649381
A2	-142.373234	8	300.746468
A3	-142.772075	6	297.544151
fitted	-152.232546	4	312.465092
R	-171.309565	2	346.61913

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.8727	6	<0.0001
Test 2	16.9029	3	0.00074
Test 3	0.797683	2	0.6711
Test 4	18.9209	2	<0.0001

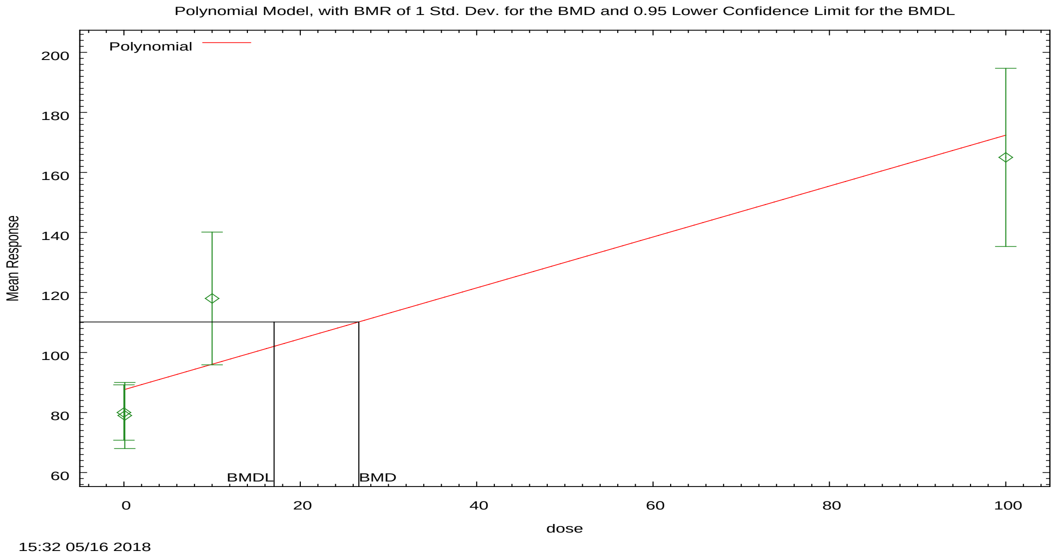


Figure 142. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 26.6376

BMDL at the 95% confidence level = 17.0313

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.49476	6.6466
rho	1.95201	0
beta_0	87.5703	80
beta_1	0.848249	0
beta_2	0	0

beta_3	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	80	87.6	12.9	22.6	-1.06
0.1	10	79	87.7	15.4	22.6	-1.21
10	10	118	96.1	30.9	24.7	2.81
100	10	165	172	41.5	43.8	-0.534

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-150.82469	5	311.649381
A2	-142.373234	8	300.746468
A3	-142.772075	6	297.544151
fitted	-152.232546	4	312.465092
R	-171.309565	2	346.61913

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.8727	6	<0.0001
Test 2	16.9029	3	0.00074
Test 3	0.797683	2	0.6711
Test 4	18.9209	2	<0.0001

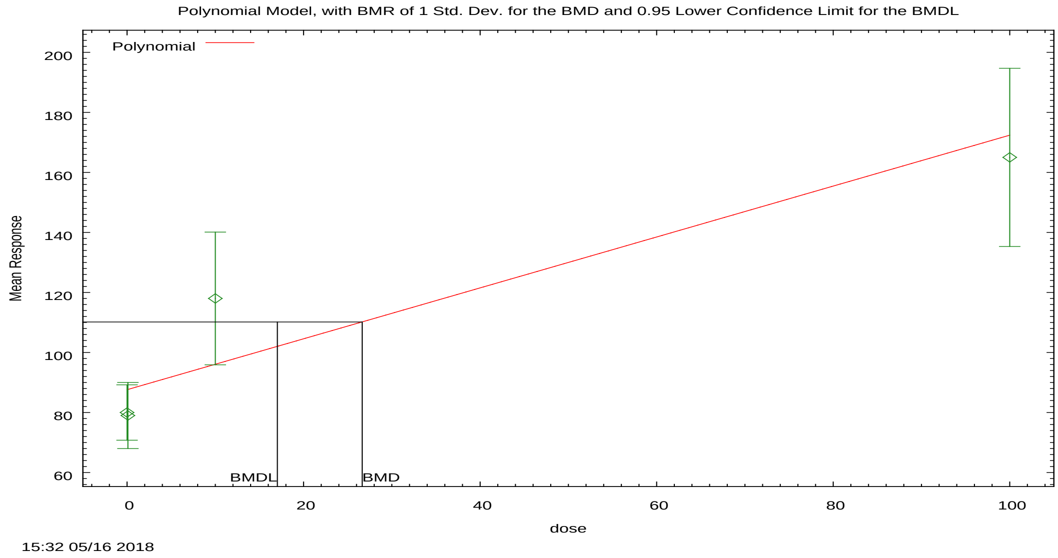


Figure 143. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 26.6376

BMDL at the 95% confidence level = 17.0313

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.49473	6.6466
rho	1.952	0
beta_0	87.5703	79.2939
beta_1	0.84825	0
beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	80	87.6	12.9	22.6	-1.06
0.1	10	79	87.7	15.4	22.6	-1.21
10	10	118	96.1	30.9	24.7	2.81
100	10	165	172	41.5	43.8	-0.534

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-150.82469	5	311.649381
A2	-142.373234	8	300.746468
A3	-142.772075	6	297.544151
fitted	-152.232546	4	312.465092
R	-171.309565	2	346.61913

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.8727	6	<0.0001
Test 2	16.9029	3	0.00074
Test 3	0.797683	2	0.6711
Test 4	18.9209	2	<0.0001

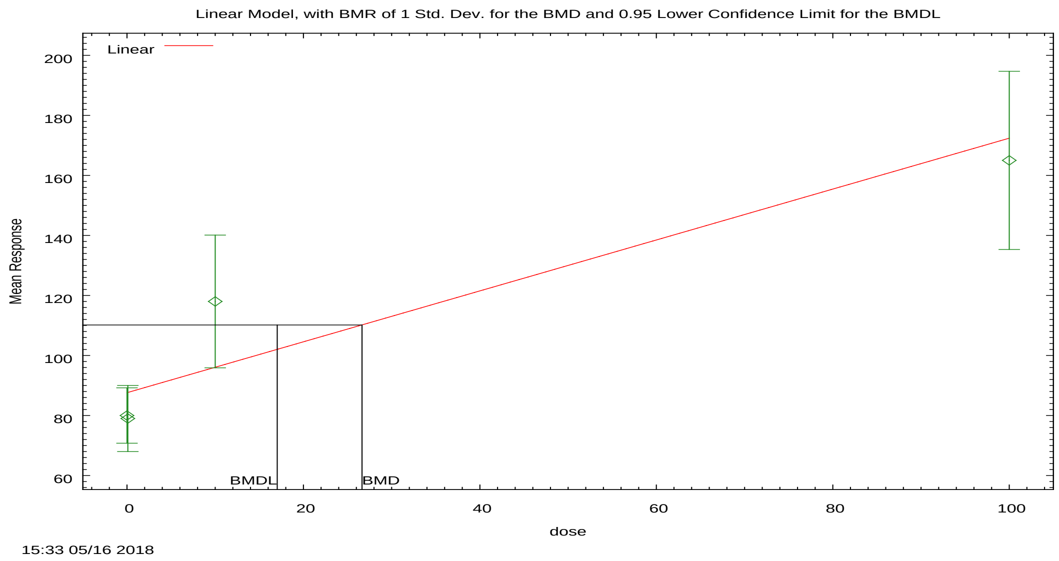


Figure 144. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alkaline Phosphatase in Males (90-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 26.6376

BMDL at the 95% confidence level = 17.0313

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.49476	6.6466
rho	1.95201	0
beta_0	87.5703	89.0008
beta_1	0.848249	0.78108

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	80	87.6	12.9	22.6	-1.06
0.1	10	79	87.7	15.4	22.6	-1.21
10	10	118	96.1	30.9	24.7	2.81
100	10	165	172	41.5	43.8	-0.534

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-150.82469	5	311.649381
A2	-142.373234	8	300.746468
A3	-142.772075	6	297.544151
fitted	-152.232546	4	312.465092
R	-171.309565	2	346.61913

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.8727	6	<0.0001
Test 2	16.9029	3	0.00074
Test 3	0.797683	2	0.6711
Test 4	18.9209	2	<0.0001

BMDS WIZARD OUTPUT REPORT

H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats – Alkaline Phosphatase (U/L) in Males at 12-month timepoint

1.17. BMDS Summary of Alkaline Phosphatase (U/L) Males 12 months (2 Year Rats GenX)

Table 17. Summary of BMD Modeling Results for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.00186	329.74	16.0	12.4	1.30	No models met all model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). No BMDL was selected.
Exponential (M4) Exponential (M5)[c]	0.0202	324.56	0.690	0.312	2.21	
Hill	0.0226	324.36	0.615	0.589	1.05	
Power[d] Polynomial 2°[e] Linear	0.00228	329.33	11.5	8.10	1.42	
Polynomial 3°	<0.0001	502.76	0.808	0.0319	25.3	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001, BMDS Test 3 *p*-value = 0.759), no model was selected as a best-fitting model.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[e] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

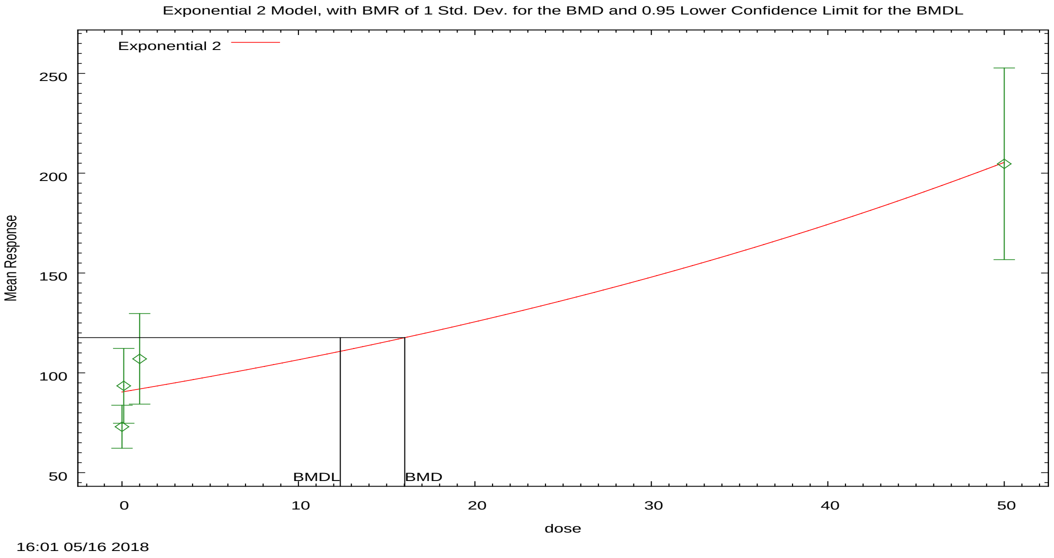


Figure 145. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 16.0244

BMDL at the 95% confidence level = 12.3721

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-2.78302	-6.18686
rho	2.08447	2.76421
a	90.4273	89.4073
b	0.0164117	0.0166338
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	73	90.43	15.06	27.2	-2.026
0.1	10	93.5	90.58	26.22	27.25	0.3394
1	10	107	91.92	31.7	27.67	1.723
50	10	204.7	205.4	67.12	63.98	-0.03635

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-165.5237	5	341.0474

A2	-154.3064	8	324.6128
A3	-154.5829	6	321.1657
R	-185.9252	2	375.8503
2	-160.8715	4	329.7431

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.24	6	<0.0001
Test 2	22.43	3	<0.0001
Test 3	0.5529	2	0.7585
Test 4	12.58	2	0.001857

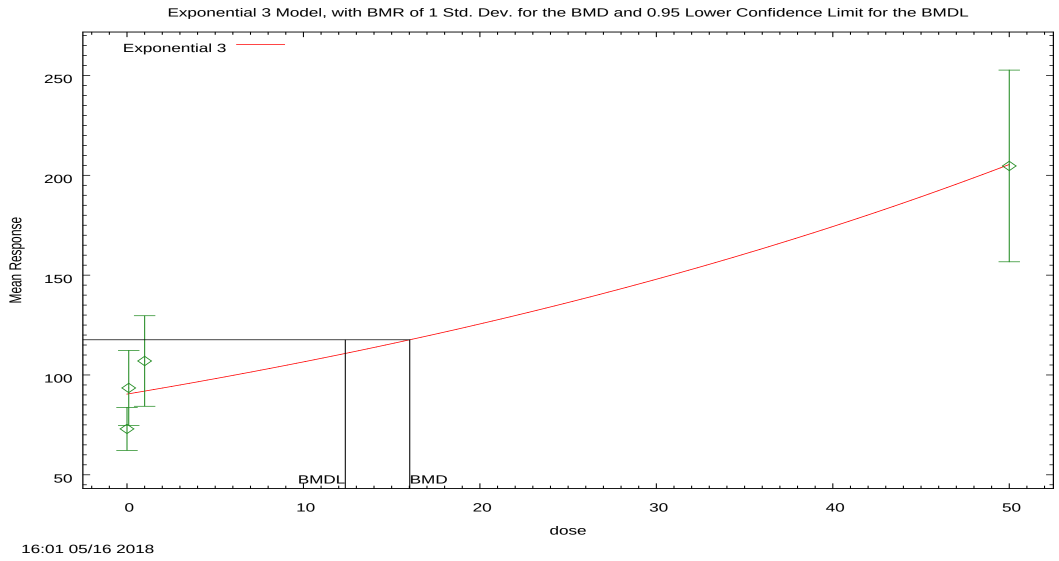


Figure 146. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 16.0244

BMDL at the 95% confidence level = 12.3721

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-2.78302	-6.18686
rho	2.08446	2.76421
a	90.4273	89.4073
b	0.0164117	0.0166338
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	73	90.43	15.06	27.2	-2.026
0.1	10	93.5	90.58	26.22	27.25	0.3394
1	10	107	91.92	31.7	27.67	1.723
50	10	204.7	205.4	67.12	63.98	-0.03635

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-165.5237	5	341.0474
A2	-154.3064	8	324.6128
A3	-154.5829	6	321.1657
R	-185.9252	2	375.8503
3	-160.8715	4	329.7431

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	63.24	6	<0.0001
Test 2	22.43	3	<0.0001
Test 3	0.5529	2	0.7585
Test 5a	12.58	2	0.001857

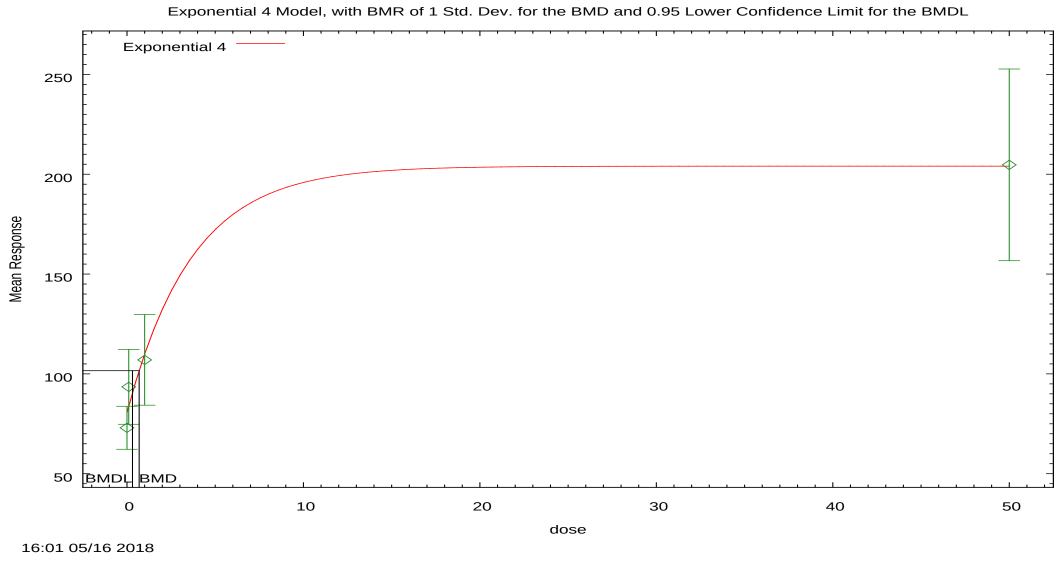


Figure 147. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.689781

BMDL at the 95% confidence level = 0.311869

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.36848	-6.18686
rho	2.38557	2.76421
a	80.4861	69.35
b	0.271622	0.0532044
c	2.53522	3.09928
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	73	80.49	15.06	21.11	-1.121
0.1	10	93.5	83.8	26.22	22.15	1.385
1	10	107	109.9	31.7	30.6	-0.2972
50	10	204.7	204	67.12	64.04	0.03213

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-165.5237	5	341.0474
A2	-154.3064	8	324.6128
A3	-154.5829	6	321.1657
R	-185.9252	2	375.8503
4	-157.2824	5	324.5648

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.24	6	<0.0001
Test 2	22.43	3	<0.0001
Test 3	0.5529	2	0.7585
Test 6a	5.399	1	0.02015

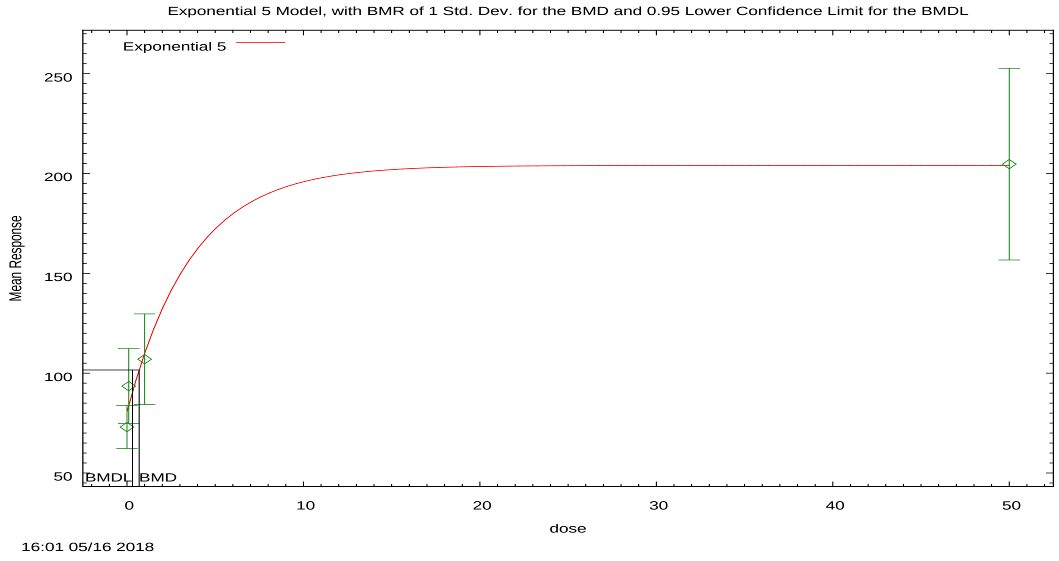


Figure 148. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.689781

BMDL at the 95% confidence level = 0.311869

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.36848	-6.18686
rho	2.38557	2.76421
a	80.4861	69.35
b	0.271622	0.0532044

c	2.53522	3.09928
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	73	80.49	15.06	21.11	-1.121
0.1	10	93.5	83.8	26.22	22.15	1.385
1	10	107	109.9	31.7	30.6	-0.2972
50	10	204.7	204	67.12	64.04	0.03213

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-165.5237	5	341.0474
A2	-154.3064	8	324.6128
A3	-154.5829	6	321.1657
R	-185.9252	2	375.8503
5	-157.2824	5	324.5648

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.24	6	<0.0001
Test 2	22.43	3	<0.0001
Test 3	0.5529	2	0.7585
Test 7a	5.399	1	0.02015

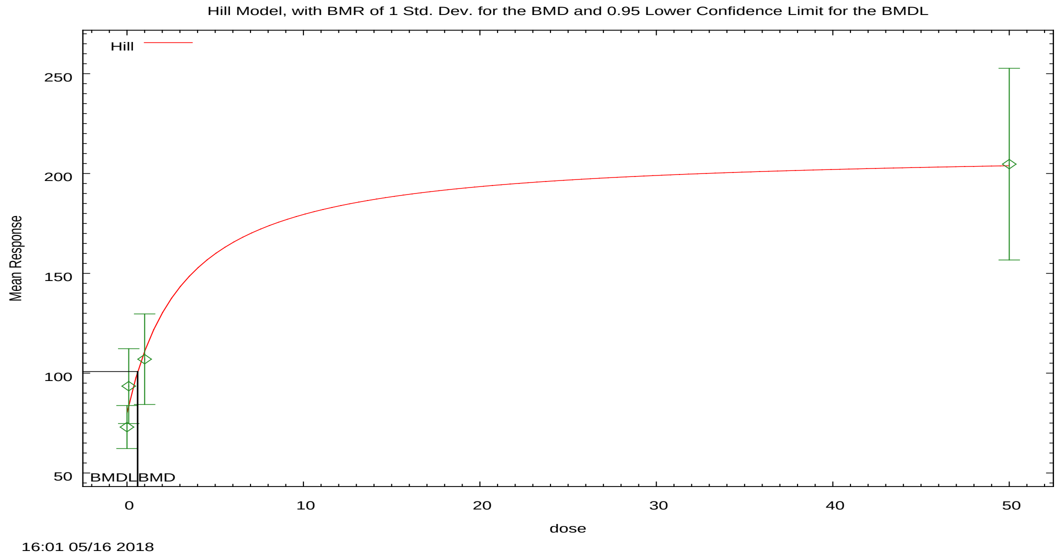


Figure 149. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.615474

BMDL at the 95% confidence level = 0.588643

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.47685	7.38154
rho	2.40759	0
intercept	79.9709	73
v	131.519	131.7

n	1	0.245207
k	3.2713	83.0261

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	73	80	15.1	20.8	-1.06
0.1	10	93.5	83.9	26.2	22.1	1.38
1	10	107	111	31.7	30.8	-0.386
50	10	205	203	67.1	64.1	0.0635

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-165.523688	5	341.047376
A2	-154.306424	8	324.612848
A3	-154.582873	6	321.165747
fitted	-157.180973	5	324.361945
R	-185.925167	2	375.850335

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.2375	6	<0.0001
Test 2	22.4345	3	<0.0001
Test 3	0.552899	2	0.7585
Test 4	5.1962	1	0.02264

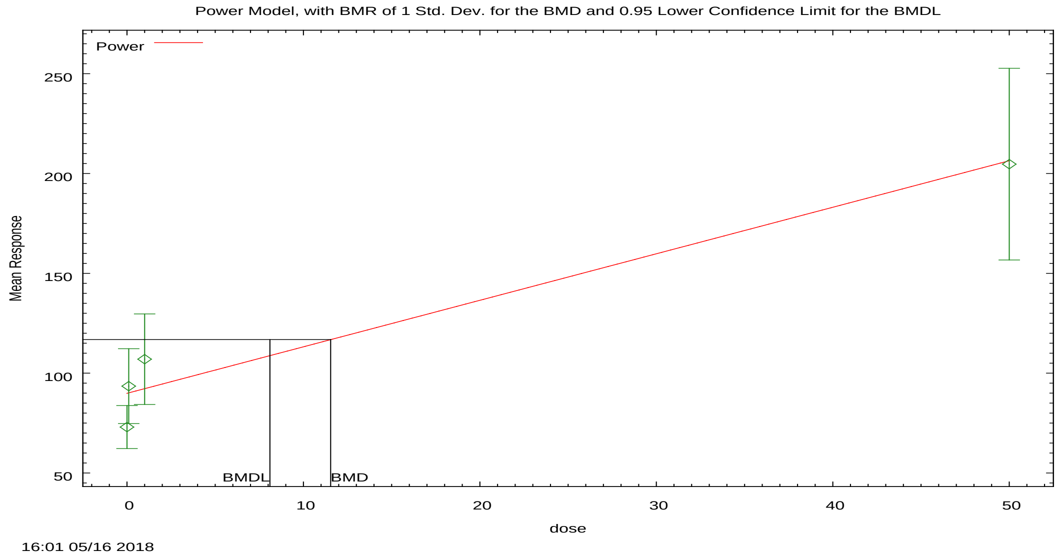


Figure 150. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 11.5414

BMDL at the 95% confidence level = 8.10154

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.82854	7.38154
rho	2.09209	0
control	89.9371	73
slope	2.33044	40.0502

power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	73	89.9	15.1	26.9	-1.99
0.1	10	93.5	90.2	26.2	27	0.39
1	10	107	92.3	31.7	27.6	1.69
50	10	205	206	67.1	64.2	-0.0867

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-165.523688	5	341.047376
A2	-154.306424	8	324.612848
A3	-154.582873	6	321.165747
fitted	-160.667071	4	329.334142
R	-185.925167	2	375.850335

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.2375	6	<0.0001
Test 2	22.4345	3	<0.0001
Test 3	0.552899	2	0.7585
Test 4	12.1684	2	0.002279

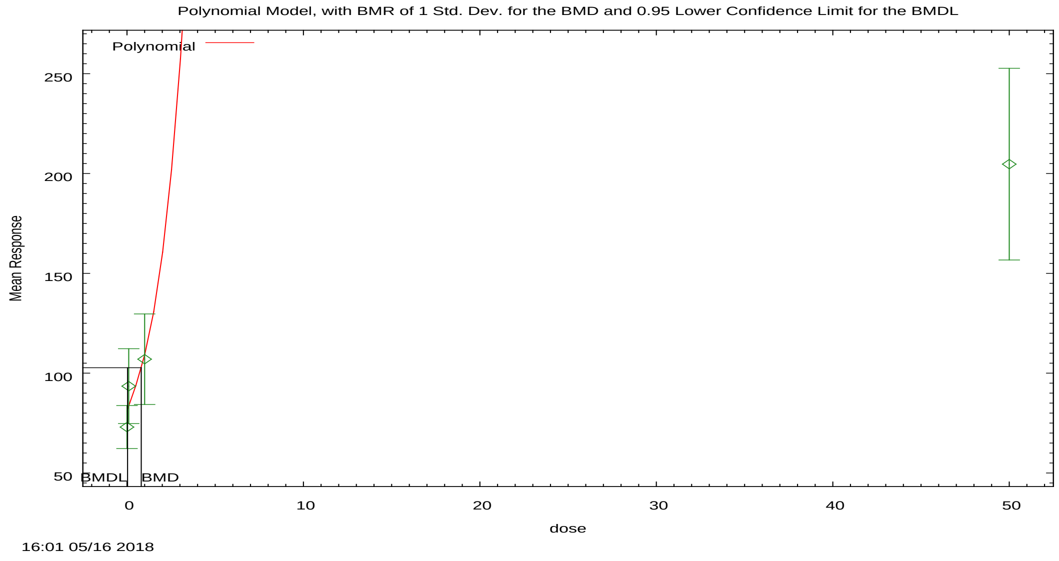


Figure 151. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.808167

BMDL at the 95% confidence level = 0.0319281

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-3.99342	7.38154
rho	2.30613	0
beta_0	81.1399	73

beta_1	24.3069	224.379
beta_2	0	0
beta_3	3.69216	3.79479

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	73	81.1	15.1	21.6	-1.19
0.1	10	93.5	83.6	26.2	22.3	1.4
1	10	107	109	31.7	30.4	-0.223
50	10	205	463000	67.1	463000	-3.16

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-165.523688	5	341.047376
A2	-154.306424	8	324.612848
A3	-154.582873	6	321.165747
fitted	-246.381182	5	502.762365
R	-185.925167	2	375.850335

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.2375	6	<0.0001
Test 2	22.4345	3	<0.0001
Test 3	0.552899	2	0.7585
Test 4	183.597	1	<0.0001

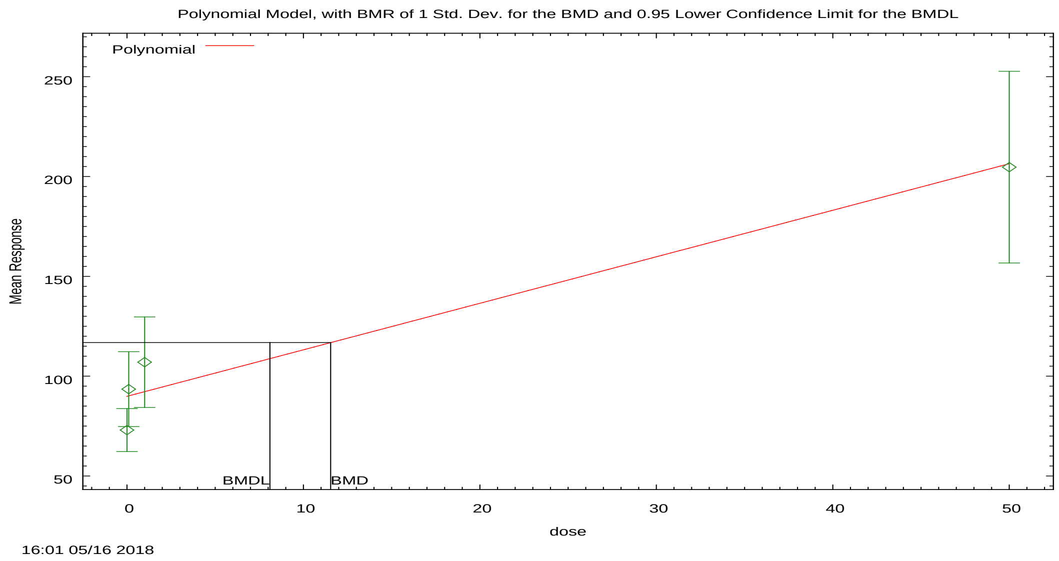


Figure 152. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 11.5414

BMDL at the 95% confidence level = 8.10154

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.82853	7.38154
rho	2.09208	0
beta_0	89.9371	81.424
beta_1	2.33044	27.0223

beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	73	89.9	15.1	26.9	-1.99
0.1	10	93.5	90.2	26.2	27	0.39
1	10	107	92.3	31.7	27.6	1.69
50	10	205	206	67.1	64.2	-0.0867

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-165.523688	5	341.047376
A2	-154.306424	8	324.612848
A3	-154.582873	6	321.165747
fitted	-160.667071	4	329.334142
R	-185.925167	2	375.850335

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.2375	6	<0.0001
Test 2	22.4345	3	<0.0001
Test 3	0.552899	2	0.7585
Test 4	12.1684	2	0.002279

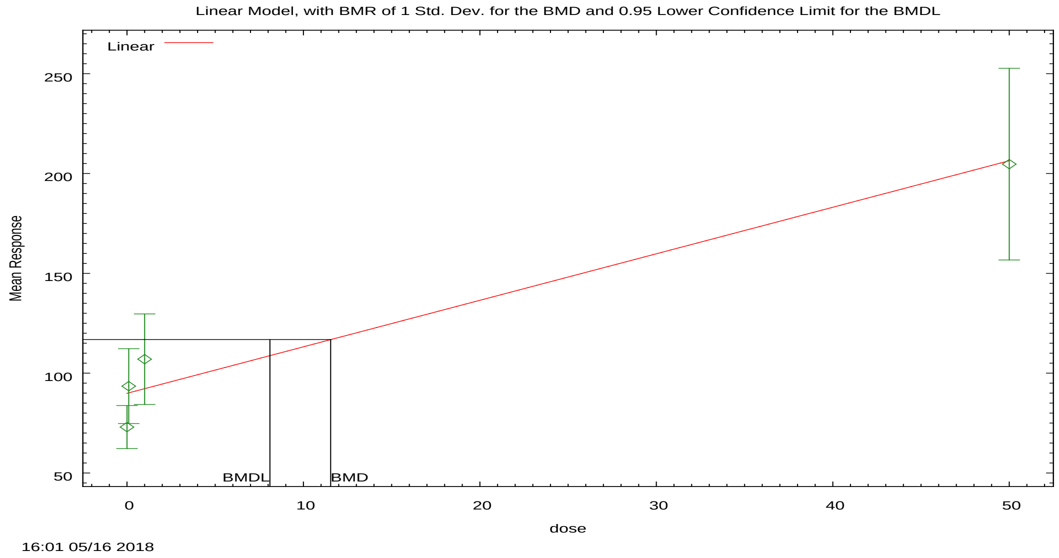


Figure 153. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alkaline Phosphatase in Males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 11.5414

BMDL at the 95% confidence level = 8.10154

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.82853	7.38154
rho	2.09208	0
beta_0	89.9371	90.2265
beta_1	2.33044	2.29538

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	73	89.9	15.1	26.9	-1.99
0.1	10	93.5	90.2	26.2	27	0.39
1	10	107	92.3	31.7	27.6	1.69
50	10	205	206	67.1	64.2	-0.0867

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-165.523688	5	341.047376
A2	-154.306424	8	324.612848
A3	-154.582873	6	321.165747
fitted	-160.667071	4	329.334142
R	-185.925167	2	375.850335

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	63.2375	6	<0.0001
Test 2	22.4345	3	<0.0001
Test 3	0.552899	2	0.7585
Test 4	12.1684	2	0.002279

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Alanine Aminotransferase (U/L) in Females

1.18. BMDS Summary of Alanine Aminotransferase (U/L) Females (90 Day Mice GenX)

Table 18. Summary of BMD Modeling Results for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.0421	226.75	3.07	1.92	1.60	No models met all model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). No BMDL was selected.
Exponential (M3)	0.0292	227.17	4.68	2.22	2.11	
Exponential (M4)	0.00999	229.05	2.96	1.65	1.79	
Exponential (M5)	N/A[b]	229.17	4.65	0.547	8.50	
Hill	0.0292	227.17	3.96	error[c]	error	
Power	0.0928	225.17	4.83	2.08	2.32	
Polynomial 3°	0.0919	225.19	4.08	3.37	1.21	
Polynomial 2°	0.0845	225.36	3.70	2.77	1.33	
Linear	0.0362	227.05	2.96	1.65	1.79	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.00197, BMDS Test 3 *p*-value = 0.554), no model was selected as a best-fitting model.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

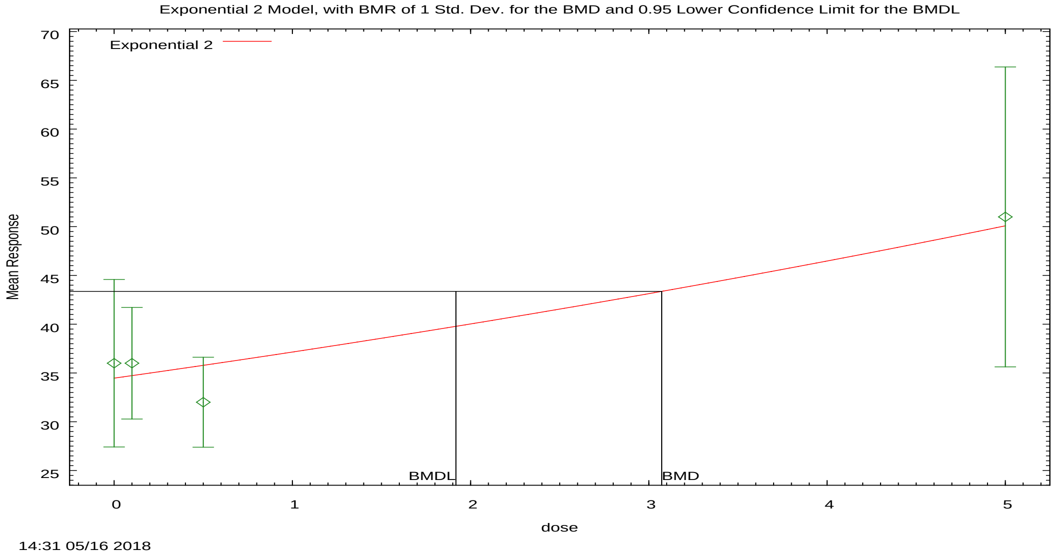


Figure 154. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 3.07219

BMDL at the 95% confidence level = 1.91774

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-9.37773	-12.8534
rho	3.88374	4.81423
a	34.4695	34.3083
b	0.0747248	0.0773011
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	36	34.47	12	8.9	0.5441
0.1	10	36	34.73	8	9.02	0.4457
0.5	9	32	35.78	6	9.56	-1.186
5	9	51	50.08	20	18.38	0.1496

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.0335	5	236.0671

A2	-105.6173	8	227.2345
A3	-106.2087	6	224.4174
R	-118.8274	2	241.6548
2	-109.377	4	226.7541

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	26.42	6	0.0001859
Test 2	14.83	3	0.001965
Test 3	1.183	2	0.5535
Test 4	6.337	2	0.04207

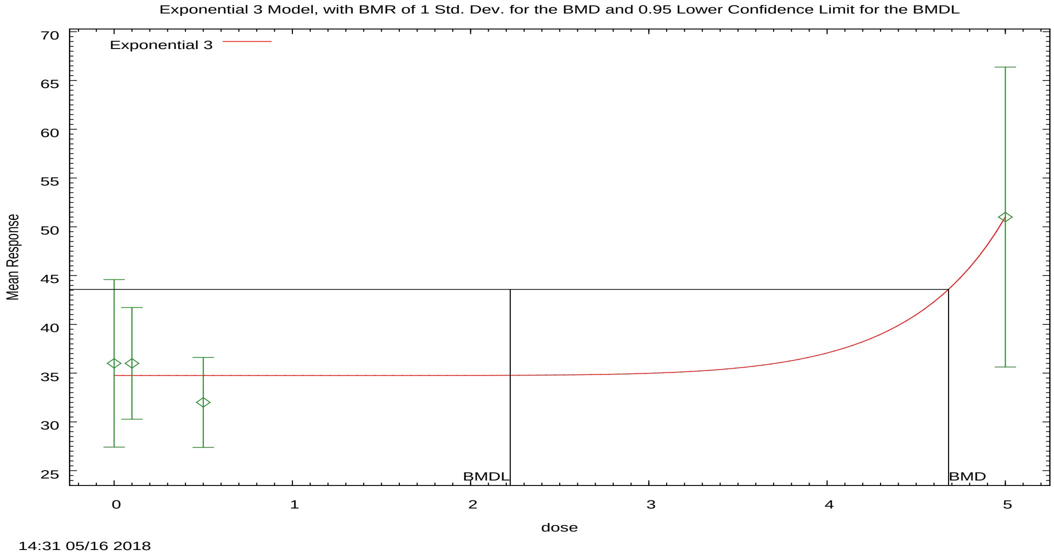


Figure 155. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.68144

BMDL at the 95% confidence level = 2.22228

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-9.69539	-12.8534
rho	3.95976	4.81423
a	34.7586	34.3083
b	0.177438	0.0773011
c	n/a	0
d	8.00925	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	36	34.76	12	8.83	0.4447
0.1	10	36	34.76	8	8.83	0.4447
0.5	9	32	34.76	6	8.83	-0.9376
5	9	51	51	20	18.86	0.0000000912

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.0335	5	236.0671
A2	-105.6173	8	227.2345
A3	-106.2087	6	224.4174
R	-118.8274	2	241.6548
3	-108.5866	5	227.1732

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	26.42	6	0.0001859
Test 2	14.83	3	0.001965
Test 3	1.183	2	0.5535
Test 5a	4.756	1	0.0292

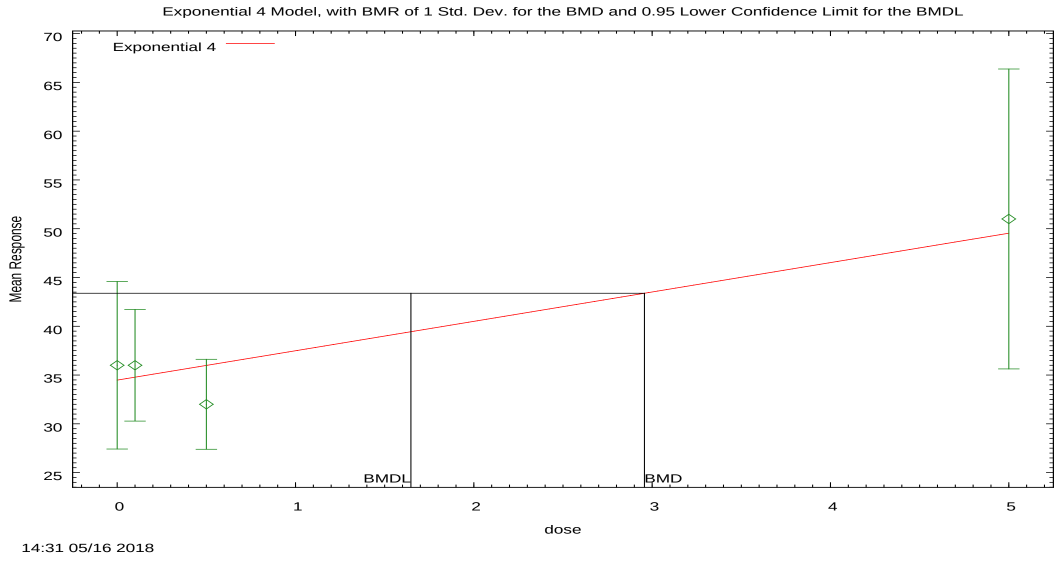


Figure 156. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.95667

BMDL at the 95% confidence level = 1.64717

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-9.72233	-12.8534
rho	3.98146	4.81423
a	34.4785	30.4
b	0.0000118979	0.0679252
c	7343.68	3.35526
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	36	34.48	12	8.91	0.5403
0.1	10	36	34.78	8	9.06	0.4259
0.5	9	32	35.98	6	9.7	-1.233
5	9	51	49.54	20	18.32	0.2393

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.0335	5	236.0671
A2	-105.6173	8	227.2345
A3	-106.2087	6	224.4174
R	-118.8274	2	241.6548
4	-109.5268	5	229.0536

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	26.42	6	0.0001859
Test 2	14.83	3	0.001965
Test 3	1.183	2	0.5535
Test 6a	6.636	1	0.009993

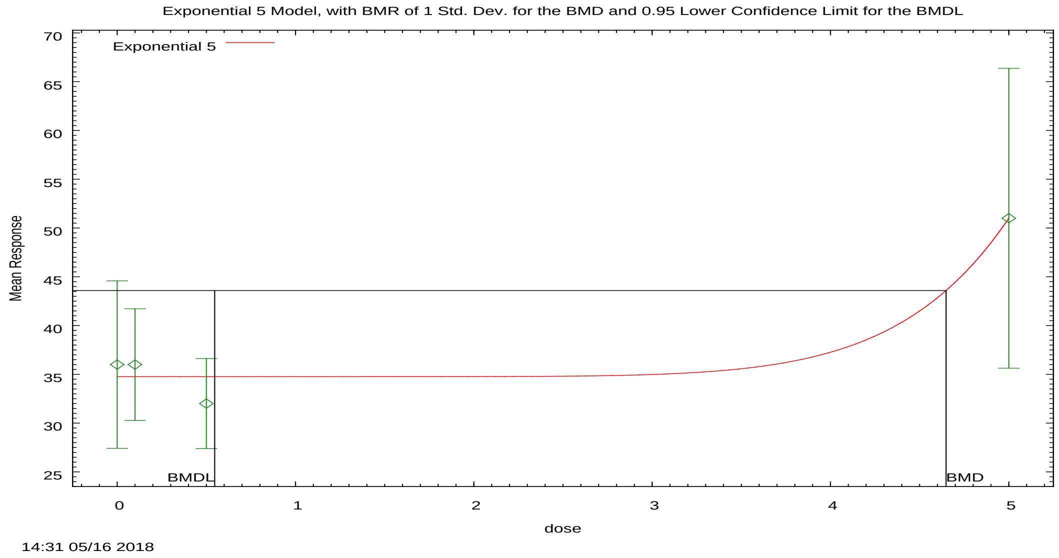


Figure 157. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.64816

BMDL at the 95% confidence level = 0.546826

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-9.69539	-12.8534
rho	3.95976	4.81423
a	34.7586	30.4
b	0.128205	0.0679252

c	21.0879	3.35526
d	8.43124	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	36	34.76	12	8.83	0.4447
0.1	10	36	34.76	8	8.83	0.4447
0.5	9	32	34.76	6	8.83	-0.9376
5	9	51	51	20	18.86	0.000000007321

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.0335	5	236.0671
A2	-105.6173	8	227.2345
A3	-106.2087	6	224.4174
R	-118.8274	2	241.6548
5	-108.5866	6	229.1732

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	26.42	6	0.0001859
Test 2	14.83	3	0.001965
Test 3	1.183	2	0.5535
Test 7a	4.756	0	N/A

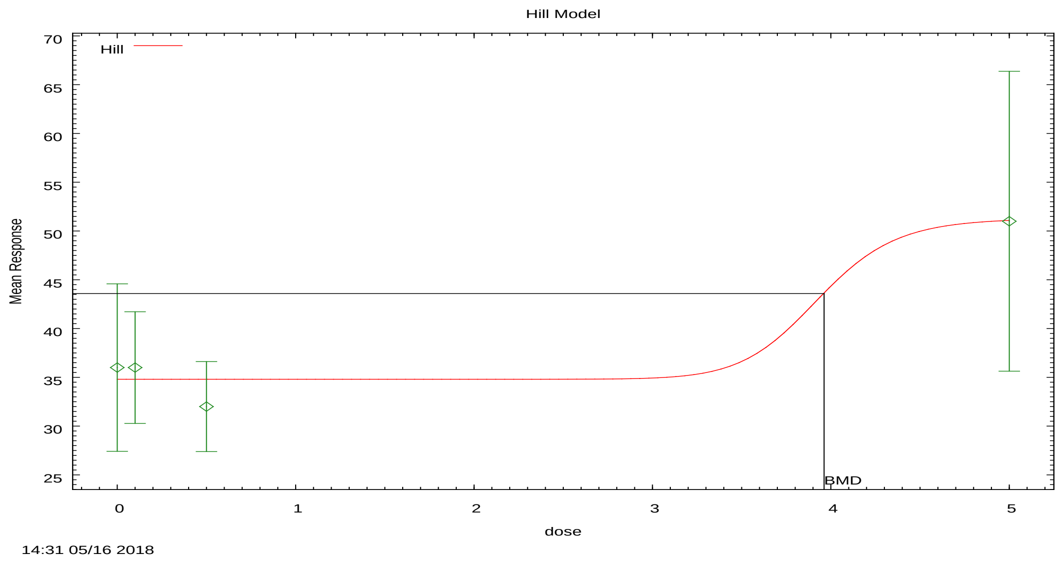


Figure 158. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.96196

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-9.69546	5.06036
rho	3.95977	0
intercept	34.7586	36
v	16.4542	15
n	18	18

k	3.92996	6.77632

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	36	34.8	12	8.83	0.445
0.1	10	36	34.8	8	8.83	0.445
0.5	9	32	34.8	6	8.83	-0.938
5	9	51	51	20	18.9	0.00000763

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.033529	5	236.067058
A2	-105.617255	8	227.23451
A3	-106.208714	6	224.417429
fitted	-108.586593	5	227.173186
R	-118.827402	2	241.654805

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	26.4203	6	0.0001859
Test 2	14.8325	3	0.001965
Test 3	1.18292	2	0.5535
Test 4	4.75576	1	0.0292

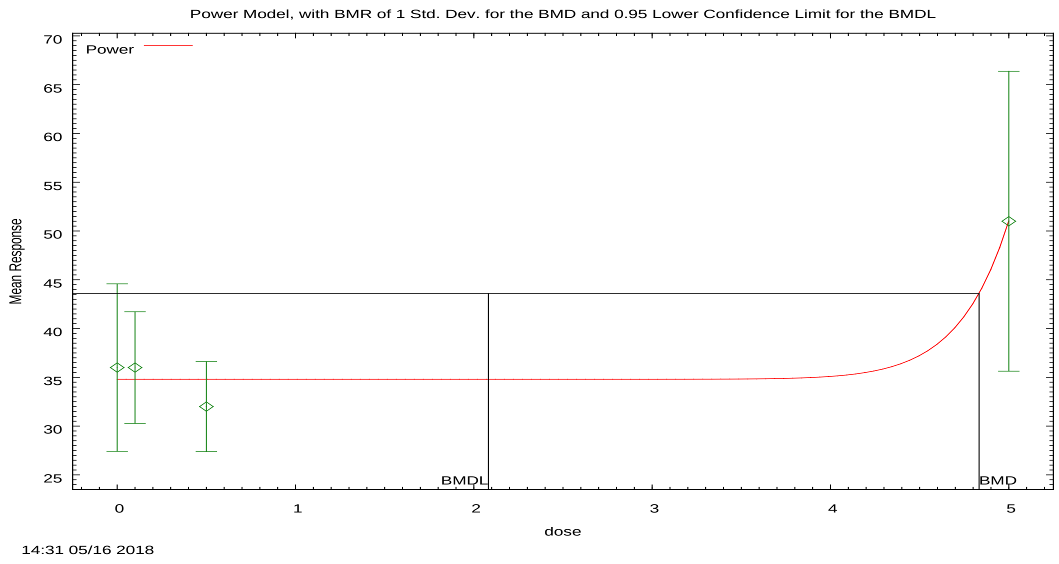


Figure 159. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.83345

BMDL at the 95% confidence level = 2.08154

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-9.69538	5.06036
rho	3.95975	0
control	34.7586	32
slope	4.25758E-12	10.0082
power	18	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	36	34.8	12	8.83	0.445
0.1	10	36	34.8	8	8.83	0.445
0.5	9	32	34.8	6	8.83	-0.938
5	9	51	51	20	18.9	-0.000000706

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.033529	5	236.067058
A2	-105.617255	8	227.23451
A3	-106.208714	6	224.417429
fitted	-108.586593	4	225.173186
R	-118.827402	2	241.654805

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	26.4203	6	0.0001859
Test 2	14.8325	3	0.001965
Test 3	1.18292	2	0.5535
Test 4	4.75576	2	0.09275

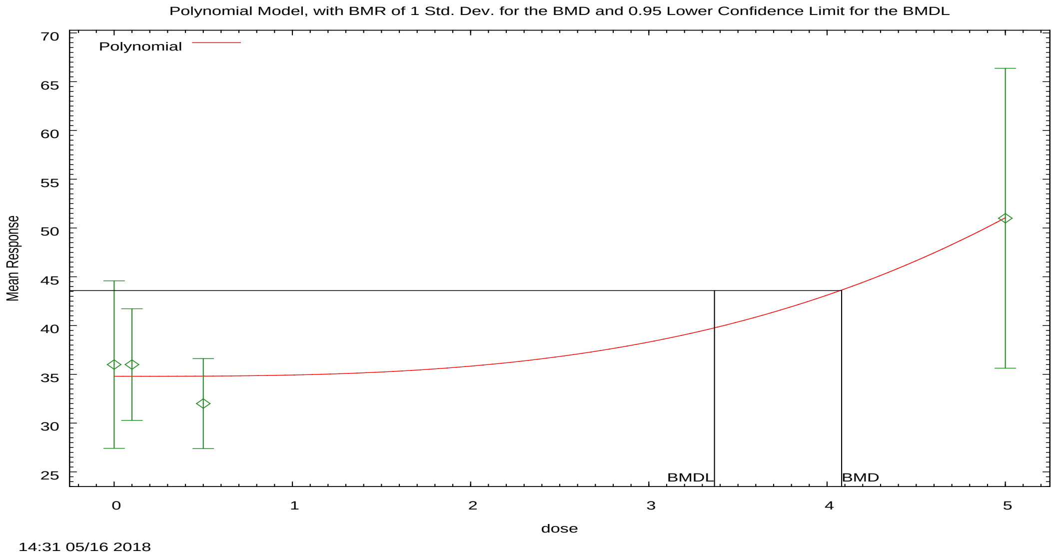


Figure 160. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.08145

BMDL at the 95% confidence level = 3.36805

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-9.69464	5.06036
rho	3.9597	0
beta_0	34.7561	36
beta_1	6.94793E-21	0

beta_2	8.42501E-21	0
beta_3	0.129837	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	36	34.8	12	8.83	0.446
0.1	10	36	34.8	8	8.83	0.446
0.5	9	32	34.8	6	8.84	-0.941
5	9	51	51	20	18.9	0.00227

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.033529	5	236.067058
A2	-105.617255	8	227.23451
A3	-106.208714	6	224.417429
fitted	-108.595863	4	225.191725
R	-118.827402	2	241.654805

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	26.4203	6	0.0001859
Test 2	14.8325	3	0.001965
Test 3	1.18292	2	0.5535
Test 4	4.7743	2	0.09189

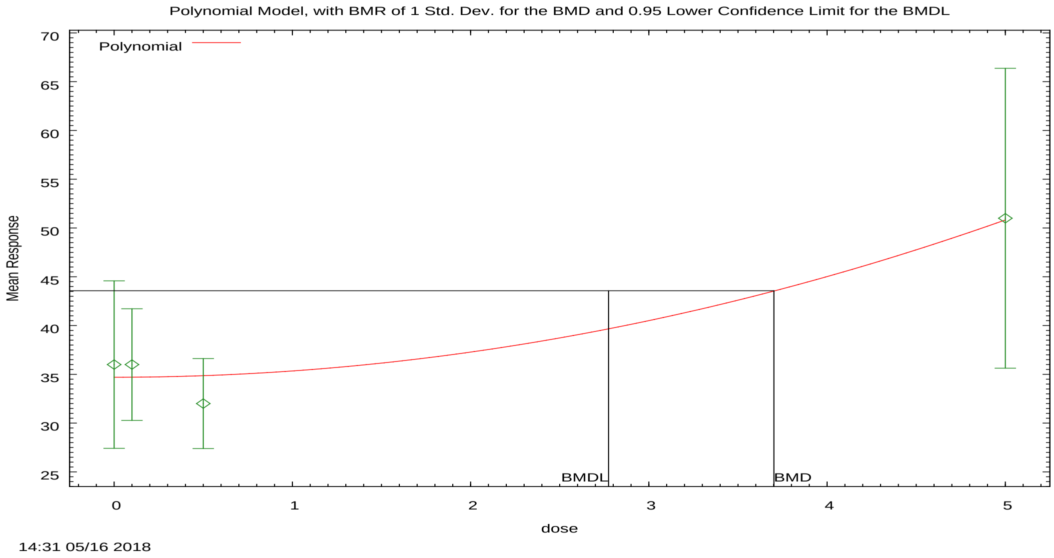


Figure 161. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.70148

BMDL at the 95% confidence level = 2.77406

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-9.68809	5.06036
rho	3.95919	0
beta_0	34.7327	36.4235
beta_1	1.03398E-26	0

beta_2	0.644978	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	36	34.7	12	8.84	0.454
0.1	10	36	34.7	8	8.84	0.451
0.5	9	32	34.9	6	8.92	-0.973
5	9	51	50.9	20	18.8	0.0228

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.033529	5	236.067058
A2	-105.617255	8	227.23451
A3	-106.208714	6	224.417429
fitted	-108.679471	4	225.358943
R	-118.827402	2	241.654805

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	26.4203	6	0.0001859
Test 2	14.8325	3	0.001965
Test 3	1.18292	2	0.5535
Test 4	4.94151	2	0.08452

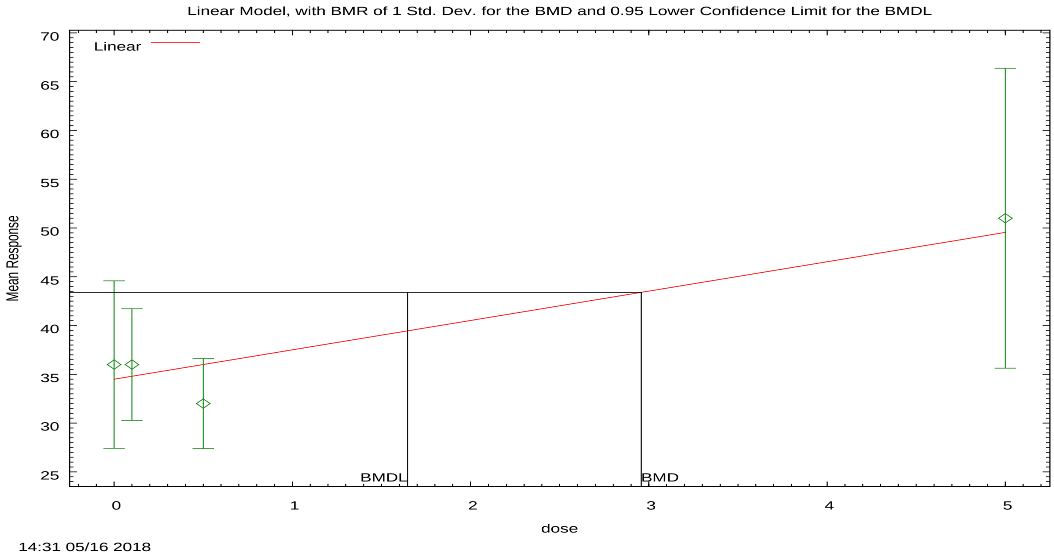


Figure 162. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alanine Aminotransferase in Females (90-day mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.95668

BMDL at the 95% confidence level = 1.64721

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-9.72219	5.06036
rho	3.98142	0
beta_0	34.4785	34.1208
beta_1	3.01207	3.30654

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	36	34.5	12	8.91	0.54
0.1	10	36	34.8	8	9.06	0.426
0.5	9	32	36	6	9.7	-1.23
5	9	51	49.5	20	18.3	0.239

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.033529	5	236.067058
A2	-105.617255	8	227.23451
A3	-106.208714	6	224.417429
fitted	-109.526767	4	227.053534
R	-118.827402	2	241.654805

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	26.4203	6	0.0001859
Test 2	14.8325	3	0.001965
Test 3	1.18292	2	0.5535
Test 4	6.63611	2	0.03622

BMDS WIZARD OUTPUT REPORT

Summary of H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats – Alanine Aminotransferase (U/L) at 12-month timepoint in Males

1.19. BMDS Summary of Alanine Aminotransferase (U/L) Males 12 months (2 Year Rats GenX)

Table 19. Summary of BMD Modeling Results for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.0403	269.38	8.75	6.57	1.33	No models met all model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). No BMDL was selected.
Exponential (M3)	0.0139	271.01	34.5	6.70	5.15	
Exponential (M4)	0.00847	271.89	4.99	3.18	1.57	
Exponential (M5)	N/A[b]	273.01	23.0	1.04	22.2	
Hill	N/A[b]	273.01	30.3	error[c]	error	
Power	0.0486	269.01	44.0	3.43	12.8	
Polynomial 3°	0.0486	269.01	23.1	3.43	6.74	
Polynomial 2°	0.0484	269.01	15.7	12.5	1.25	
Linear	0.0313	269.89	4.99	3.18	1.57	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001, BMDS Test 3 *p*-value = 0.213), no model was selected as a best-fitting model.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

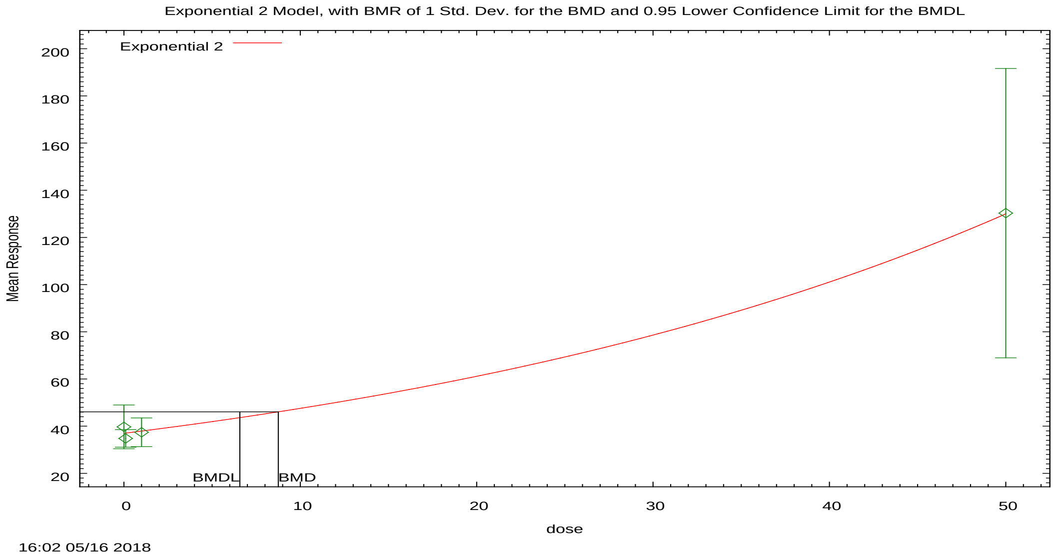


Figure 163. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 8.75352

BMDL at the 95% confidence level = 6.57192

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-8.1416	-9.5406
rho	3.47864	3.80156
a	36.975	36.9077
b	0.0251427	0.0252212
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	39.7	36.97	12.97	9.1	0.9467
0.1	10	34.8	37.07	5.2	9.14	-0.7845
1	10	37.4	37.92	8.51	9.51	-0.1717
50	10	130.3	130	85.73	81.06	0.01251

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.9305	5	347.861

A2	-125.9302	8	267.8604
A3	-127.4788	6	266.9576
R	-182.2661	2	368.5321
2	-130.6895	4	269.3789

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	112.7	6	<0.0001
Test 2	86	3	<0.0001
Test 3	3.097	2	0.2125
Test 4	6.421	2	0.04033

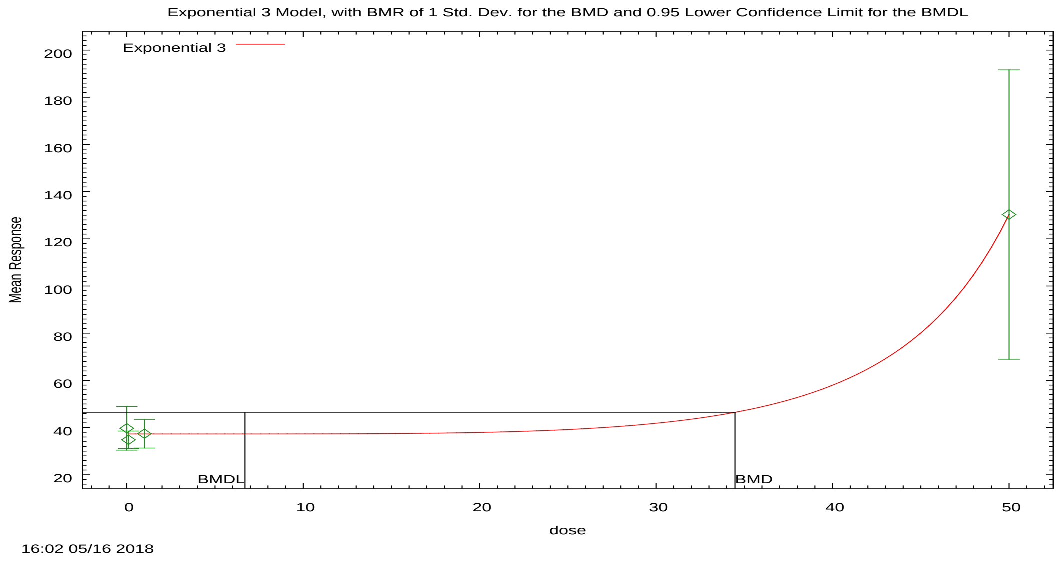


Figure 164. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 34.4731

BMDL at the 95% confidence level = 6.69773

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-8.18733	-9.5406
rho	3.48767	3.80156
a	37.3	36.9077
b	0.0209812	0.0252212
c	n/a	0
d	4.67298	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	39.7	37.3	12.97	9.18	0.8266
0.1	10	34.8	37.3	5.2	9.18	-0.861
1	10	37.4	37.3	8.51	9.18	0.03444
50	10	130.3	130.3	85.73	81.33	-0.0000002128

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.9305	5	347.861
A2	-125.9302	8	267.8604
A3	-127.4788	6	266.9576
R	-182.2661	2	368.5321
3	-130.5029	5	271.0058

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	112.7	6	<0.0001
Test 2	86	3	<0.0001
Test 3	3.097	2	0.2125
Test 5a	6.048	1	0.01392

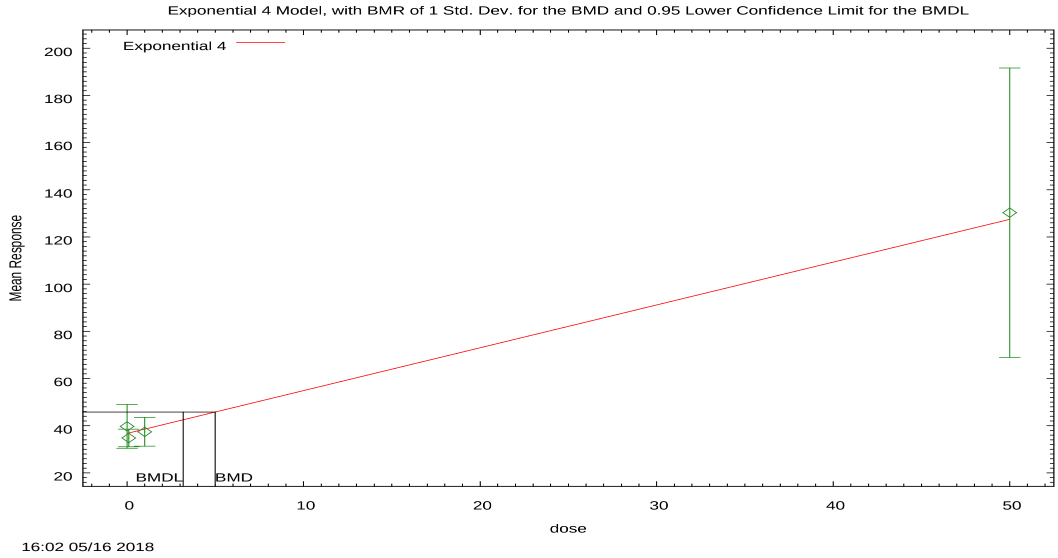


Figure 165. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.98667

BMDL at the 95% confidence level = 3.1776

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-8.26968	-9.5406
rho	3.5176	3.80156
a	36.7276	33.06
b	0.0000066833	0.0553539
c	7396.78	4.13838
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	39.7	36.73	12.97	9.05	1.038
0.1	10	34.8	36.91	5.2	9.13	-0.7304
1	10	37.4	38.54	8.51	9.85	-0.3668
50	10	130.3	127.5	85.73	80.78	0.1103

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.9305	5	347.861
A2	-125.9302	8	267.8604
A3	-127.4788	6	266.9576
R	-182.2661	2	368.5321
4	-130.9443	5	271.8885

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	112.7	6	<0.0001
Test 2	86	3	<0.0001
Test 3	3.097	2	0.2125
Test 6a	6.931	1	0.008472

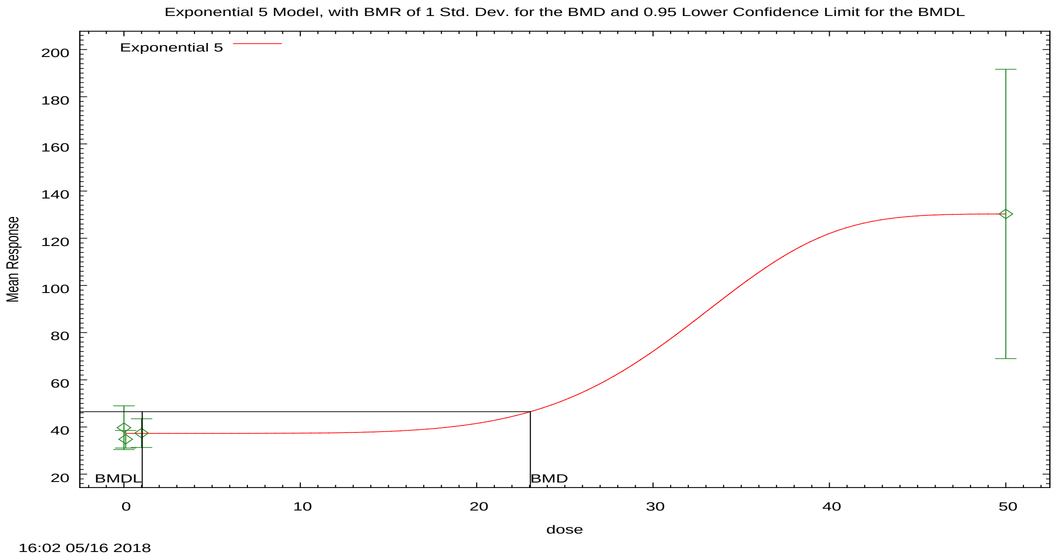


Figure 166. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 23.0428

BMDL at the 95% confidence level = 1.0372

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-8.18733	-9.5406
rho	3.48767	3.80156
a	37.3	33.06
b	0.0291834	0.0553539

c	3.49374	4.13838
d	5.70564	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	39.7	37.3	12.97	9.18	0.8266
0.1	10	34.8	37.3	5.2	9.18	-0.861
1	10	37.4	37.3	8.51	9.18	0.03444
50	10	130.3	130.3	85.73	81.33	-0.00000009512

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.9305	5	347.861
A2	-125.9302	8	267.8604
A3	-127.4788	6	266.9576
R	-182.2661	2	368.5321
5	-130.5029	6	273.0058

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	112.7	6	<0.0001
Test 2	86	3	<0.0001
Test 3	3.097	2	0.2125
Test 7a	6.048	0	N/A

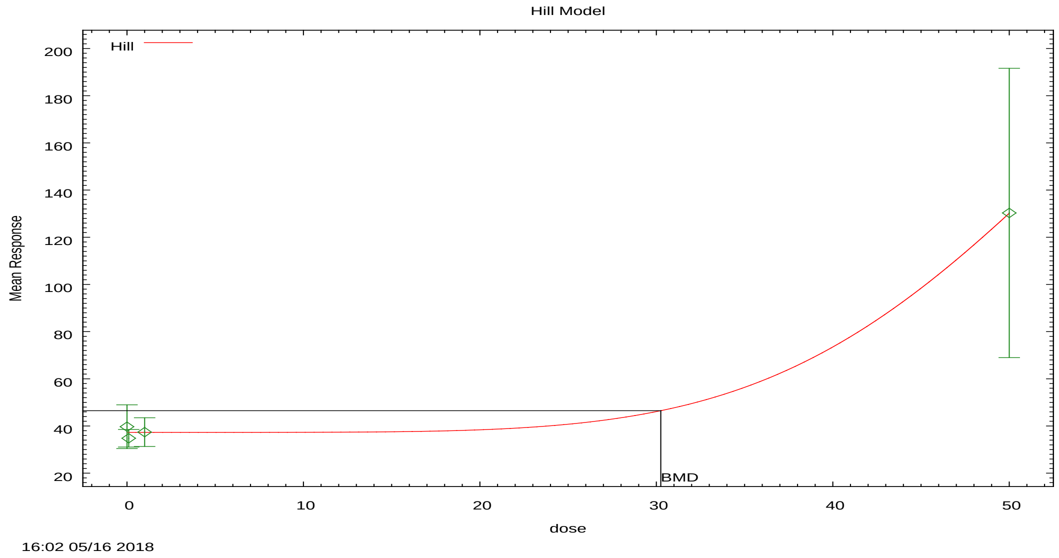


Figure 167. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 30.2517

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-8.18733	7.55188
rho	3.48767	0
intercept	37.3	39.7

v	316.418	90.6
n	5.24194	1
k	59.0994	73.8934

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	39.7	37.3	13	9.18	0.827
0.1	10	34.8	37.3	5.2	9.18	-0.861
1	10	37.4	37.3	8.51	9.18	0.0344
50	10	130	130	85.7	81.3	-0.000000189

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.930484	5	347.860968
A2	-125.930214	8	267.860427
A3	-127.47881	6	266.95762
fitted	-130.502905	6	273.00581
R	-182.266066	2	368.532131

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	112.672	6	<0.0001
Test 2	86.0005	3	<0.0001
Test 3	3.09719	2	0.2125
Test 4	6.04819	0	N/A

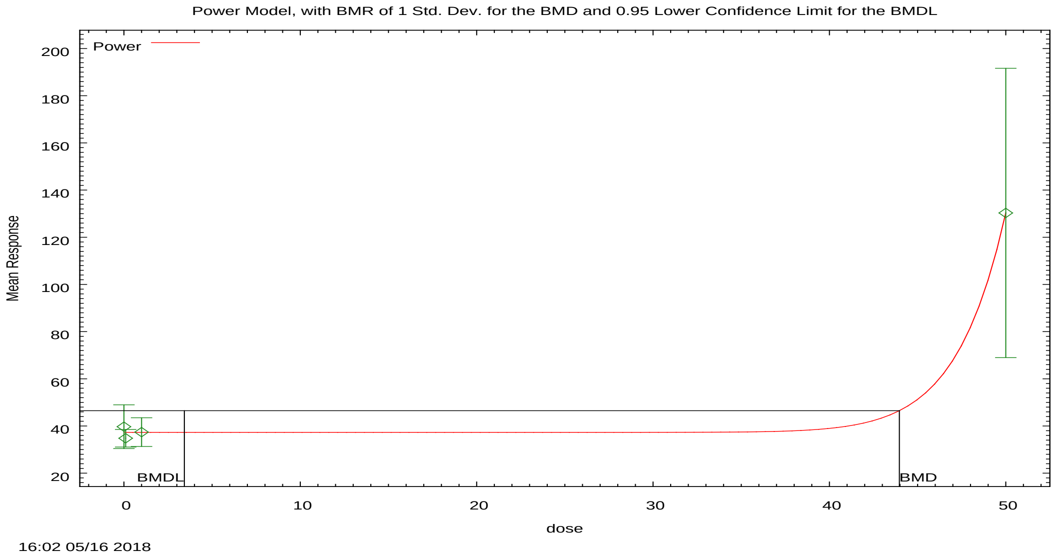


Figure 168. Plot of mean response by dose with fitted curve for Power model with modeled variance for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 43.965

BMDL at the 95% confidence level = 3.42661

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-8.18733	7.55188
rho	3.48767	0
control	37.3	34.8
slope	2.43794E-29	2.6

power	18	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	39.7	37.3	13	9.18	0.827
0.1	10	34.8	37.3	5.2	9.18	-0.861
1	10	37.4	37.3	8.51	9.18	0.0344
50	10	130	130	85.7	81.3	0.000000496

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.930484	5	347.860968
A2	-125.930214	8	267.860427
A3	-127.47881	6	266.95762
fitted	-130.502905	4	269.00581
R	-182.266066	2	368.532131

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	112.672	6	<0.0001
Test 2	86.0005	3	<0.0001
Test 3	3.09719	2	0.2125
Test 4	6.04819	2	0.0486

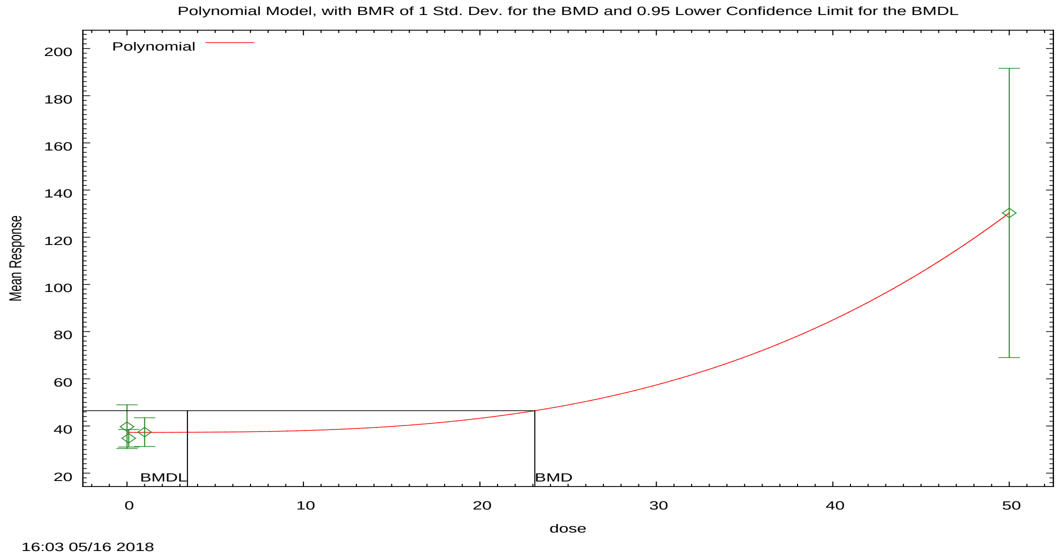


Figure 169. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 23.1094

BMDL at the 95% confidence level = 3.42656

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-8.18731	7.55188
rho	3.48766	0
beta_0	37.2998	39.7
beta_1	0	0

beta_2	1.25456E-22	0
beta_3	0.000744001	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	39.7	37.3	13	9.18	0.827
0.1	10	34.8	37.3	5.2	9.18	-0.861
1	10	37.4	37.3	8.51	9.18	0.0343
50	10	130	130	85.7	81.3	0.00000633

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.930484	5	347.860968
A2	-125.930214	8	267.860427
A3	-127.47881	6	266.95762
fitted	-130.502975	4	269.005951
R	-182.266066	2	368.532131

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	112.672	6	<0.0001
Test 2	86.0005	3	<0.0001
Test 3	3.09719	2	0.2125
Test 4	6.04833	2	0.0486

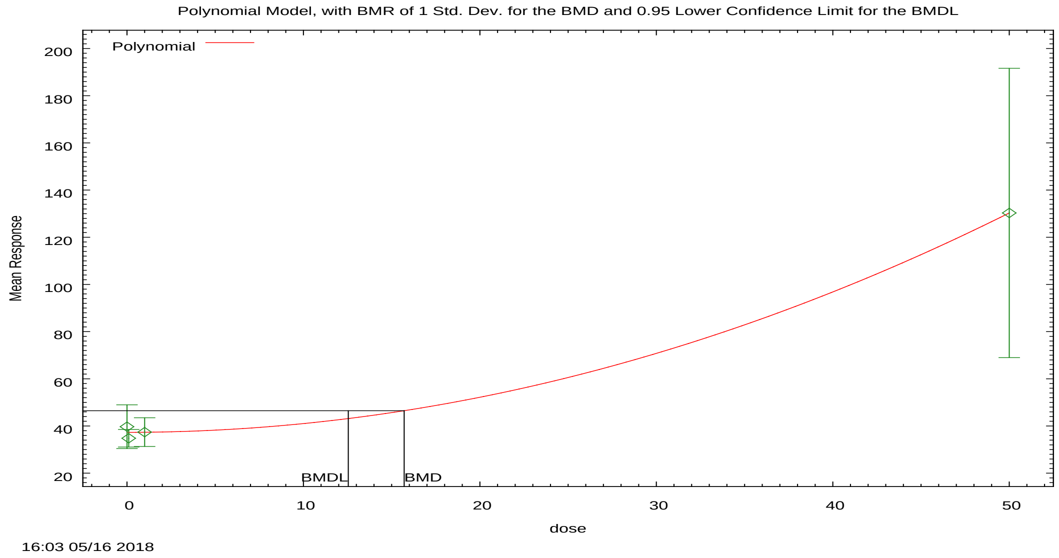


Figure 170. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 15.7074

BMDL at the 95% confidence level = 12.5405

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-8.18644	7.55188
rho	3.48751	0
beta_0	37.2876	37.3954
beta_1	6.93845E-23	0

beta_2	0.0372006	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	39.7	37.3	13	9.18	0.831
0.1	10	34.8	37.3	5.2	9.18	-0.857
1	10	37.4	37.3	8.51	9.19	0.0259
50	10	130	130	85.7	81.3	0.000424

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.930484	5	347.860968
A2	-125.930214	8	267.860427
A3	-127.47881	6	266.95762
fitted	-130.506701	4	269.013402
R	-182.266066	2	368.532131

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	112.672	6	<0.0001
Test 2	86.0005	3	<0.0001
Test 3	3.09719	2	0.2125
Test 4	6.05578	2	0.04842

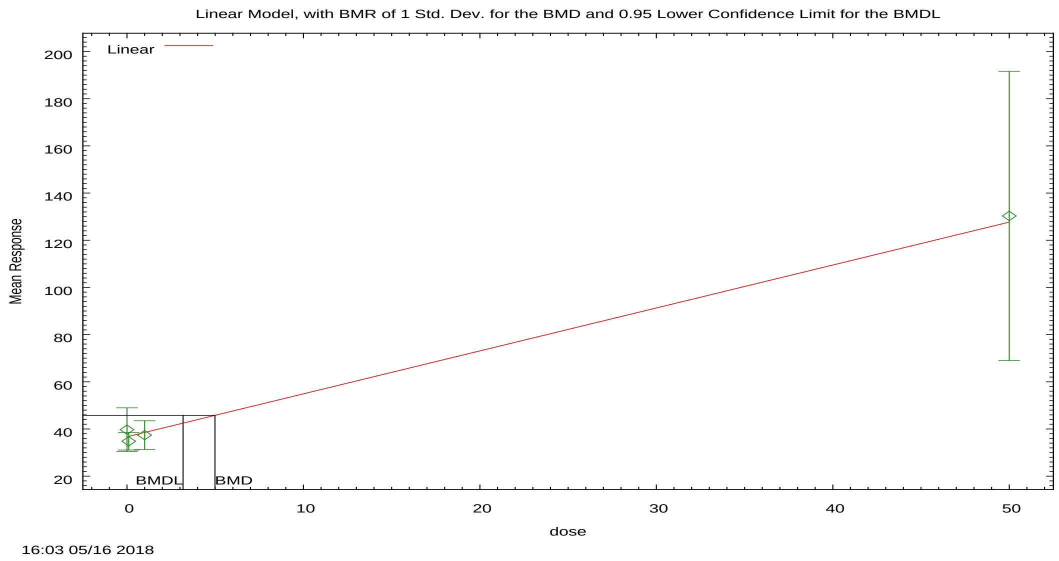


Figure 171. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Alanine Aminotransferase in males at 12 months (2-year rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.98735

BMDL at the 95% confidence level = 3.17816

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-8.26958	7.55188
rho	3.51757	0
beta_0	36.7276	36.6219
beta_1	1.8151	1.87304

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	39.7	36.7	13	9.05	1.04
0.1	10	34.8	36.9	5.2	9.13	-0.73
1	10	37.4	38.5	8.51	9.85	-0.367
50	10	130	127	85.7	80.8	0.11

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.930484	5	347.860968
A2	-125.930214	8	267.860427
A3	-127.47881	6	266.95762
fitted	-130.944168	4	269.888336
R	-182.266066	2	368.532131

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	112.672	6	<0.0001
Test 2	86.0005	3	<0.0001
Test 3	3.09719	2	0.2125
Test 4	6.93072	2	0.03126

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Aspartate Aminotransferase (U/L) in Males

1.20. BMDS Summary of Aspartate Aminotransferase (U/L) (28 Day Mice GenX)

Table 20. Summary of BMD Modeling Results for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.229	341.37	4.22	3.31	1.27	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. Selected BMDL is from model with lowest AIC and lowest BMDL.
Exponential (M4)	0.538	340.80	1.69	1.18	1.44	
Exponential (M5)	N/A[c]	342.60	2.01	1.02	1.97	
Hill	N/A[c]	342.53	2.76	error[d]	error	
Power	0.657	340.61	1.99	1.19	1.67	
Polynomial 3°[e] Polynomial 2°	0.638	340.64	1.93	1.19	1.62	
Linear	**0.827**	**338.80**	**1.69**	**1.18**	**1.44**	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were 0.43, 0.24, -1.08, 0.56, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] No available degrees of freedom to calculate a goodness of fit value.

[d] BMD or BMDL computation failed for this model.

[e] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model.

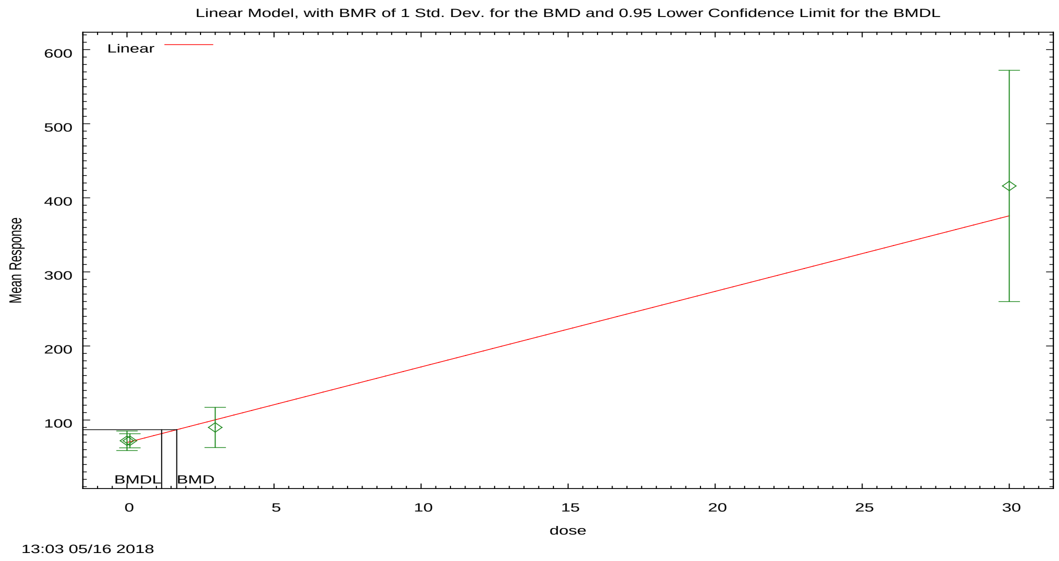


Figure 172. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.69171

BMDL at the 95% confidence level = 1.17843

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.18857	9.42582
rho	3.03741	0
beta_0	69.653	66.364
beta_1	10.223	11.6176

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	69.7	18.5	17.3	0.429
0.1	10	72	70.7	13.3	17.7	0.237
3	10	90	100	38	30.1	-1.08
30	10	416	376	218	224	0.559

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.409094	5	422.818187
A2	-163.182702	8	342.365403

A3	-165.208319	6	342.416637
fitted	-165.397938	4	338.795876
R	-227.865145	2	459.73029

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.365	6	<0.0001
Test 2	86.4528	3	<0.0001
Test 3	4.05123	2	0.1319
Test 4	0.379239	2	0.8273

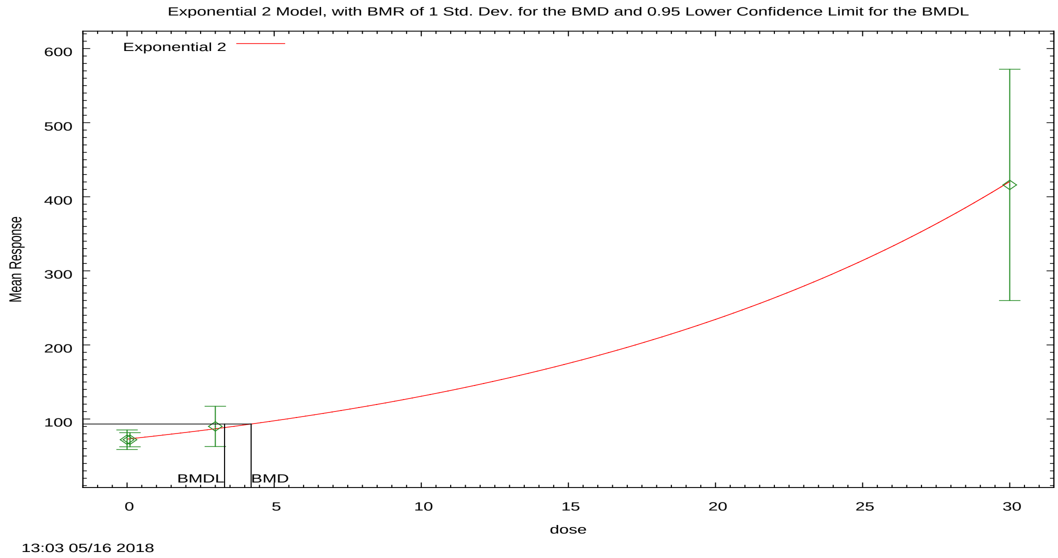


Figure 173. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.21632

BMDL at the 95% confidence level = 3.31493

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.56675	-6.39771
rho	2.70341	2.86362
a	72.8571	72.9518
b	0.0584388	0.058146
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	72.86	18.5	20.36	-0.1331
0.1	10	72	73.28	13.3	20.52	-0.1979
3	10	90	86.82	38	25.8	0.39
30	10	416	420.6	218.3	217.7	-0.06671

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.4091	5	422.8182
A2	-163.1827	8	342.3654
A3	-165.2083	6	342.4166
R	-227.8651	2	459.7303
2	-166.683	4	341.366

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.4	6	<0.0001
Test 2	86.45	3	<0.0001

Test 3	4.051	2	0.1319
Test 4	2.949	2	0.2289

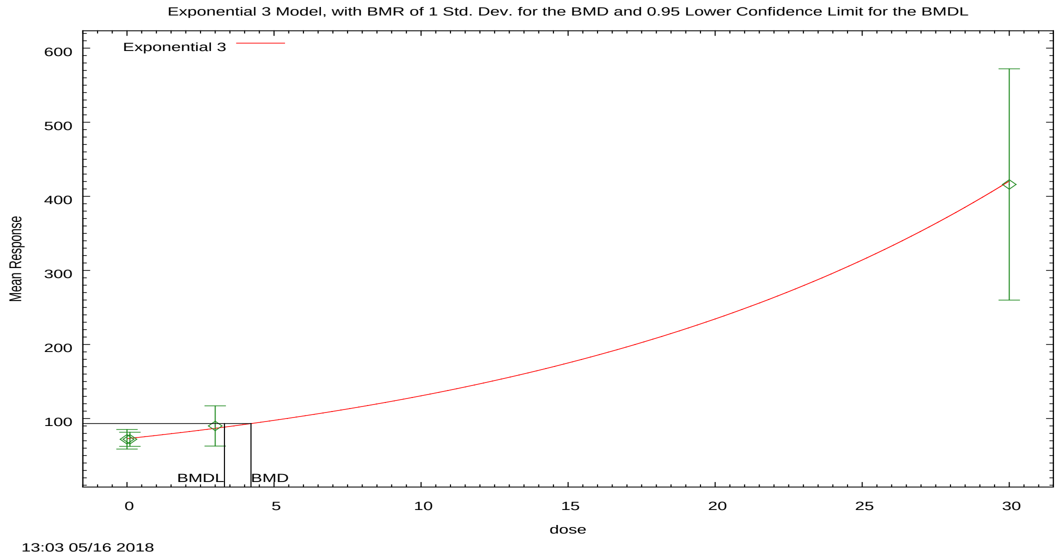


Figure 174. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.21632

BMDL at the 95% confidence level = 3.31493

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.56675	-6.39771

rho	2.70341	2.86362
a	72.8571	72.9518
b	0.0584388	0.058146
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	72.86	18.5	20.36	-0.1331
0.1	10	72	73.28	13.3	20.52	-0.1979
3	10	90	86.82	38	25.8	0.39
30	10	416	420.6	218.3	217.7	-0.06671

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.4091	5	422.8182
A2	-163.1827	8	342.3654
A3	-165.2083	6	342.4166
R	-227.8651	2	459.7303
3	-166.683	4	341.366

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.4	6	<0.0001
Test 2	86.45	3	<0.0001
Test 3	4.051	2	0.1319
Test 5a	2.949	2	0.2289

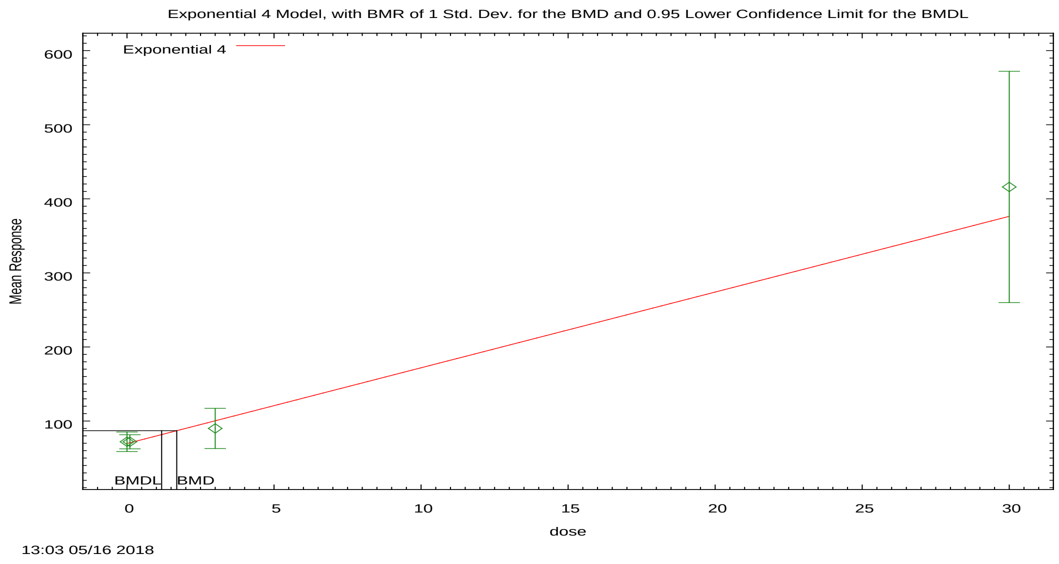


Figure 175. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.6917

BMDL at the 95% confidence level = 1.17843

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-7.18858	-6.39771
rho	3.03741	2.86362
a	69.653	68.4
b	0.000000376747	0.0000277649

c	389577	6081.87
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	69.65	18.5	17.29	0.4291
0.1	10	72	70.68	13.3	17.68	0.2369
3	10	90	100.3	38	30.1	-1.084
30	10	416	376.3	218.3	224.2	0.5594

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.4091	5	422.8182
A2	-163.1827	8	342.3654
A3	-165.2083	6	342.4166
R	-227.8651	2	459.7303
4	-165.3979	5	340.7959

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.4	6	<0.0001
Test 2	86.45	3	<0.0001
Test 3	4.051	2	0.1319
Test 6a	0.3792	1	0.538

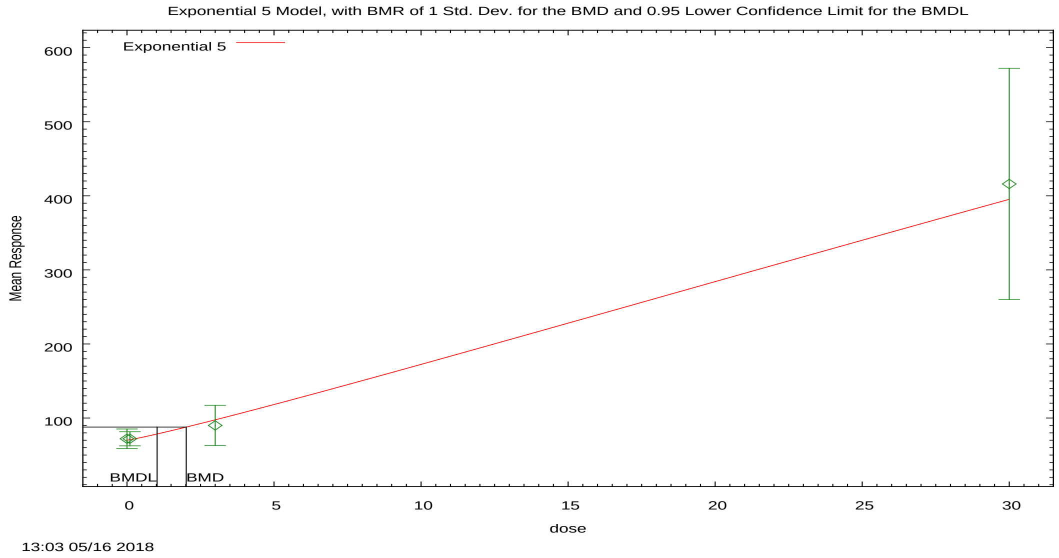


Figure 176. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.01432

BMDL at the 95% confidence level = 1.02455

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-6.63959	-6.39771
rho	2.91695	2.86362
a	70.0359	68.4
b	0.00683709	0.0000277649

c	30.1922	6081.87
d	1.10645	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	70.04	18.5	17.77	0.3496
0.1	10	72	70.68	13.3	18	0.232
3	10	90	97.57	38	28.82	-0.8313
30	10	416	395.3	218.3	221.7	0.295

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.4091	5	422.8182
A2	-163.1827	8	342.3654
A3	-165.2083	6	342.4166
R	-227.8651	2	459.7303
5	-165.3024	6	342.6049

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.4	6	<0.0001
Test 2	86.45	3	<0.0001
Test 3	4.051	2	0.1319
Test 7a	0.1882	0	N/A

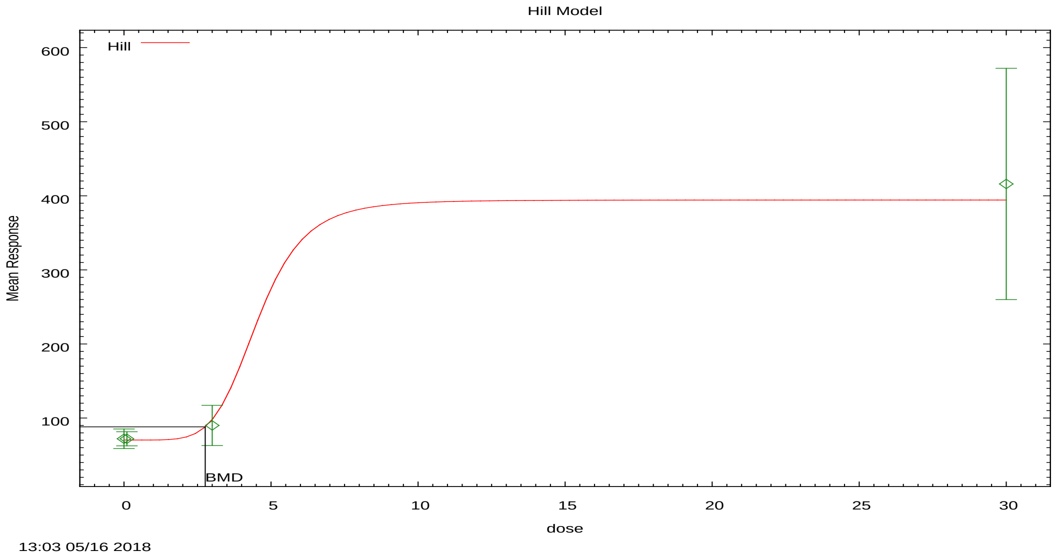


Figure 177. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.76269

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-6.70047	9.42582
rho	2.92962	0
intercept	70.319	72
v	323.505	344

n	5.69046	18
k	4.55306	44.2454

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	70.3	18.5	17.8	0.298
0.1	10	72	70.3	13.3	17.8	0.298
3	10	90	97.9	38	28.9	-0.861
30	10	416	394	218	222	0.316

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.409094	5	422.818187
A2	-163.182702	8	342.365403
A3	-165.208319	6	342.416637
fitted	-165.26618	6	342.532359
R	-227.865145	2	459.73029

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.365	6	<0.0001
Test 2	86.4528	3	<0.0001
Test 3	4.05123	2	0.1319
Test 4	0.115722	0	N/A

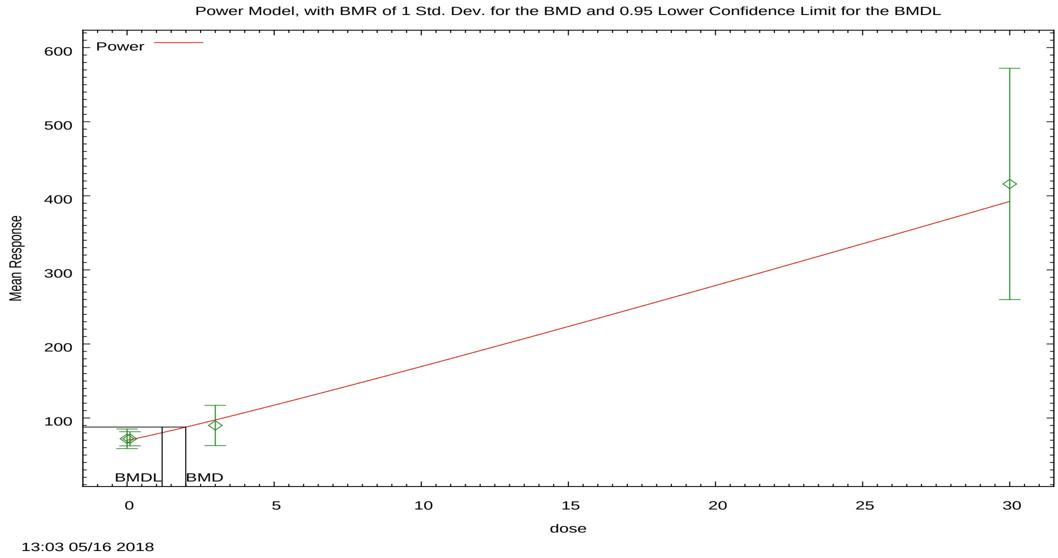


Figure 178. Plot of mean response by dose with fitted curve for Power model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.99497

BMDL at the 95% confidence level = 1.19209

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-6.63048	9.42582
rho	2.91504	0
control	70.0063	72
slope	8.46672	4.40498
power	1.07297	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	70	18.5	17.8	0.355
0.1	10	72	70.7	13.3	18	0.224
3	10	90	97.5	38	28.8	-0.826
30	10	416	396	218	222	0.292

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.409094	5	422.818187
A2	-163.182702	8	342.365403
A3	-165.208319	6	342.416637
fitted	-165.307186	5	340.614372
R	-227.865145	2	459.73029

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.365	6	<0.0001
Test 2	86.4528	3	<0.0001
Test 3	4.05123	2	0.1319
Test 4	0.197735	1	0.6566

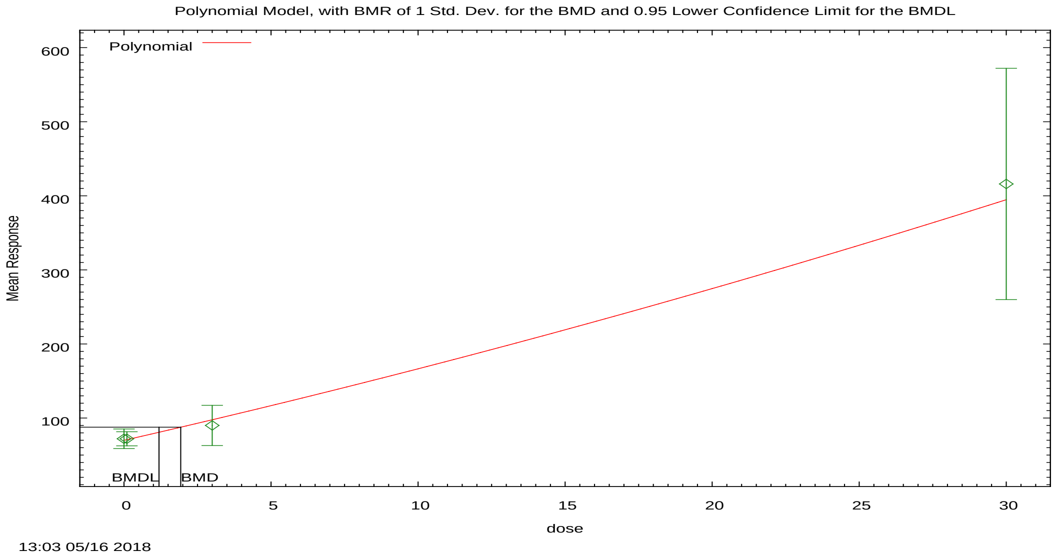


Figure 179. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.92984

BMDL at the 95% confidence level = 1.19025

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-6.64847	9.42582
rho	2.91913	0
beta_0	69.9046	72
beta_1	9.06936	0

beta_2	0.0585628	2.26248
beta_3	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	69.9	18.5	17.7	0.374
0.1	10	72	70.8	13.3	18.1	0.208
3	10	90	97.6	38	28.9	-0.837
30	10	416	395	218	222	0.304

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.409094	5	422.818187
A2	-163.182702	8	342.365403
A3	-165.208319	6	342.416637
fitted	-165.319127	5	340.638255
R	-227.865145	2	459.73029

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.365	6	<0.0001
Test 2	86.4528	3	<0.0001
Test 3	4.05123	2	0.1319
Test 4	0.221618	1	0.6378

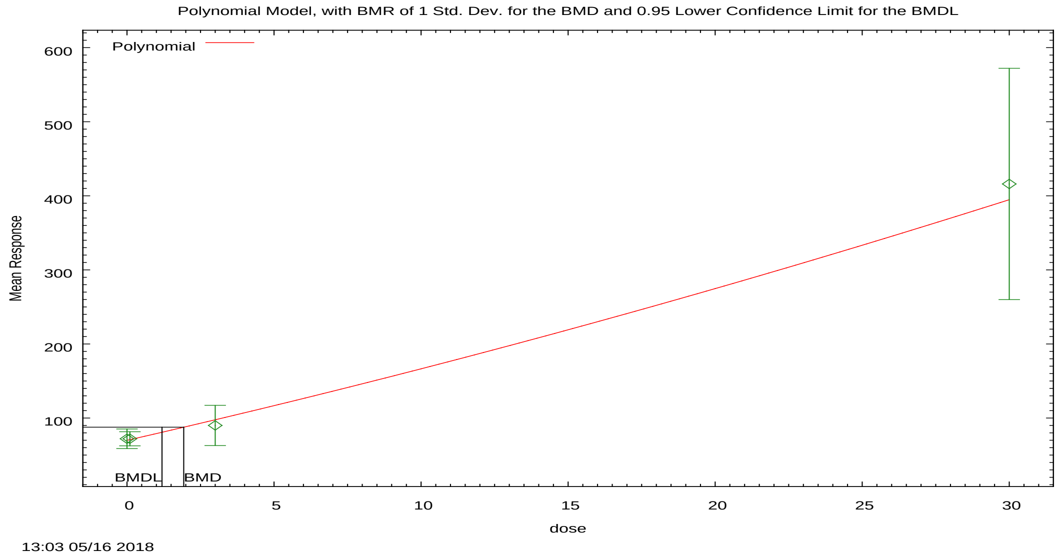


Figure 180. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Aspartate Aminotransferase in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.92984

BMDL at the 95% confidence level = 1.19025

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-6.64847	9.42582
rho	2.91913	0
beta_0	69.9045	71.7297
beta_1	9.06937	5.48785

beta_2	0.0585626	0.199594

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	72	69.9	18.5	17.7	0.374
0.1	10	72	70.8	13.3	18.1	0.208
3	10	90	97.6	38	28.9	-0.837
30	10	416	395	218	222	0.304

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-206.409094	5	422.818187
A2	-163.182702	8	342.365403
A3	-165.208319	6	342.416637
fitted	-165.319127	5	340.638255
R	-227.865145	2	459.73029

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	129.365	6	<0.0001
Test 2	86.4528	3	<0.0001
Test 3	4.05123	2	0.1319
Test 4	0.221618	1	0.6378

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Aspartate Aminotransferase (U/L) in Males

1.21. BMDS Summary of Aspartate Aminotransferase (U/L) Males (90 Day Mice GenX)

Table 21. Summary of BMD Modeling Results for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)[b]	0.0397	309.68	1.63	1.07	1.52	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)[c]	0.0397	309.68	1.63	1.07	1.52	
Exponential (M4) Exponential (M5)[d]	0.244	306.59	0.325	0.141	2.31	
Hill	**0.264**	**306.48**	**0.303**	**0.169**	**1.80**	
Power[e] Polynomial 3°[f] Polynomial 2°[g] Linear	0.0816	308.24	1.06	0.579	1.83	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.08, -0.02, 0.23, -0.16, respectively.

[b] The Exponential (M2) model may appear equivalent to the Exponential (M3) model, however differences exist in digits not displayed in the table.

[c] The Exponential (M3) model may appear equivalent to the Exponential (M2) model, however differences exist in digits not displayed in the table.

[d] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[e] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[g] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

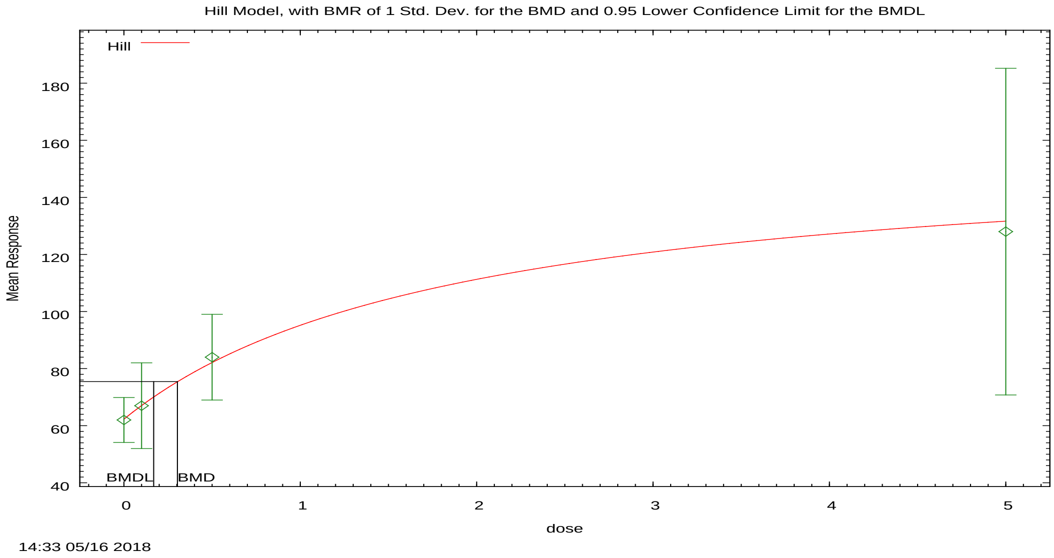


Figure 181. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.303154

BMDL at the 95% confidence level = 0.168638

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-13.9353	7.52335
rho	4.61691	0
intercept	62.3436	62
v	95.9827	66

n	1	0.405435
k	1.9185	8.375

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	62.3	11	13.1	-0.083
0.1	10	67	67.1	21	15.5	-0.0201
0.5	10	84	82.2	21	24.8	0.231
5	10	128	132	80	73.6	-0.159

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.359715	5	346.719429
A2	-146.582458	8	309.164915
A3	-147.613821	6	307.227642
fitted	-148.237838	5	306.475676
R	-175.169766	2	354.339532

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.1746	6	<0.0001
Test 2	43.5545	3	<0.0001
Test 3	2.06273	2	0.3565
Test 4	1.24803	1	0.2639

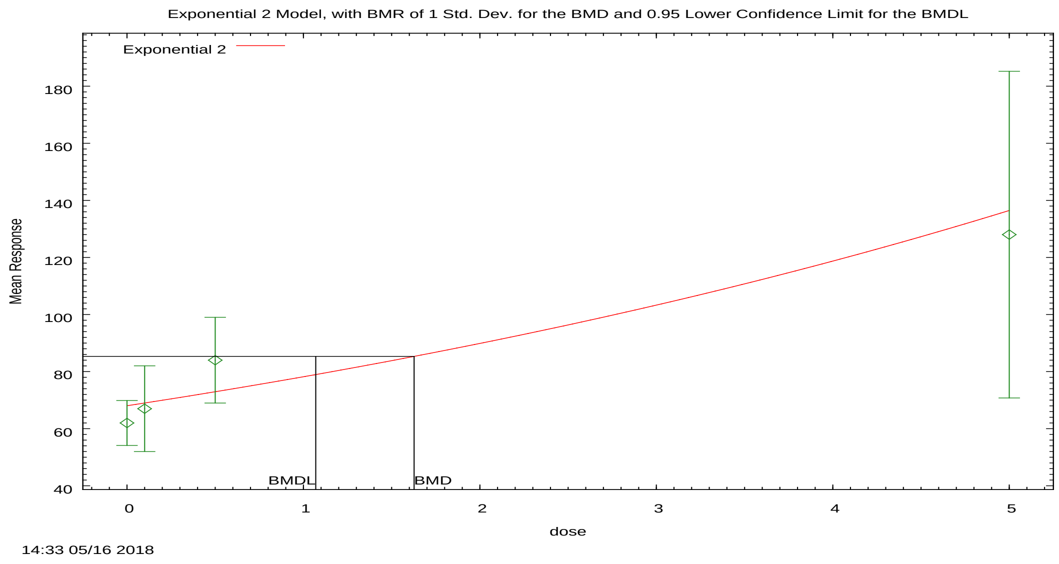


Figure 182. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.6272

BMDL at the 95% confidence level = 1.06964

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-12.5205	-15.1386
rho	4.31775	4.89888
a	68.0377	68.3067
b	0.139181	0.128329

c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	68.04	11	17.29	-1.104
0.1	10	67	68.99	21	17.82	-0.3533
0.5	10	84	72.94	21	20.1	1.74
5	10	128	136.5	80	77.69	-0.344

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.3597	5	346.7194
A2	-146.5825	8	309.1649
A3	-147.6138	6	307.2276
R	-175.1698	2	354.3395
2	-150.8395	4	309.679

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.17	6	<0.0001
Test 2	43.55	3	<0.0001
Test 3	2.063	2	0.3565
Test 4	6.451	2	0.03973

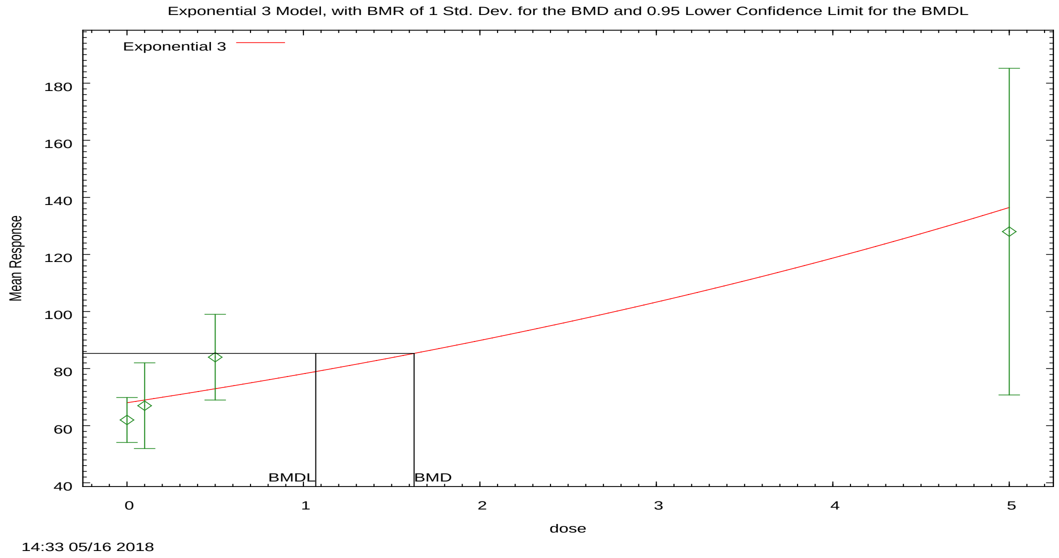


Figure 183. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.62721

BMDL at the 95% confidence level = 1.06964

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-12.5206	-15.1386
rho	4.31776	4.89888
a	68.0377	68.3067
b	0.139181	0.128329

c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	68.04	11	17.29	-1.104
0.1	10	67	68.99	21	17.82	-0.3533
0.5	10	84	72.94	21	20.1	1.74
5	10	128	136.5	80	77.69	-0.344

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.3597	5	346.7194
A2	-146.5825	8	309.1649
A3	-147.6138	6	307.2276
R	-175.1698	2	354.3395
3	-150.8395	4	309.679

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.17	6	<0.0001
Test 2	43.55	3	<0.0001
Test 3	2.063	2	0.3565
Test 5a	6.451	2	0.03973

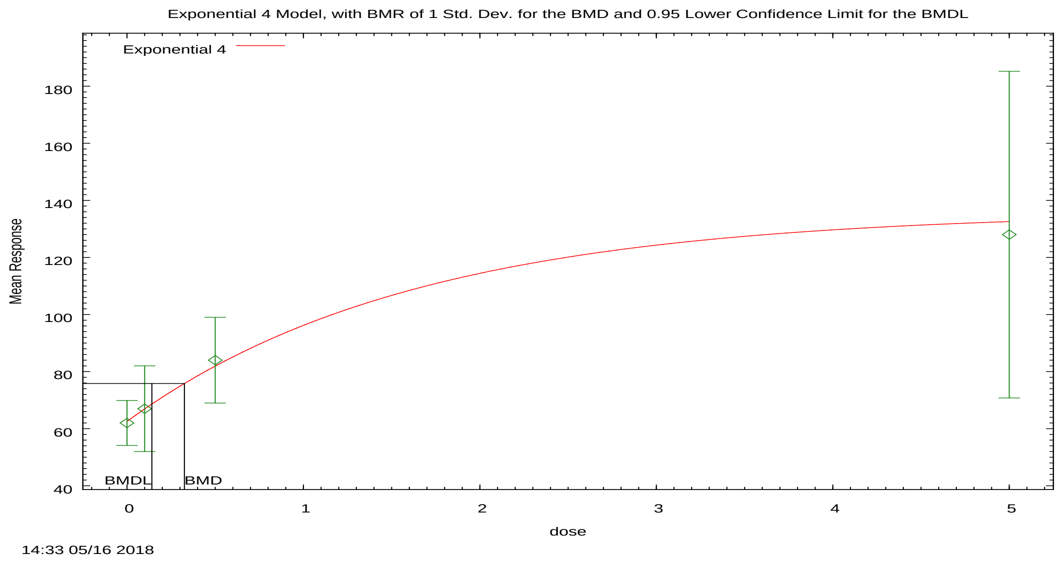


Figure 184. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.325386

BMDL at the 95% confidence level = 0.141103

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-13.715	-15.1386
rho	4.56656	4.89888
a	62.5469	58.9
b	0.61274	0.496936

c	2.17427	2.28183
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	62.55	11	13.28	-0.1303
0.1	10	67	66.91	21	15.49	0.01793
0.5	10	84	81.93	21	24.59	0.2664
5	10	128	132.6	80	73.78	-0.1956

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.3597	5	346.7194
A2	-146.5825	8	309.1649
A3	-147.6138	6	307.2276
R	-175.1698	2	354.3395
4	-148.293	5	306.586

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.17	6	<0.0001
Test 2	43.55	3	<0.0001
Test 3	2.063	2	0.3565
Test 6a	1.358	1	0.2438

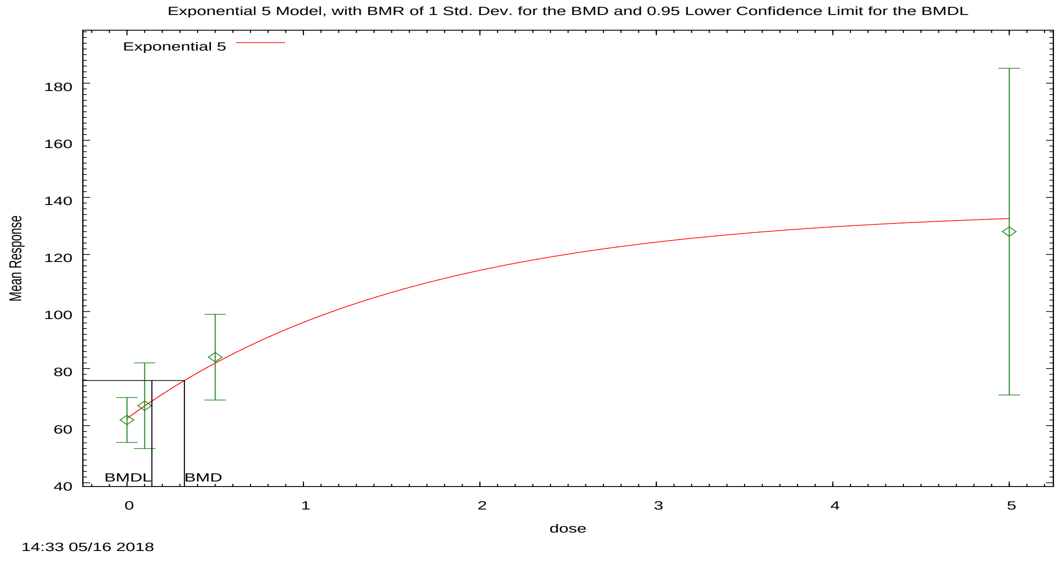


Figure 185. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.325386

BMDL at the 95% confidence level = 0.141103

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-13.7149	-15.1386
rho	4.56655	4.89888
a	62.5469	58.9
b	0.612739	0.496936

c	2.17427	2.28183
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	62.55	11	13.28	-0.1303
0.1	10	67	66.91	21	15.49	0.01793
0.5	10	84	81.93	21	24.59	0.2664
5	10	128	132.6	80	73.78	-0.1956

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.3597	5	346.7194
A2	-146.5825	8	309.1649
A3	-147.6138	6	307.2276
R	-175.1698	2	354.3395
5	-148.293	5	306.586

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.17	6	<0.0001
Test 2	43.55	3	<0.0001
Test 3	2.063	2	0.3565
Test 7a	1.358	1	0.2438

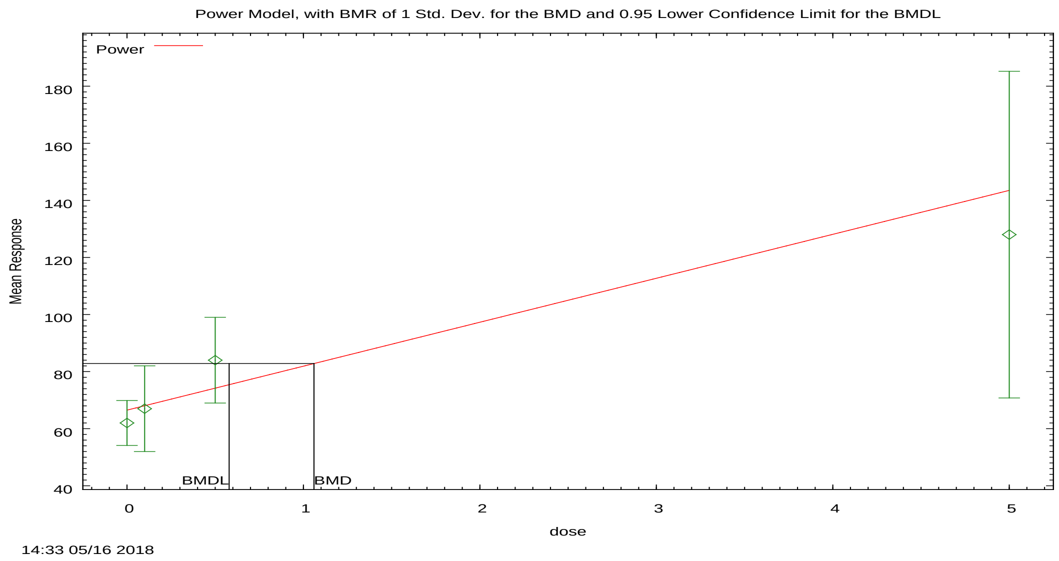


Figure 186. Plot of mean response by dose with fitted curve for Power model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.05967

BMDL at the 95% confidence level = 0.579048

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-11.6677	7.52335
rho	4.10907	0
control	66.539	62
slope	15.3746	23.2973
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	66.5	11	16.3	-0.881
0.1	10	67	68.1	21	17.1	-0.199
0.5	10	84	74.2	21	20.4	1.52
5	10	128	143	80	78.9	-0.618

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.359715	5	346.719429
A2	-146.582458	8	309.164915
A3	-147.613821	6	307.227642
fitted	-150.119997	4	308.239995
R	-175.169766	2	354.339532

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.1746	6	<0.0001
Test 2	43.5545	3	<0.0001
Test 3	2.06273	2	0.3565
Test 4	5.01235	2	0.08158

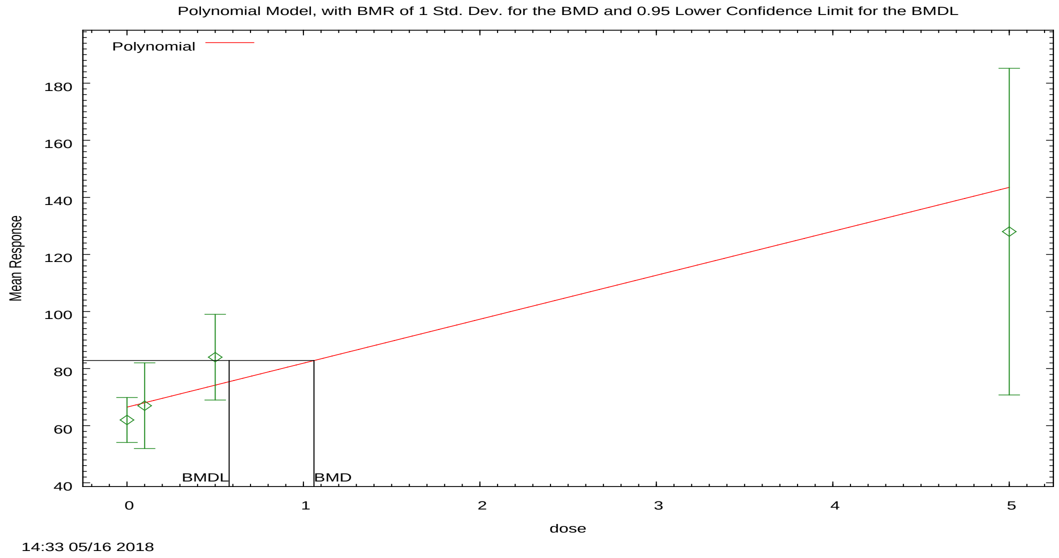


Figure 187. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.05967

BMDL at the 95% confidence level = 0.579048

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-11.6677	7.52335
rho	4.10908	0
beta_0	66.539	62
beta_1	15.3746	51.5832

beta_2	0	0
beta_3	0	1.6644

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	66.5	11	16.3	-0.881
0.1	10	67	68.1	21	17.1	-0.199
0.5	10	84	74.2	21	20.4	1.52
5	10	128	143	80	78.9	-0.618

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.359715	5	346.719429
A2	-146.582458	8	309.164915
A3	-147.613821	6	307.227642
fitted	-150.119997	4	308.239995
R	-175.169766	2	354.339532

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.1746	6	<0.0001
Test 2	43.5545	3	<0.0001
Test 3	2.06273	2	0.3565
Test 4	5.01235	2	0.08158

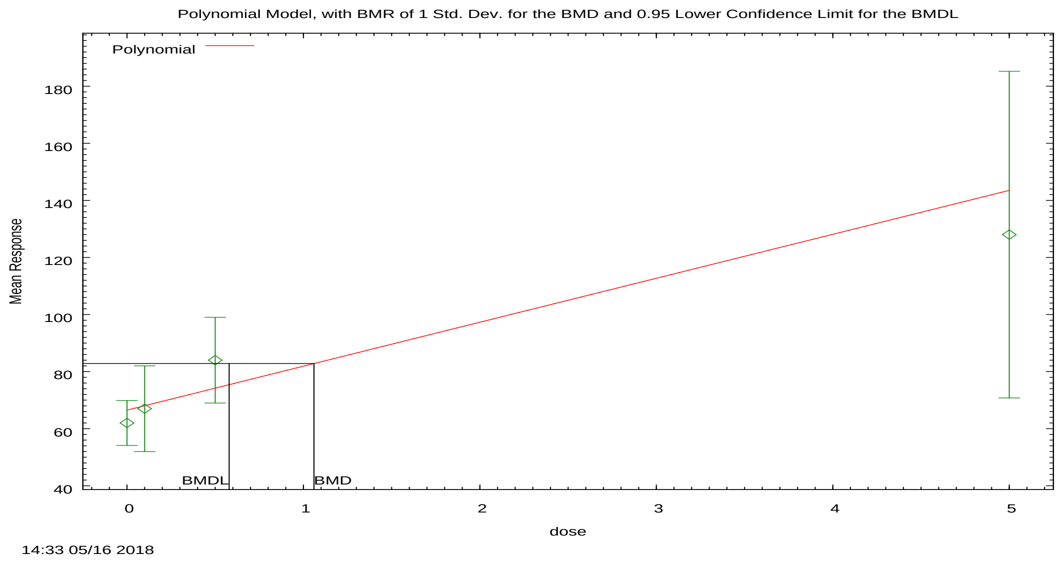


Figure 188. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.05967

BMDL at the 95% confidence level = 0.579048

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-11.6676	7.52335
rho	4.10907	0
beta_0	66.539	62.1539
beta_1	15.3746	47.1787

beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	66.5	11	16.3	-0.881
0.1	10	67	68.1	21	17.1	-0.199
0.5	10	84	74.2	21	20.4	1.52
5	10	128	143	80	78.9	-0.618

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.359715	5	346.719429
A2	-146.582458	8	309.164915
A3	-147.613821	6	307.227642
fitted	-150.119997	4	308.239995
R	-175.169766	2	354.339532

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.1746	6	<0.0001
Test 2	43.5545	3	<0.0001
Test 3	2.06273	2	0.3565
Test 4	5.01235	2	0.08158

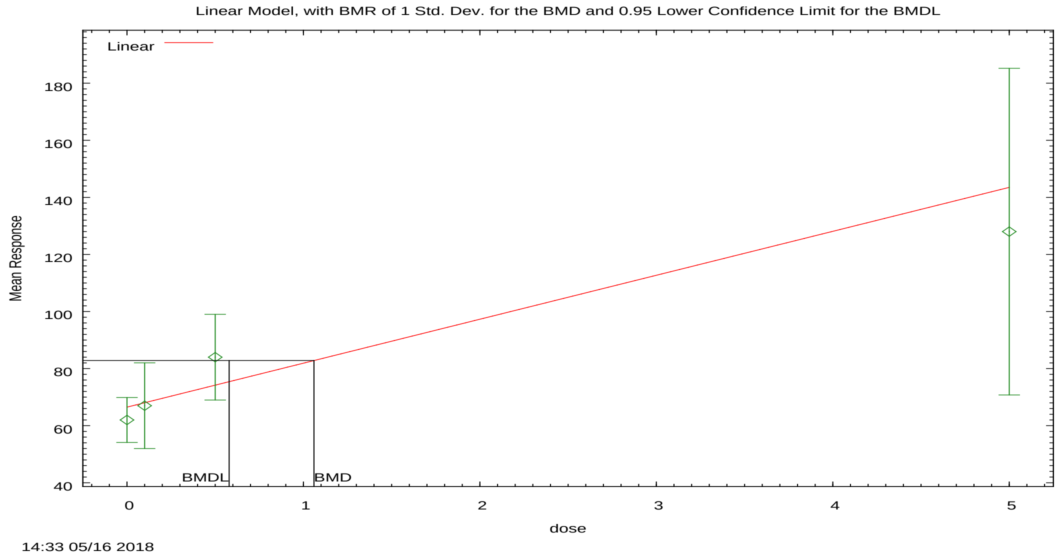


Figure 189. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Aspartate Aminotransferase in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.05967

BMDL at the 95% confidence level = 0.579048

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-11.6677	7.52335
rho	4.10907	0
beta_0	66.539	68.2684
beta_1	15.3746	12.1297

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	62	66.5	11	16.3	-0.881
0.1	10	67	68.1	21	17.1	-0.199
0.5	10	84	74.2	21	20.4	1.52
5	10	128	143	80	78.9	-0.618

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-168.359715	5	346.719429
A2	-146.582458	8	309.164915
A3	-147.613821	6	307.227642
fitted	-150.119997	4	308.239995
R	-175.169766	2	354.339532

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.1746	6	<0.0001
Test 2	43.5545	3	<0.0001
Test 3	2.06273	2	0.3565
Test 4	5.01235	2	0.08158

BMDS WIZARD OUTPUT REPORT

Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Sorbitol Dehydrogenase (U/L) in Females

1.22. BMDS Summary of Sorbitol Dehydrogenase (U/L) Females (28 Day Mice GenX)

Table 22. Summary of BMD Modeling Results for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	**0.760**	**202.94**	**8.38**	**6.29**	1.33	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.493	204.86	10.2	6.32	1.61	
Exponential (M4)	0.290	205.51	5.77	3.81	1.51	
Exponential (M5)	N/A[b]	206.87	9.20	3.18	2.89	
Hill	N/A[b]	206.87	9.18	error[c]	error	
Power	0.490	204.87	9.20	4.00	2.30	
Polynomial 3°	0.499	204.85	11.6	4.01	2.89	
Polynomial 2°	0.497	204.85	10.1	4.01	2.53	
Linear	0.571	203.51	5.77	3.81	1.51	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were -0.56, 0.75, -0.22, 0.03, respectively.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

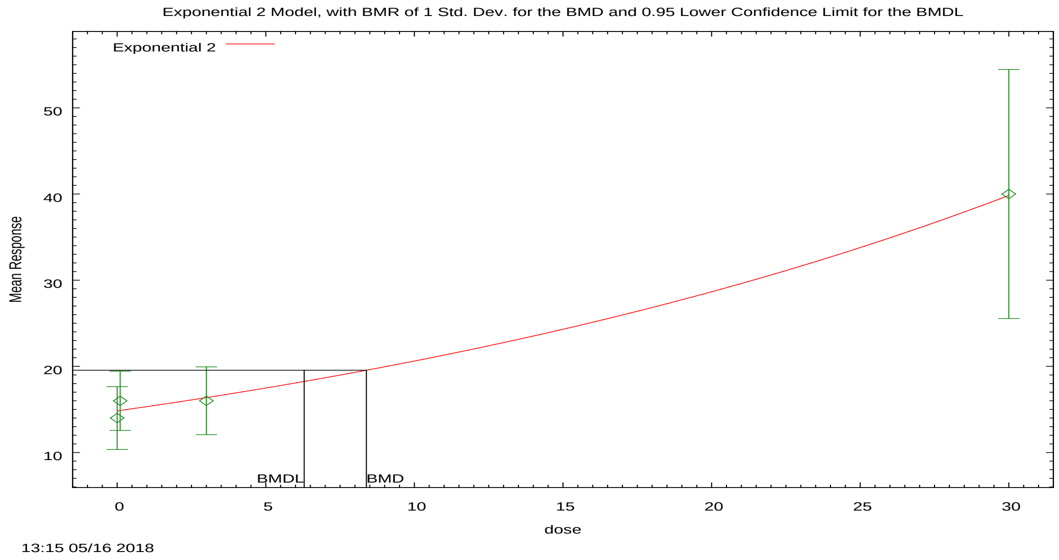


Figure 190. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Sorbitol Dehydrogenase in Females

(28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 8.38417

BMDL at the 95% confidence level = 6.29287

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.53233	-4.38245
rho	2.83099	2.80856
a	14.831	14.7983
b	0.0329331	0.0330832
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	14.83	5.1	4.72	-0.5572
0.1	10	16	14.88	4.8	4.74	0.7475
3	10	16	16.37	5.5	5.42	-0.2163
30	10	40	39.83	20.2	19.1	0.02755

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.9461	5	237.8923

A2	-96.97566	8	209.9513
A3	-97.19629	6	206.3926
R	-128.2687	2	260.5375
2	-97.47089	4	202.9418

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.59	6	<0.0001
Test 2	33.94	3	<0.0001
Test 3	0.4413	2	0.802
Test 4	0.5492	2	0.7599

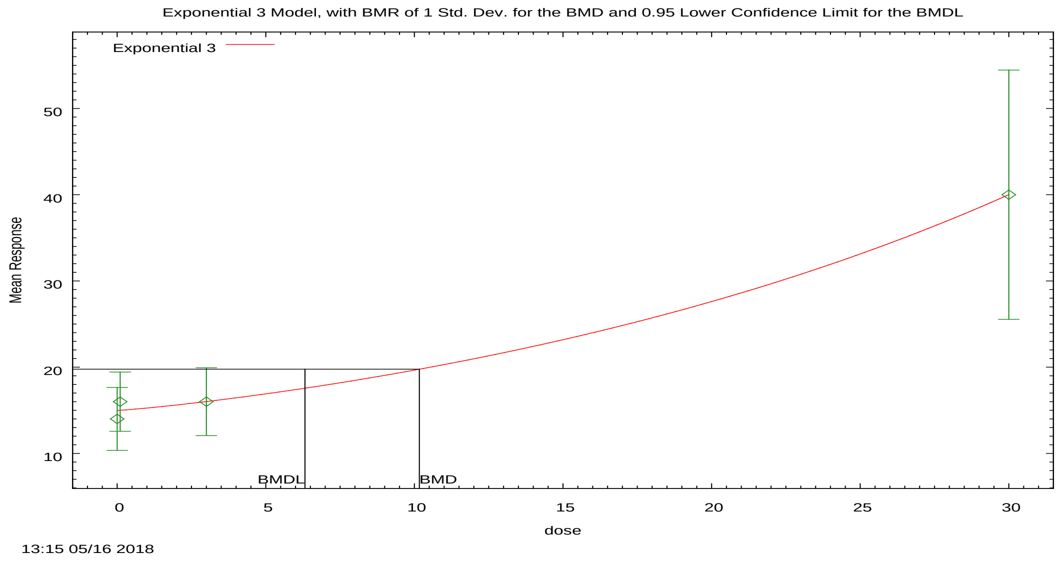


Figure 191. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 10.1665

BMDL at the 95% confidence level = 6.31813

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.51977	-4.38245
rho	2.82595	2.80856
a	14.9835	14.7983
b	0.0328197	0.0330832
c	n/a	0
d	1.16951	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	14.98	5.1	4.78	-0.6503
0.1	10	16	15	4.8	4.79	0.6587
3	10	16	16.01	5.5	5.25	-0.007944
30	10	40	40	20.2	19.15	-0.0004674

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.9461	5	237.8923
A2	-96.97566	8	209.9513
A3	-97.19629	6	206.3926
R	-128.2687	2	260.5375
3	-97.4308	5	204.8616

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	62.59	6	<0.0001
Test 2	33.94	3	<0.0001
Test 3	0.4413	2	0.802
Test 5a	0.469	1	0.4934

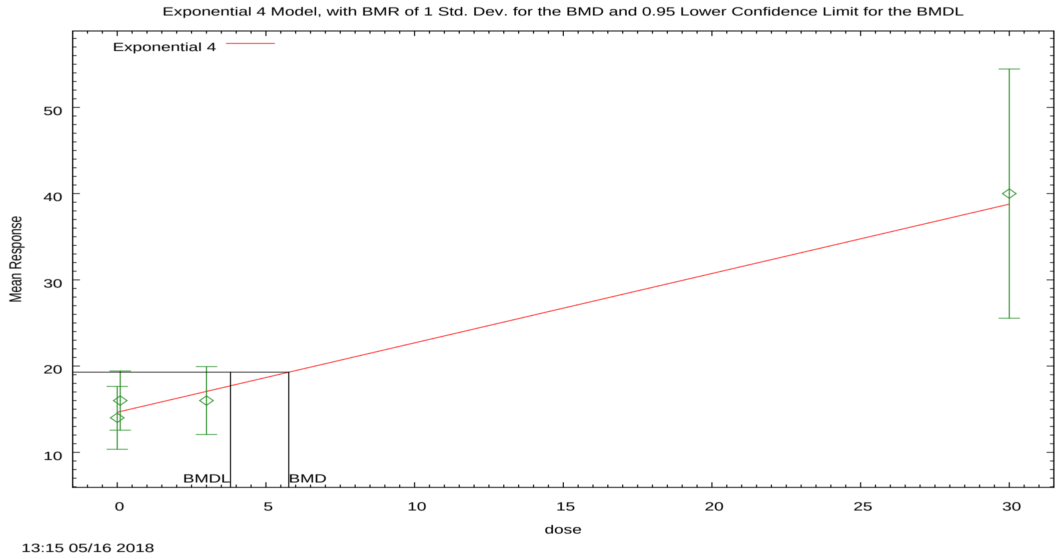


Figure 192. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 5.76843

BMDL at the 95% confidence level = 3.80958

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.70037	-4.38245
rho	2.89424	2.80856
a	14.6511	13.3
b	0.00000048235	0.000224083
c	113815	300.752
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	14.65	5.1	4.64	-0.4438
0.1	10	16	14.73	4.8	4.68	0.8577
3	10	16	17.06	5.5	5.78	-0.5817
30	10	40	38.78	20.2	18.98	0.2032

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.9461	5	237.8923
A2	-96.97566	8	209.9513
A3	-97.19629	6	206.3926
R	-128.2687	2	260.5375
4	-97.75732	5	205.5146

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.59	6	<0.0001
Test 2	33.94	3	<0.0001
Test 3	0.4413	2	0.802
Test 6a	1.122	1	0.2895

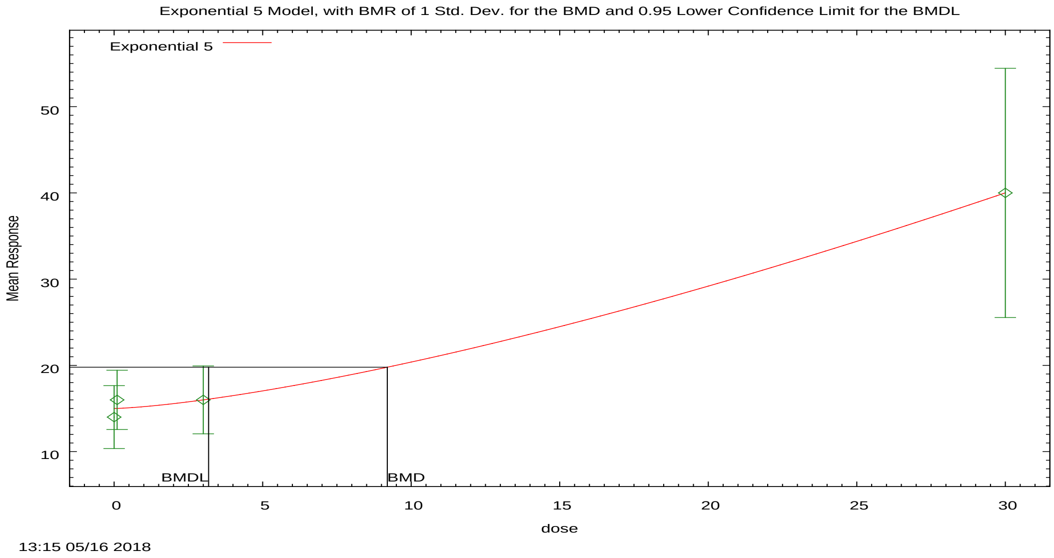


Figure 193. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 9.19545

BMDL at the 95% confidence level = 3.17978

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-4.52007	-4.38245
rho	2.82611	2.80856
a	14.9966	13.3
b	0.000536969	0.000224083

c	538.921	300.752
d	1.39883	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	15	5.1	4.79	-0.6581
0.1	10	16	15.01	4.8	4.79	0.6564
3	10	16	16	5.5	5.25	0.002225
30	10	40	40	20.2	19.16	-0.0004013

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.9461	5	237.8923
A2	-96.97566	8	209.9513
A3	-97.19629	6	206.3926
R	-128.2687	2	260.5375
5	-97.43429	6	206.8686

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.59	6	<0.0001
Test 2	33.94	3	<0.0001
Test 3	0.4413	2	0.802
Test 7a	0.476	0	N/A

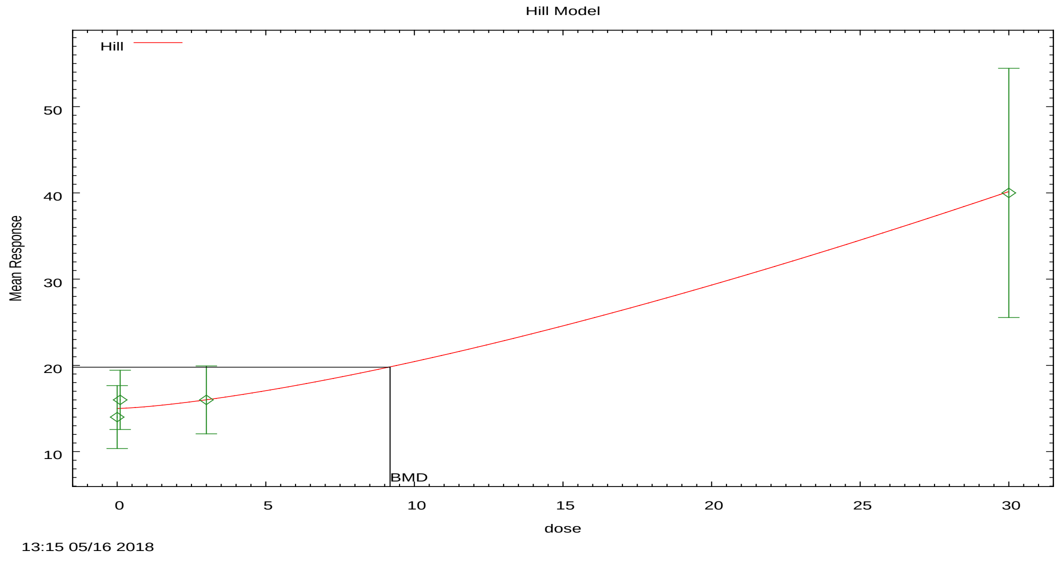


Figure 194. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 9.18221

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.52007	4.80267
rho	2.82611	0
intercept	14.9967	14
v	2989.43	26
n	1.40179	0.663874

k	904.87	44.625

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	15	5.1	4.79	-0.658
0.1	10	16	15	4.8	4.79	0.656
3	10	16	16	5.5	5.25	0.00231
30	10	40	40	20.2	19.2	-0.000401

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.946143	5	237.892286
A2	-96.975661	8	209.951322
A3	-97.196287	6	206.392573
fitted	-97.434324	6	206.868648
R	-128.268737	2	260.537474

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.5862	6	<0.0001
Test 2	33.941	3	<0.0001
Test 3	0.441251	2	0.802
Test 4	0.476075	0	N/A

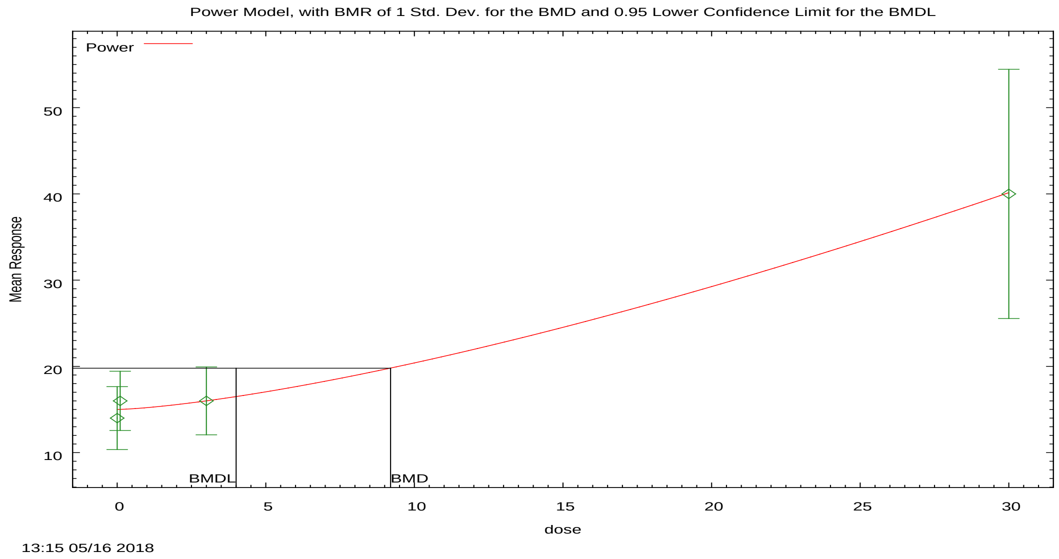


Figure 195. Plot of mean response by dose with fitted curve for Power model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 9.1984

BMDL at the 95% confidence level = 4.00238

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.52007	4.80267
rho	2.82611	0
control	14.9966	14
slope	0.215183	6.32358
power	1.39815	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	15	5.1	4.79	-0.658
0.1	10	16	15	4.8	4.79	0.656
3	10	16	16	5.5	5.25	0.0022
30	10	40	40	20.2	19.2	-0.000401

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.946143	5	237.892286
A2	-96.975661	8	209.951322
A3	-97.196287	6	206.392573
fitted	-97.434286	5	204.868572
R	-128.268737	2	260.537474

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.5862	6	<0.0001
Test 2	33.941	3	<0.0001
Test 3	0.441251	2	0.802
Test 4	0.475999	1	0.4902

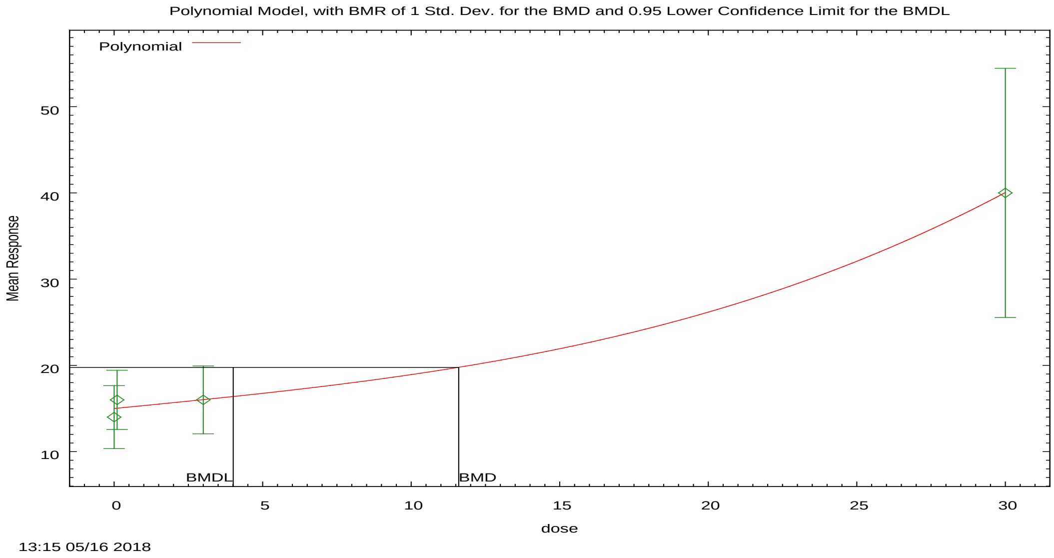


Figure 196. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 11.5999

BMDL at the 95% confidence level = 4.00852

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.51875	4.80267
rho	2.82552	0
beta_0	14.9776	14
beta_1	0.337764	20.7336
beta_2	0	0

beta_3	0.000551898	0.223213

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	15	5.1	4.78	-0.647
0.1	10	16	15	4.8	4.79	0.652
3	10	16	16	5.5	5.25	-0.00346
30	10	40	40	20.2	19.2	-0.00194

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.946143	5	237.892286
A2	-96.975661	8	209.951322
A3	-97.196287	6	206.392573
fitted	-97.425014	5	204.850029
R	-128.268737	2	260.537474

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.5862	6	<0.0001
Test 2	33.941	3	<0.0001
Test 3	0.441251	2	0.802
Test 4	0.457455	1	0.4988

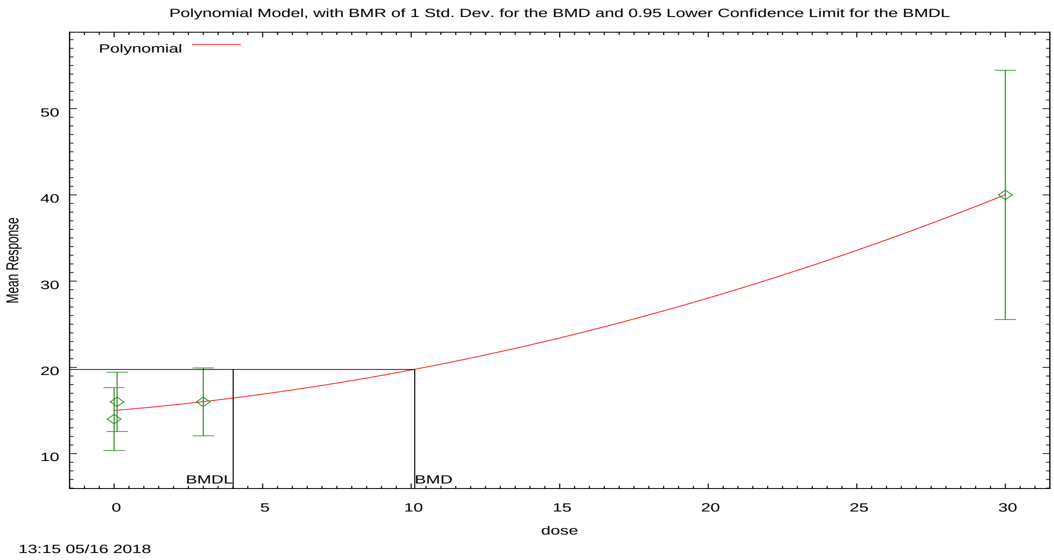


Figure 197. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 10.1185

BMDL at the 95% confidence level = 4.00732

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.51944	4.80267
rho	2.82578	0
beta_0	14.9795	14.9664
beta_1	0.288303	0.303817
beta_2	0.0181987	0.0176875

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	15	5.1	4.78	-0.648
0.1	10	16	15	4.8	4.79	0.654
3	10	16	16	5.5	5.25	-0.00494
30	10	40	40	20.2	19.2	-0.00122

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.946143	5	237.892286
A2	-96.975661	8	209.951322
A3	-97.196287	6	206.392573
fitted	-97.426827	5	204.853653
R	-128.268737	2	260.537474

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.5862	6	<0.0001
Test 2	33.941	3	<0.0001
Test 3	0.441251	2	0.802
Test 4	0.46108	1	0.4971

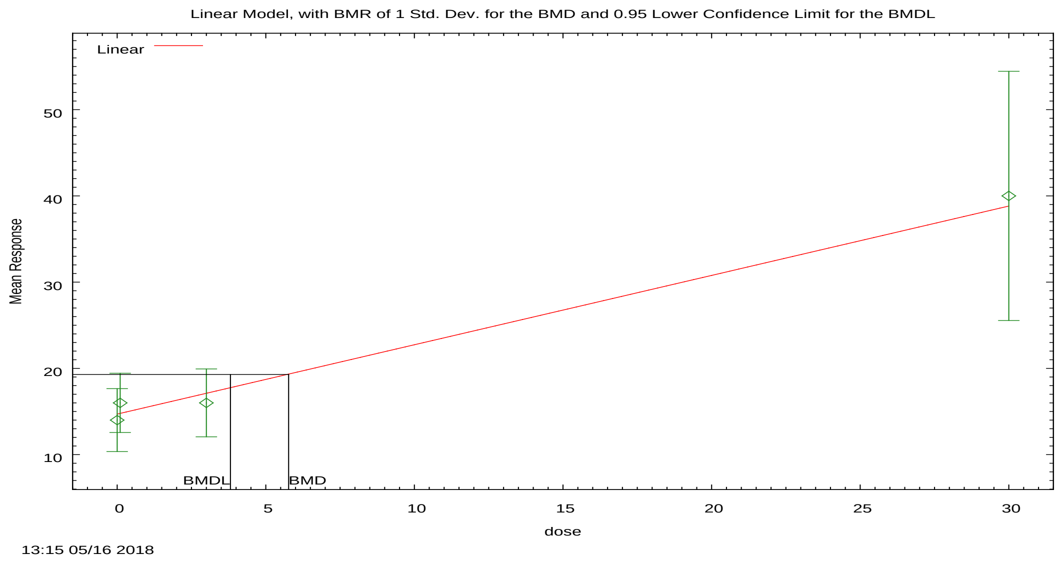


Figure 198. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Sorbitol Dehydrogenase in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 5.76847

BMDL at the 95% confidence level = 3.8096

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-4.70038	4.80267
rho	2.89425	0
beta_0	14.6511	14.4909
beta_1	0.804312	0.847022

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	14	14.7	5.1	4.64	-0.444
0.1	10	16	14.7	4.8	4.68	0.858
3	10	16	17.1	5.5	5.78	-0.582
30	10	40	38.8	20.2	19	0.203

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.946143	5	237.892286
A2	-96.975661	8	209.951322
A3	-97.196287	6	206.392573
fitted	-97.757311	4	203.514621
R	-128.268737	2	260.537474

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.5862	6	<0.0001
Test 2	33.941	3	<0.0001
Test 3	0.441251	2	0.802
Test 4	1.12205	2	0.5706

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Sorbitol Dehydrogenase (U/L) in Females

1.23. BMDS Summary of Sorbitol Dehydrogenase (U/L) Females (90 Day Mice GenX)

Table 23. Summary of BMD Modeling Results for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	<0.0001	194.11	3.87	2.56	1.51	No models met all model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). No BMDL was selected.
Exponential (M3)	<0.0001	195.56	4.77	2.67	1.79	
Exponential (M4)	<0.0001	205.81	error[b]	0	error	
Exponential (M5)	N/A[c]	207.81	error[b]	0	error	
Hill	N/A[c]	197.56	4.79	error[b]	error	
Power	<0.0001	195.56	4.83	2.42	2.00	
Polynomial 3°	<0.0001	193.56	4.53	3.35	1.35	
Polynomial 2°	<0.0001	193.61	4.31	3.34	1.29	
Linear	<0.0001	194.21	3.74	2.28	1.64	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001, BMDS Test 3 *p*-value = 0.135), no model was selected as a best-fitting model.
[b] BMD or BMDL computation failed for this model.
[c] No available degrees of freedom to calculate a goodness of fit value.

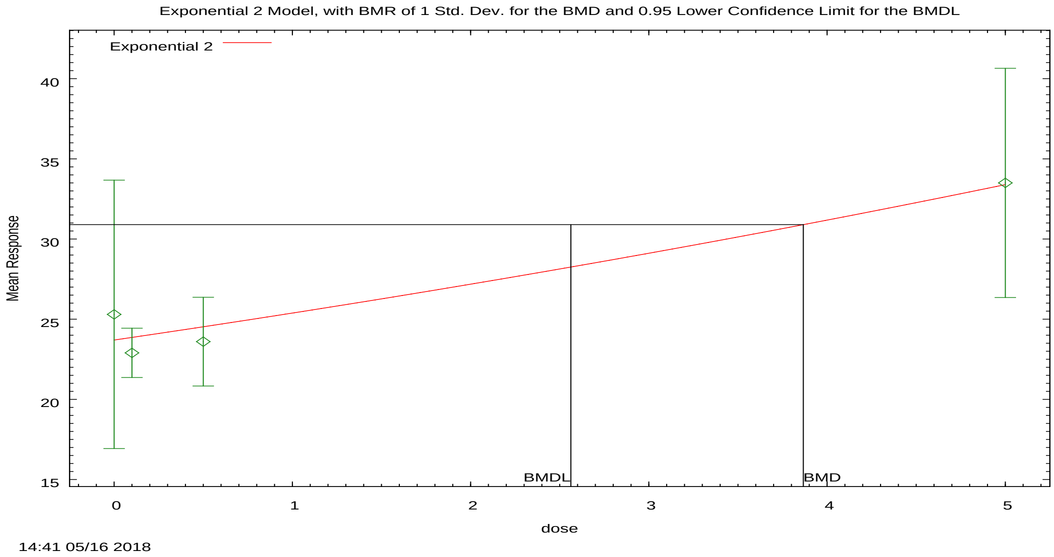


Figure 199. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 3.86673

BMDL at the 95% confidence level = 2.56258

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.13752	-16.9882
rho	0.887614	6.23567
a	23.6987	23.6811
b	0.0685802	0.0684587
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	25.3	23.7	11.7	7.2	0.7037
0.1	9	22.9	23.86	2	7.22	-0.3997
0.5	9	23.6	24.53	3.6	7.31	-0.3799
5	9	33.5	33.39	9.3	8.38	0.03863

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.85805	5	195.7161

A2	-78.81587	8	173.6317
A3	-80.8164	6	173.6328
R	-97.90648	2	199.813
2	-93.05697	4	194.1139

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	38.18	6	<0.0001
Test 2	28.08	3	<0.0001
Test 3	4.001	2	0.1353
Test 4	24.48	2	<0.0001

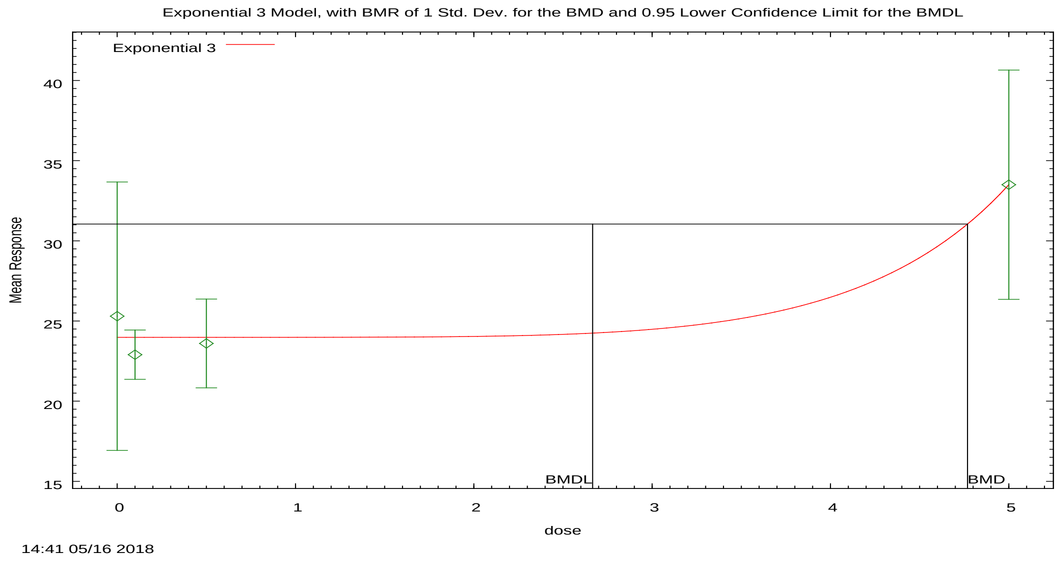


Figure 200. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.76845

BMDL at the 95% confidence level = 2.66627

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.200899	-16.9882
rho	1.29377	6.23567
a	23.9821	23.6811
b	0.16356	0.0684587
c	n/a	0
d	5.44847	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	25.3	23.98	11.7	7.06	0.59
0.1	9	22.9	23.98	2	7.06	-0.4596
0.5	9	23.6	23.98	3.6	7.06	-0.1623
5	9	33.5	33.5	9.3	8.77	-0.000003461

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.85805	5	195.7161
A2	-78.81587	8	173.6317
A3	-80.8164	6	173.6328
R	-97.90648	2	199.813
3	-92.77751	5	195.555

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	38.18	6	<0.0001
Test 2	28.08	3	<0.0001
Test 3	4.001	2	0.1353
Test 5a	23.92	1	<0.0001

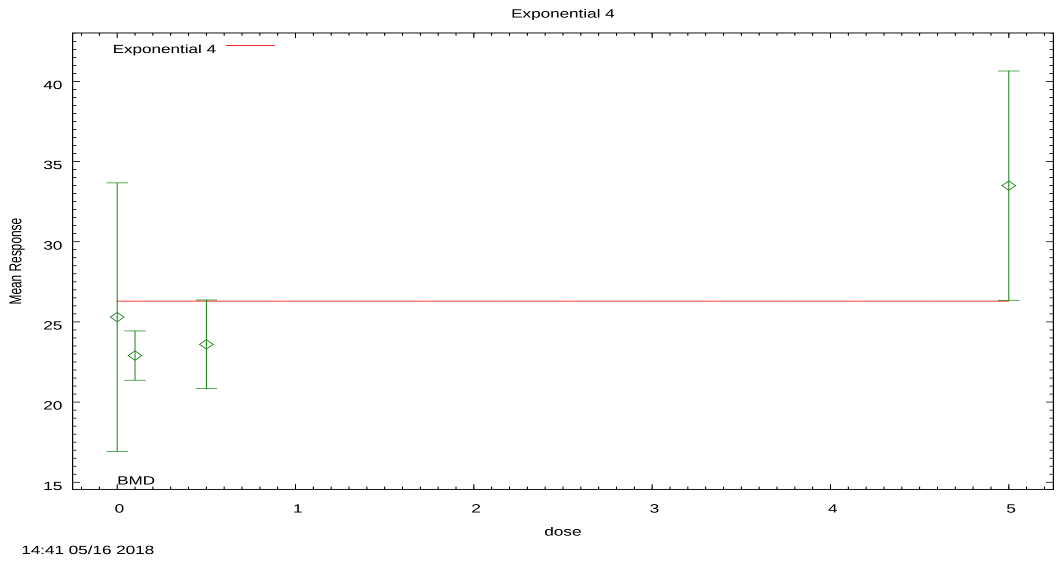


Figure 201. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = error

BMDL at the 95% confidence level = 0

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	51.292	-16.9882
rho	-14.3754	6.23567
a	26.2973	21.755
b	0.0742061	0.0604162
c	1	3.07975
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	25.3	26.3	11.7	8.55	-0.3688
0.1	9	22.9	26.3	2	8.55	-1.192
0.5	9	23.6	26.3	3.6	8.55	-0.9462
5	9	33.5	26.3	9.3	8.55	2.527

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.85805	5	195.7161
A2	-78.81587	8	173.6317
A3	-80.8164	6	173.6328
R	-97.90648	2	199.813
4	-97.90648	5	205.813

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	38.18	6	<0.0001
Test 2	28.08	3	<0.0001
Test 3	4.001	2	0.1353
Test 6a	34.18	1	<0.0001

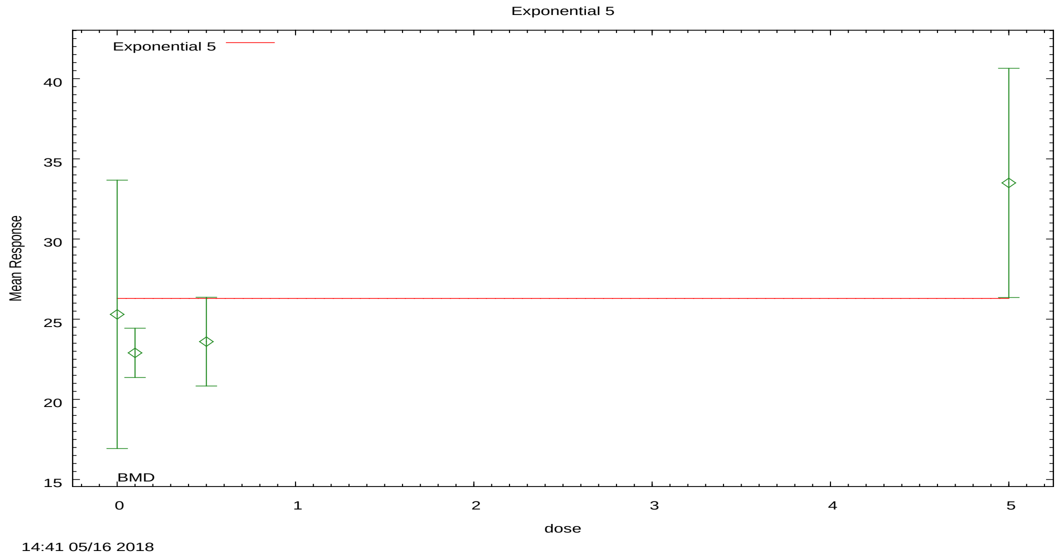


Figure 202. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = error

BMDL at the 95% confidence level = 0

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	47.8211	-16.9882
rho	-13.3138	6.23567
a	26.2973	21.755
b	0.0298942	0.0604162

c	1	3.07975
d	1.00001	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	25.3	26.3	11.7	8.55	-0.3688
0.1	9	22.9	26.3	2	8.55	-1.192
0.5	9	23.6	26.3	3.6	8.55	-0.9462
5	9	33.5	26.3	9.3	8.55	2.527

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.85805	5	195.7161
A2	-78.81587	8	173.6317
A3	-80.8164	6	173.6328
R	-97.90648	2	199.813
5	-97.90648	6	207.813

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	38.18	6	<0.0001
Test 2	28.08	3	<0.0001
Test 3	4.001	2	0.1353
Test 7a	34.18	0	N/A

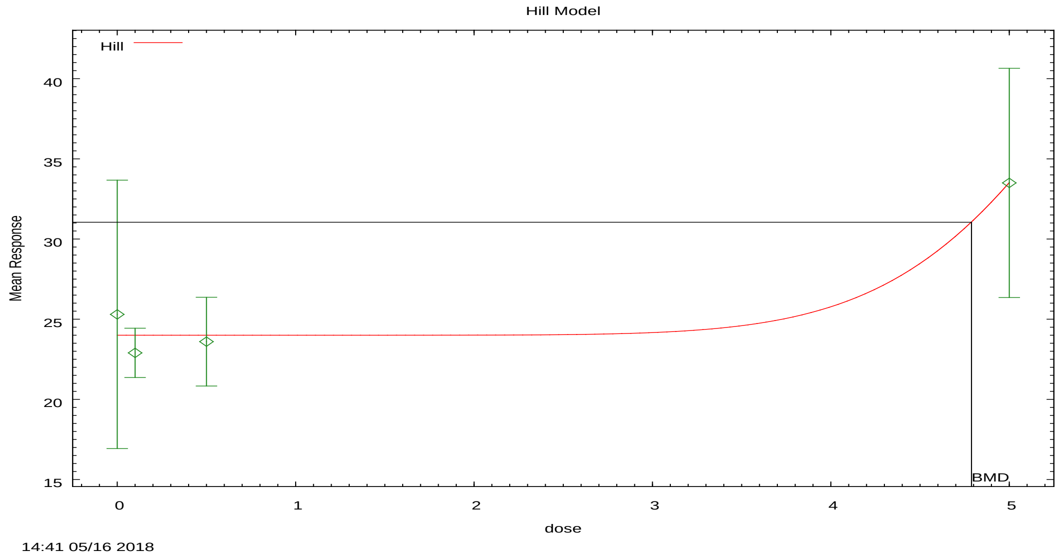


Figure 203. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.78804

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-0.200962	4.13376
rho	1.29379	0
intercept	23.9821	25.3
v	46.0799	8.2

n	8.38549	1
k	5.87047	6.86364

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	25.3	24	11.7	7.06	0.59
0.1	9	22.9	24	2	7.06	-0.46
0.5	9	23.6	24	3.6	7.06	-0.162
5	9	33.5	33.5	9.3	8.77	0.00000092

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.858049	5	195.716098
A2	-78.815874	8	173.631747
A3	-80.816402	6	173.632804
fitted	-92.777505	6	197.555009
R	-97.906482	2	199.812964

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	38.1812	6	<0.0001
Test 2	28.0844	3	<0.0001
Test 3	4.00106	2	0.1353
Test 4	23.9222	0	N/A

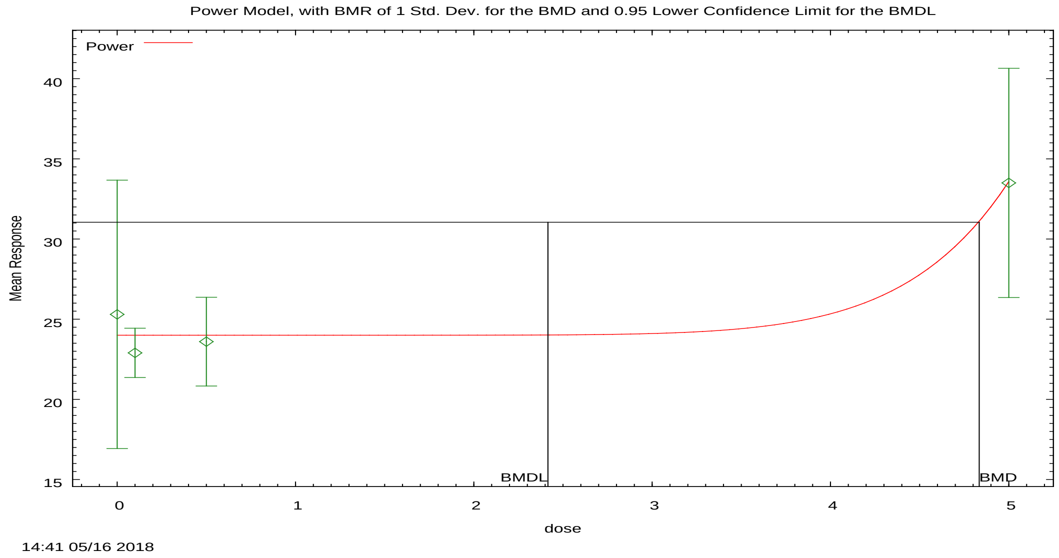


Figure 204. Plot of mean response by dose with fitted curve for Power model with modeled variance for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.83404

BMDL at the 95% confidence level = 2.4156

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-0.200961	4.13376
rho	1.29379	0
control	23.9821	22.9
slope	0.00000634556	1.58627

power	8.83596	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	25.3	24	11.7	7.06	0.59
0.1	9	22.9	24	2	7.06	-0.46
0.5	9	23.6	24	3.6	7.06	-0.162
5	9	33.5	33.5	9.3	8.77	-0.00000231

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.858049	5	195.716098
A2	-78.815874	8	173.631747
A3	-80.816402	6	173.632804
fitted	-92.777505	5	195.555009
R	-97.906482	2	199.812964

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	38.1812	6	<0.0001
Test 2	28.0844	3	<0.0001
Test 3	4.00106	2	0.1353
Test 4	23.9222	1	<0.0001

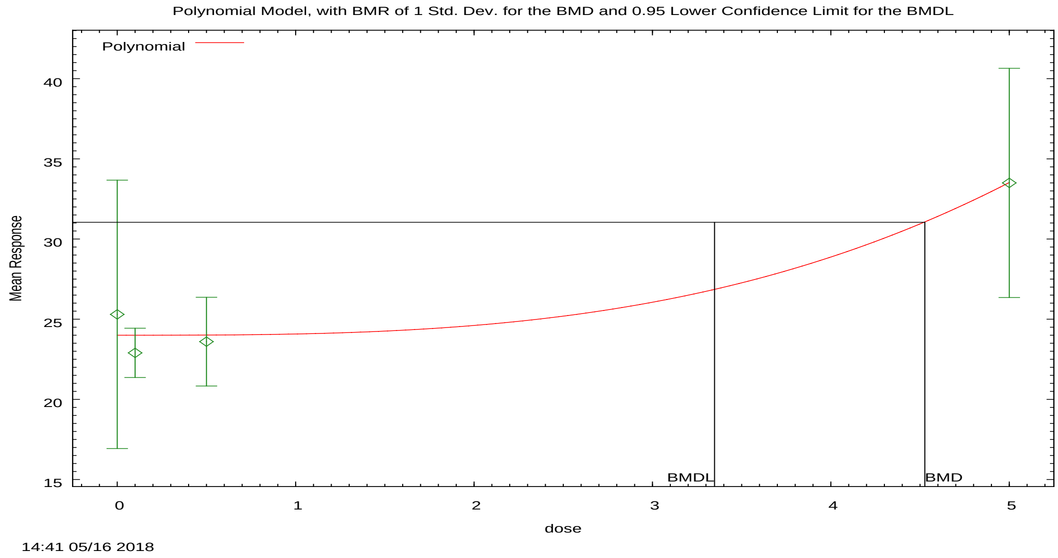


Figure 205. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.52672

BMDL at the 95% confidence level = 3.34784

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-0.187752	4.13376
rho	1.28978	0
beta_0	23.9793	25.3
beta_1	4.79108E-22	0
beta_2	0	0

beta_3	0.0761586	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	25.3	24	11.7	7.06	0.591
0.1	9	22.9	24	2	7.06	-0.458
0.5	9	23.6	24	3.6	7.07	-0.165
5	9	33.5	33.5	9.3	8.76	0.000291

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.858049	5	195.716098
A2	-78.815874	8	173.631747
A3	-80.816402	6	173.632804
fitted	-92.779965	4	193.559931
R	-97.906482	2	199.812964

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	38.1812	6	<0.0001
Test 2	28.0844	3	<0.0001
Test 3	4.00106	2	0.1353
Test 4	23.9271	2	<0.0001

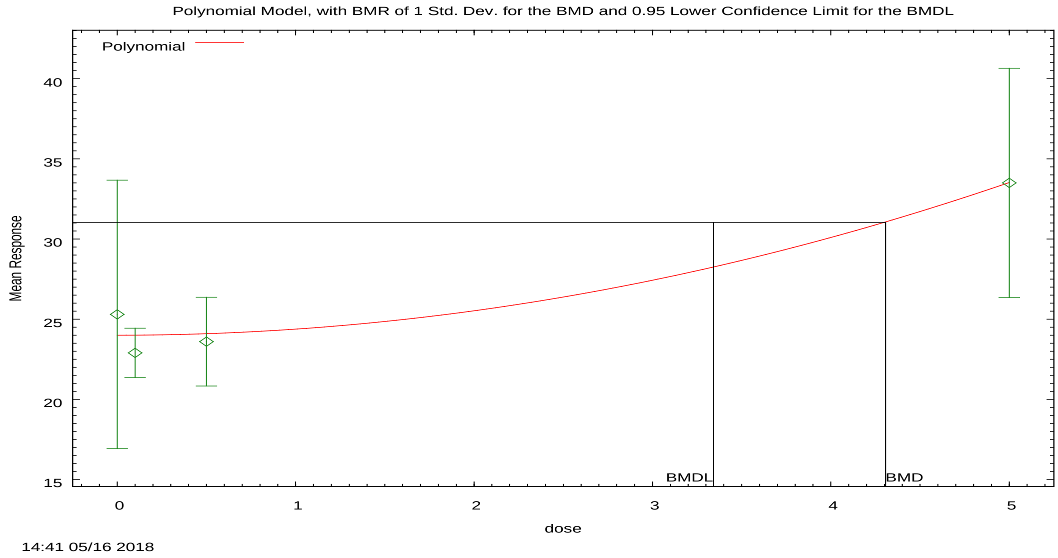


Figure 206. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.30648

BMDL at the 95% confidence level = 3.34112

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-0.0644155	4.13376
rho	1.25231	0
beta_0	23.9533	24.3494
beta_1	2.52909E-21	0
beta_2	0.381475	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	25.3	24	11.7	7.07	0.602
0.1	9	22.9	24	2	7.08	-0.448
0.5	9	23.6	24	3.6	7.09	-0.19
5	9	33.5	33.5	9.3	8.73	0.00337

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.858049	5	195.716098
A2	-78.815874	8	173.631747
A3	-80.816402	6	173.632804
fitted	-92.803595	4	193.60719
R	-97.906482	2	199.812964

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	38.1812	6	<0.0001
Test 2	28.0844	3	<0.0001
Test 3	4.00106	2	0.1353
Test 4	23.9744	2	<0.0001

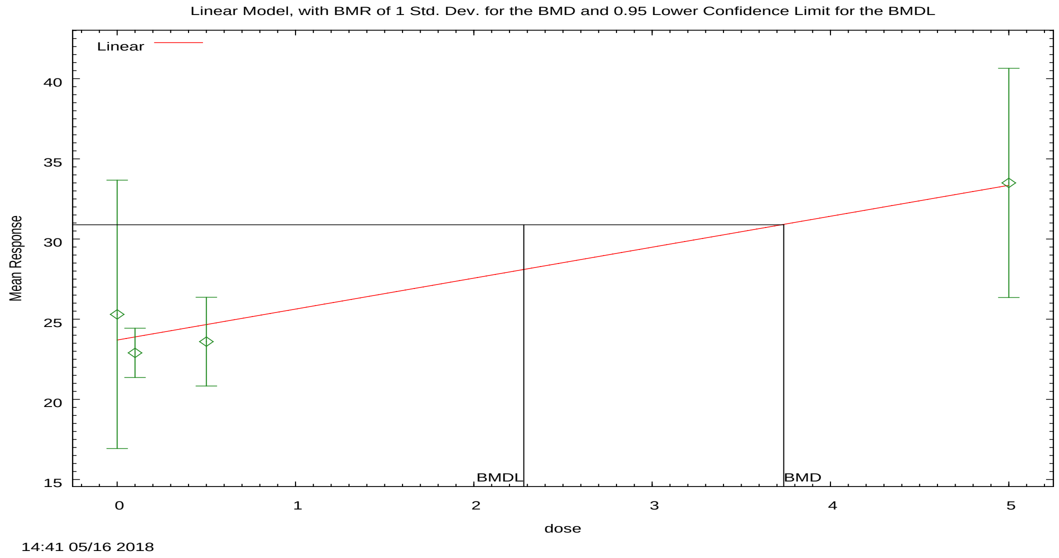


Figure 207. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Sorbitol Dehydrogenase in Females (90-day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.7379

BMDL at the 95% confidence level = 2.28009

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	1.34146	4.13376
rho	0.825818	0
beta_0	23.6658	23.5788
beta_1	1.93221	1.96154

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	25.3	23.7	11.7	7.22	0.716
0.1	9	22.9	23.9	2	7.25	-0.397
0.5	9	23.6	24.6	3.6	7.34	-0.422
5	9	33.5	33.3	9.3	8.32	0.0624

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.858049	5	195.716098
A2	-78.815874	8	173.631747
A3	-80.816402	6	173.632804
fitted	-93.107064	4	194.214128
R	-97.906482	2	199.812964

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	38.1812	6	<0.0001
Test 2	28.0844	3	<0.0001
Test 3	4.00106	2	0.1353
Test 4	24.5813	2	<0.0001

BMDS WIZARD OUTPUT REPORT

Summary of H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats – Sorbitol Dehydrogenase (U/L) at 12-month timepoint in Males

1.24. BMDS Summary of Sorbitol Dehydrogenase (U/L) Males 12 months (2 Year Rats GenX)

Table 24. Summary of BMD Modeling Results for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean

Model[a]	**Goodness of fit**		**BMD$_{1SD}$ (mg/kg/day)**	**BMDL$_{1SD}$ (mg/kg/day)**	**BMD/BMDL**	**Basis for model selection**
	***p*-value**	**AIC**				
Exponential (M2) Exponential (M3)[b]	0.738	206.75	17.6	11.6	1.52	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were not sufficiently close (> 3-fold difference), so the lowest BMDL was selected.
Exponential (M4)	**0.497**	**208.60**	**6.60**	**1.21**	**5.47**	
Exponential (M5)	N/A[c]	210.53	1.32	1.01	1.31	
Hill	N/A[c]	210.53	1.42	error[d]	error	
Power[e] Polynomial 3°[f] Polynomial 2°[g] Linear	0.761	206.68	13.0	6.95	1.87	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 1, and 50 mg/kg/day were -0.57, 0.16, 0.47, -0.07, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

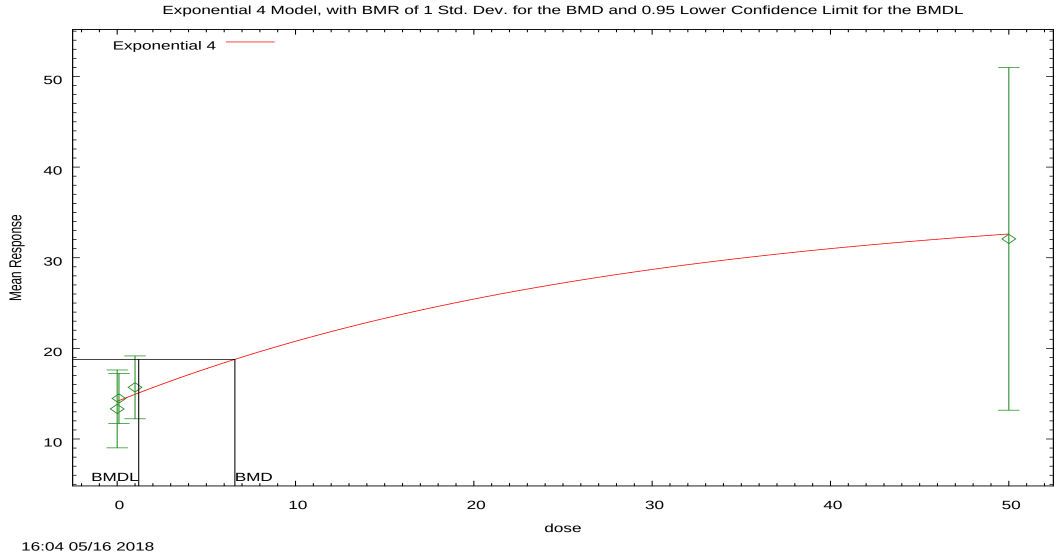
[c] No available degrees of freedom to calculate a goodness of fit value.

[d] BMD or BMDL computation failed for this model.

[e] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[g] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.



Exponential 4 Model, with BMR of 1 Std. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

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Figure 208. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 6.59887

BMDL at the 95% confidence level = 1.20614

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-7.62202	-7.70134
rho	4.03212	4.07591
a	14.1592	12.654
b	0.0353009	0.0515144
c	2.57315	2.66193
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.32	14.16	6.01	4.63	-0.5734
0.1	10	14.47	14.24	3.87	4.68	0.1569
1	10	15.7	14.93	4.85	5.15	0.4715
50	10	32.08	32.62	26.42	24.9	-0.06869

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.1674	5	256.3348
A2	-97.88906	8	211.7781
A3	-99.06893	6	210.1379
R	-128.9829	2	261.9658
4	-99.29957	5	208.5991

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.19	6	<0.0001
Test 2	50.56	3	<0.0001
Test 3	2.36	2	0.3073
Test 6a	0.4613	1	0.497

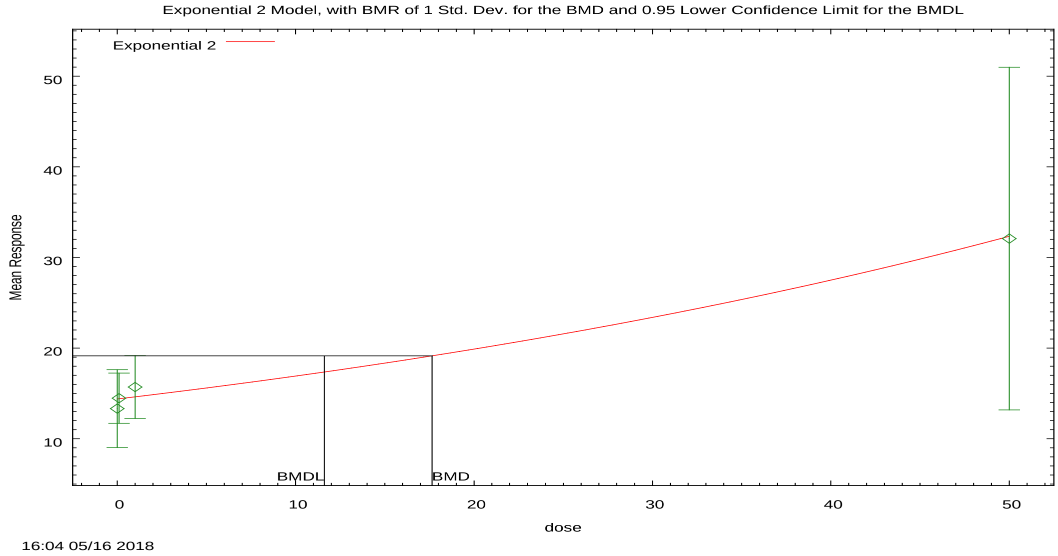

Figure 209. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 17.6448

BMDL at the 95% confidence level = 11.6067

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-7.81223	-7.70134
rho	4.10029	4.07591
a	14.386	14.372
b	0.0161975	0.0160881
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.32	14.39	6.01	4.76	-0.7083
0.1	10	14.47	14.41	3.87	4.78	0.04019
1	10	15.7	14.62	4.85	4.92	0.6936
50	10	32.08	32.33	26.42	25.04	-0.03211

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.1674	5	256.3348
A2	-97.88906	8	211.7781
A3	-99.06893	6	210.1379
R	-128.9829	2	261.9658
2	-99.37282	4	206.7456

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.19	6	<0.0001
Test 2	50.56	3	<0.0001
Test 3	2.36	2	0.3073
Test 4	0.6078	2	0.7379

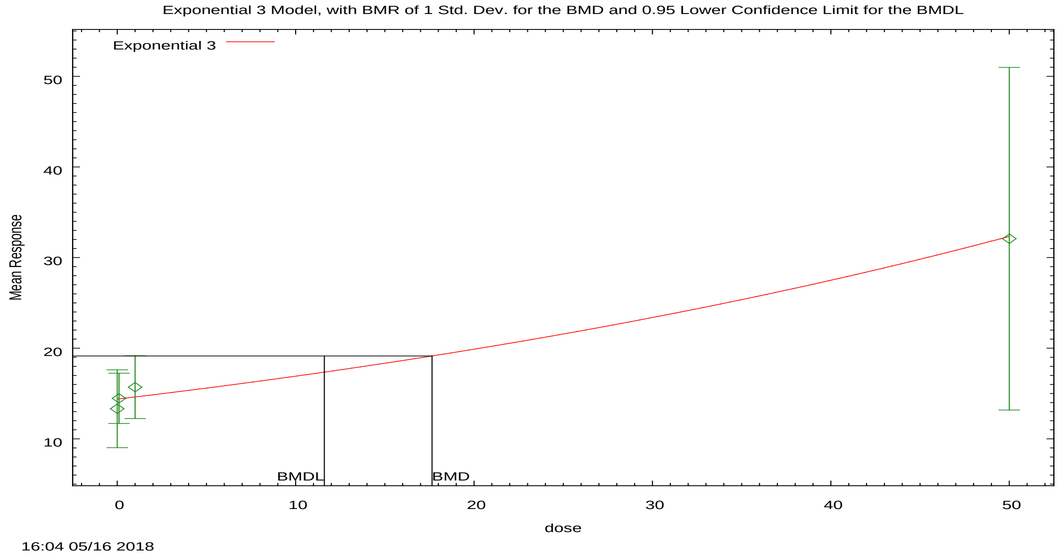

Figure 210. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 17.6448

BMDL at the 95% confidence level = 11.6067

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-7.81223	-7.70134
rho	4.10029	4.07591
a	14.386	14.372
b	0.0161975	0.0160881
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.32	14.39	6.01	4.76	-0.7083
0.1	10	14.47	14.41	3.87	4.78	0.04019
1	10	15.7	14.62	4.85	4.92	0.6936
50	10	32.08	32.33	26.42	25.04	-0.03211

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.1674	5	256.3348
A2	-97.88906	8	211.7781
A3	-99.06893	6	210.1379
R	-128.9829	2	261.9658
3	-99.37282	4	206.7456

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.19	6	<0.0001
Test 2	50.56	3	<0.0001
Test 3	2.36	2	0.3073
Test 5a	0.6078	2	0.7379

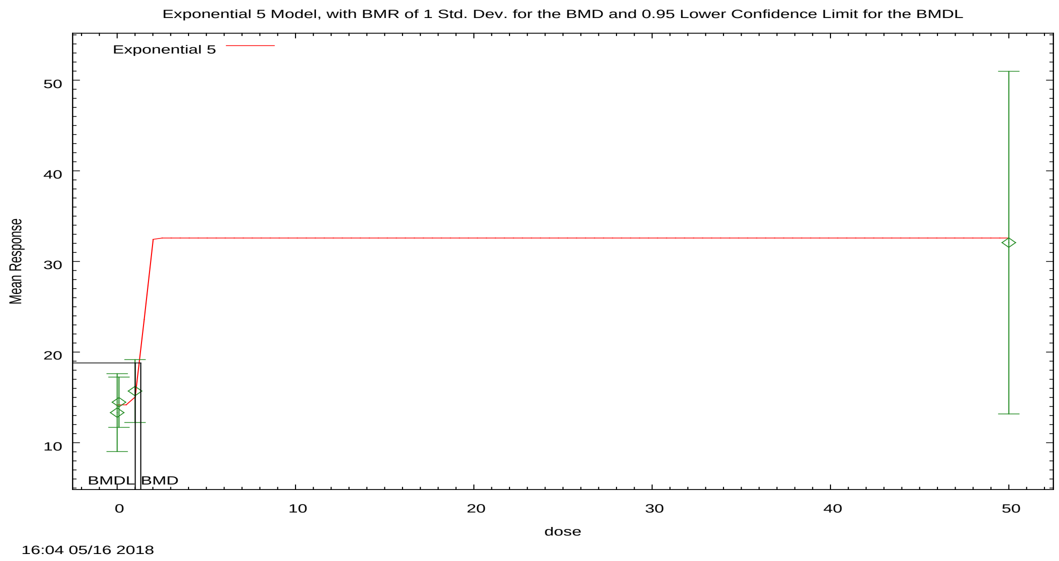

Figure 211. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.32183

BMDL at the 95% confidence level = 1.01222

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-7.65183	-7.70134
rho	4.04211	4.07591
a	14.1732	12.654
b	0.627627	0.0515144

c	2.29918	2.66193
d	6.63396	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.32	14.17	6.01	4.63	-0.5827
0.1	10	14.47	14.17	3.87	4.63	0.2027
1	10	15.7	14.99	4.85	5.19	0.4315
50	10	32.08	32.59	26.42	24.91	-0.06433

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.1674	5	256.3348
A2	-97.88906	8	211.7781
A3	-99.06893	6	210.1379
R	-128.9829	2	261.9658
5	-99.26642	6	210.5328

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.19	6	<0.0001
Test 2	50.56	3	<0.0001
Test 3	2.36	2	0.3073
Test 7a	0.395	0	N/A

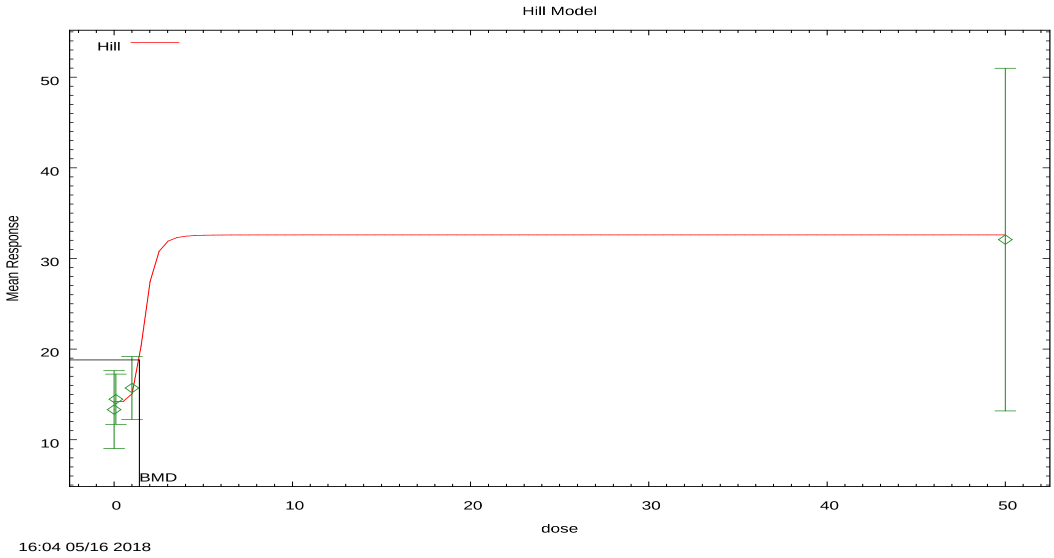

Figure 212. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.41525

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.65188	5.26373
rho	4.04213	0
intercept	14.1732	13.32
v	18.4135	18.76

n	5.69094	0.426195
k	1.71426	78.0598

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.3	14.2	6.01	4.63	-0.583
0.1	10	14.5	14.2	3.87	4.63	0.203
1	10	15.7	15	4.85	5.19	0.432
50	10	32.1	32.6	26.4	24.9	-0.0643

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.167387	5	256.334774
A2	-97.889063	8	211.778126
A3	-99.068928	6	210.137855
fitted	-99.266423	6	210.532847
R	-128.982884	2	261.965768

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.1876	6	<0.0001
Test 2	50.5566	3	<0.0001
Test 3	2.35973	2	0.3073
Test 4	0.394991	0	N/A

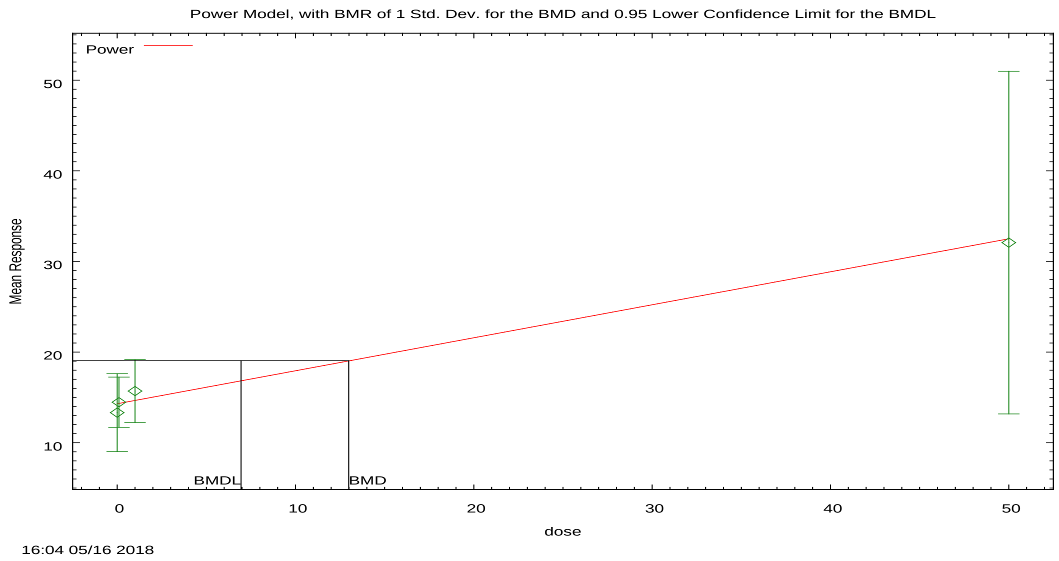

Figure 213. Plot of mean response by dose with fitted curve for Power model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 12.9849

BMDL at the 95% confidence level = 6.94645

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.71947	5.26373
rho	4.0664	0
control	14.3262	13.32
slope	0.36387	3.13168

power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.3	14.3	6.01	4.72	-0.673
0.1	10	14.5	14.4	3.87	4.75	0.0715
1	10	15.7	14.7	4.85	4.97	0.642
50	10	32.1	32.5	26.4	25	-0.0556

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.167387	5	256.334774
A2	-97.889063	8	211.778126
A3	-99.068928	6	210.137855
fitted	-99.341825	4	206.68365
R	-128.982884	2	261.965768

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.1876	6	<0.0001
Test 2	50.5566	3	<0.0001
Test 3	2.35973	2	0.3073
Test 4	0.545795	2	0.7612

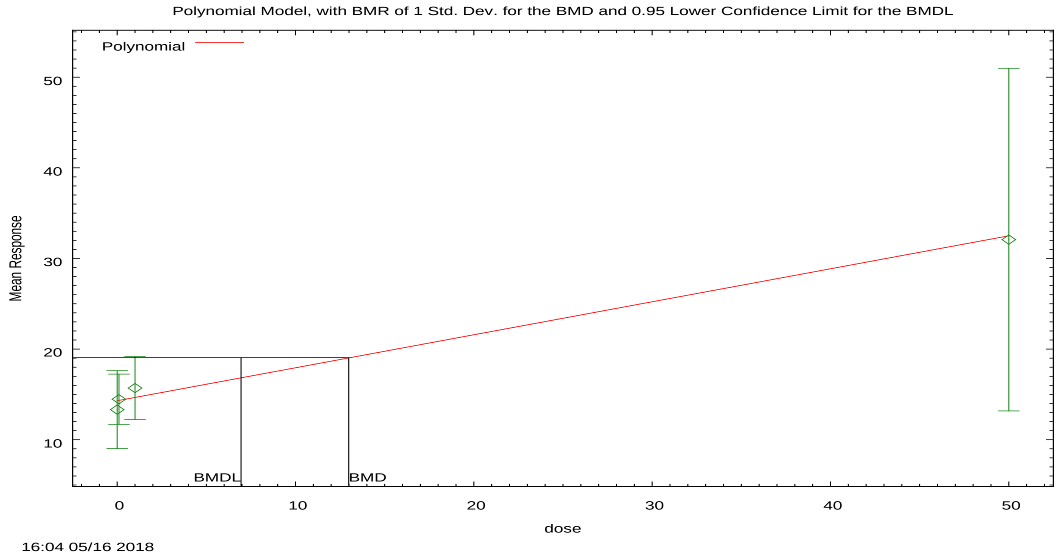

Figure 214. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 12.9849

BMDL at the 95% confidence level = 6.94645

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.71947	5.26373
rho	4.0664	0
beta_0	14.3262	13.32
beta_1	0.36387	12.5336

beta_2	7.95E-14	0
beta_3	1.59E-15	0.202253

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.3	14.3	6.01	4.72	-0.673
0.1	10	14.5	14.4	3.87	4.75	0.0715
1	10	15.7	14.7	4.85	4.97	0.642
50	10	32.1	32.5	26.4	25	-0.0556

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.167387	5	256.334774
A2	-97.889063	8	211.778126
A3	-99.068928	6	210.137855
fitted	-99.341825	4	206.68365
R	-128.982884	2	261.965768

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.1876	6	<0.0001
Test 2	50.5566	3	<0.0001
Test 3	2.35973	2	0.3073
Test 4	0.545795	2	0.7612

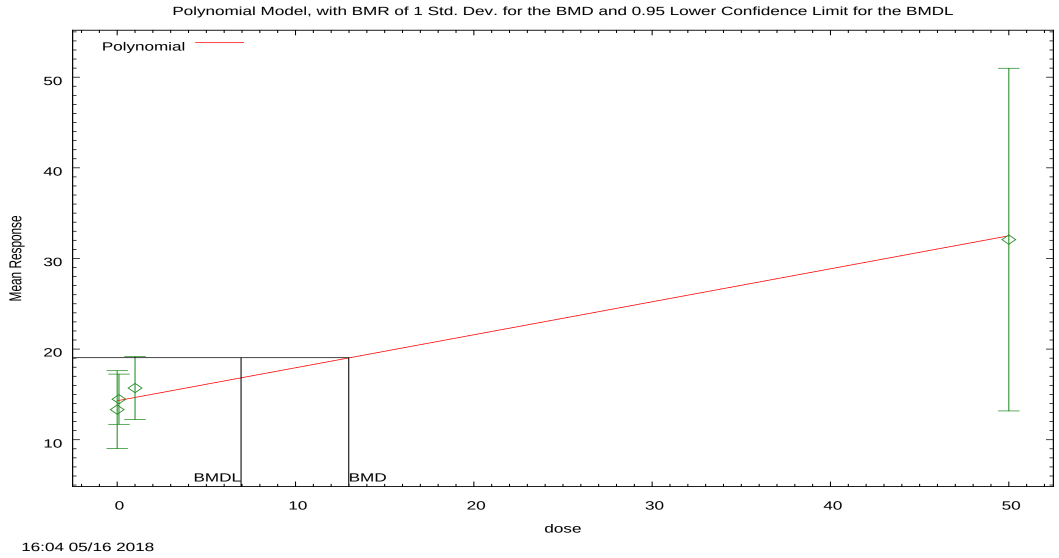

Figure 215. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 12.9849

BMDL at the 95% confidence level = 6.94645

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.71947	5.26373
rho	4.0664	0
beta_0	14.3262	13.769
beta_1	0.36387	2.0149

beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.3	14.3	6.01	4.72	-0.673
0.1	10	14.5	14.4	3.87	4.75	0.0715
1	10	15.7	14.7	4.85	4.97	0.642
50	10	32.1	32.5	26.4	25	-0.0556

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.167387	5	256.334774
A2	-97.889063	8	211.778126
A3	-99.068928	6	210.137855
fitted	-99.341825	4	206.68365
R	-128.982884	2	261.965768

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.1876	6	<0.0001
Test 2	50.5566	3	<0.0001
Test 3	2.35973	2	0.3073
Test 4	0.545795	2	0.7612

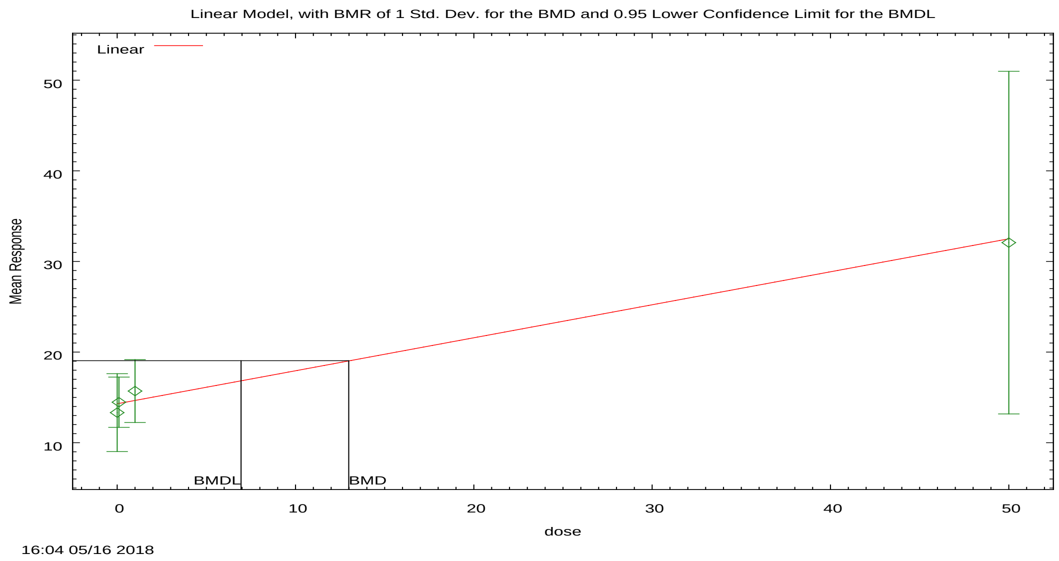

Figure 216. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Sorbitol Dehydrogenase in Males at 12 months (2-Year Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 12.9849

BMDL at the 95% confidence level = 6.94645

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.71949	5.26373
rho	4.06641	0
beta_0	14.3262	14.36
beta_1	0.363869	0.354798

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	13.3	14.3	6.01	4.72	-0.673
0.1	10	14.5	14.4	3.87	4.75	0.0715
1	10	15.7	14.7	4.85	4.97	0.642
50	10	32.1	32.5	26.4	25	-0.0556

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-123.167387	5	256.334774
A2	-97.889063	8	211.778126
A3	-99.068928	6	210.137855
fitted	-99.341825	4	206.68365
R	-128.982884	2	261.965768

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.1876	6	<0.0001
Test 2	50.5566	3	<0.0001
Test 3	2.35973	2	0.3073
Test 4	0.545795	2	0.7612

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Single Cell Hepatocellular Necrosis in Males

1.25. BMDS Summary of Liver Necrosis, Single Cell Male (28 Day Mice GenX)

Table 25. Summary of BMD Modeling Results for Single Cell Hepatocellular Necrosis in Males (28-Day Mice)

Model[a]	Goodness of fit		BMD$_{10Pct}$ (mg/kg/day)	BMDL$_{10Pct}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Gamma	1.000	17.460	1.88	0.323	5.80	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were not sufficiently close (> 3-fold difference), so the lowest BMDL was selected.
Dichotomous-Hill[b]	1.000	17.460	2.42	0.343	7.06	
Logistic	1.000	17.460	2.72	1.16	2.34	
LogLogistic[c]	1.000	17.460	2.42	0.343	7.06	
Probit	1.000	17.460	2.45	1.04	2.37	
LogProbit	**1.000**	**17.460**	**2.01**	**0.299**	**6.72**	
Weibull	1.000	17.460	1.96	0.323	6.05	
Multistage 3°	0.998	17.469	1.45	0.323	4.48	
Multistage 2°	1.000	15.472	1.36	0.323	4.23	
Quantal-Linear	0.972	15.918	0.603	0.305	1.97	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were 0, 0, 0, 0, respectively.

[b] The Dichotomous-Hill model may appear equivalent to the LogLogistic model, however differences exist in digits not displayed in the table.

[c] The LogLogistic model may appear equivalent to the Dichotomous-Hill model, however differences exist in digits not displayed in the table.

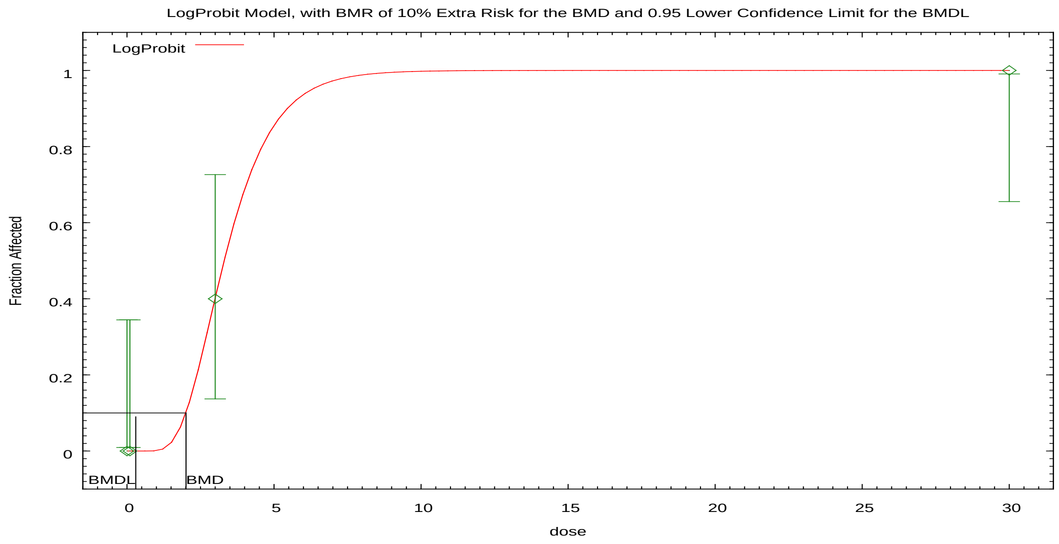

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Figure 217. Plot of incidence rate by dose with fitted curve for LogProbit model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.0069

BMDL at the 95% confidence level = 0.298834

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-3.0632E+00	-5.0920E-01
slope	2.5576	0.579932

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.000000174299	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4602

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0 d.f = 2 P-value = 1

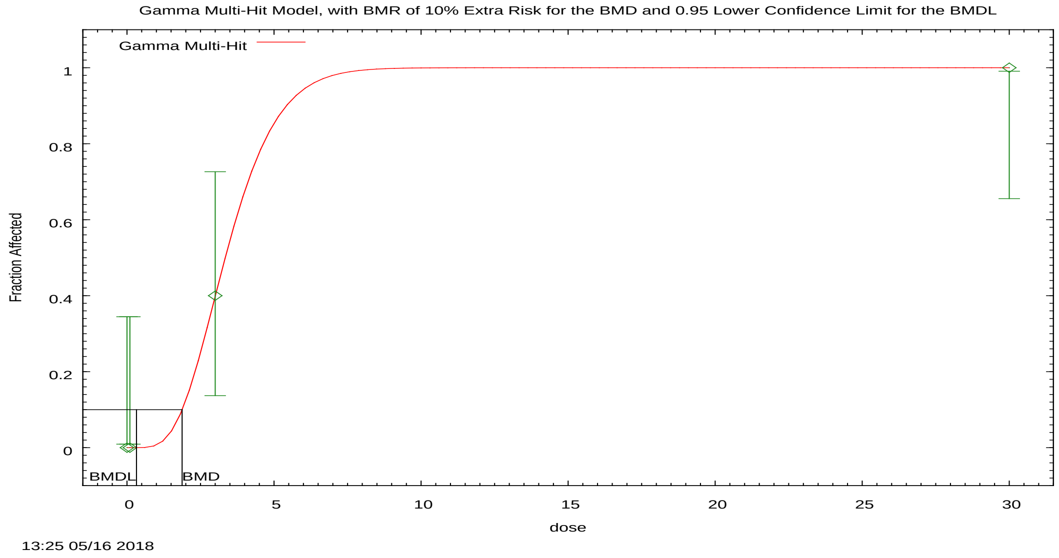

Figure 218. Plot of incidence rate by dose with fitted curve for Gamma model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Gamma Model. (Version: 2.17; Date: 6/22/2017)

The form of the probability function is: P[response]= background+(1-background)*CumGamma[slope*dose,power], where CumGamma(.) is the cumulative Gamma distribution function

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.87505

BMDL at the 95% confidence level = 0.323065

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	1.76301	0.117349
Power	6.20943	1.3

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.0000003739 96	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4602

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0   d.f = 2   P-value = 1

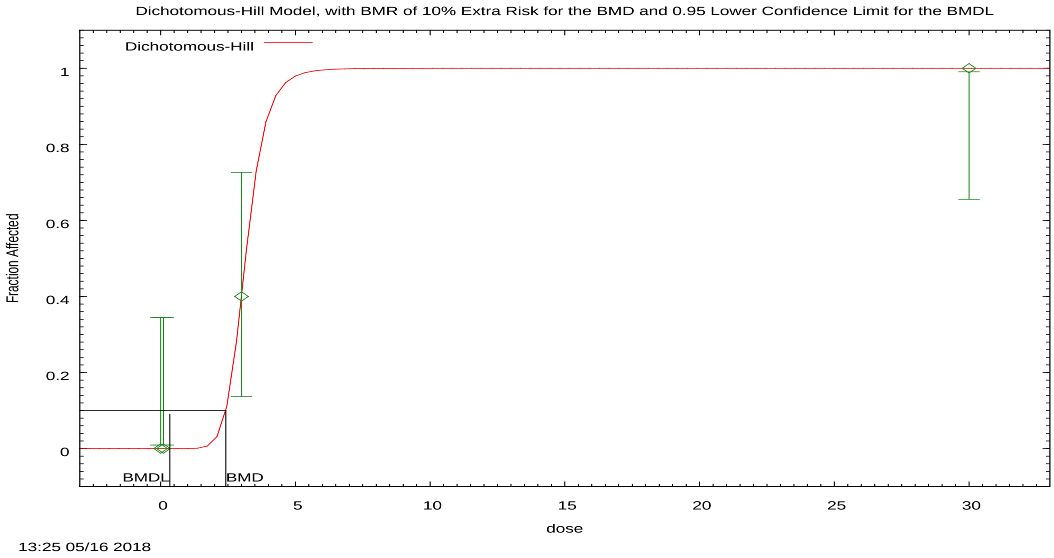

Figure 219. Plot of incidence rate by dose with fitted curve for Dichotomous-Hill model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Dichotomous Hill Model. (Version: 1.3; Date: 02/28/2013)

The form of the probability function is: P[response] = v*g +(v-v*g)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.42168

BMDL at the 95% confidence level = 0.343163

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
v	1	1
g	0	0

intercept	-9.5974E+00	-9.0088E-01
slope	8.36688	1.04549

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.000000128904	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4602

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0 d.f = 2 P-value = 1

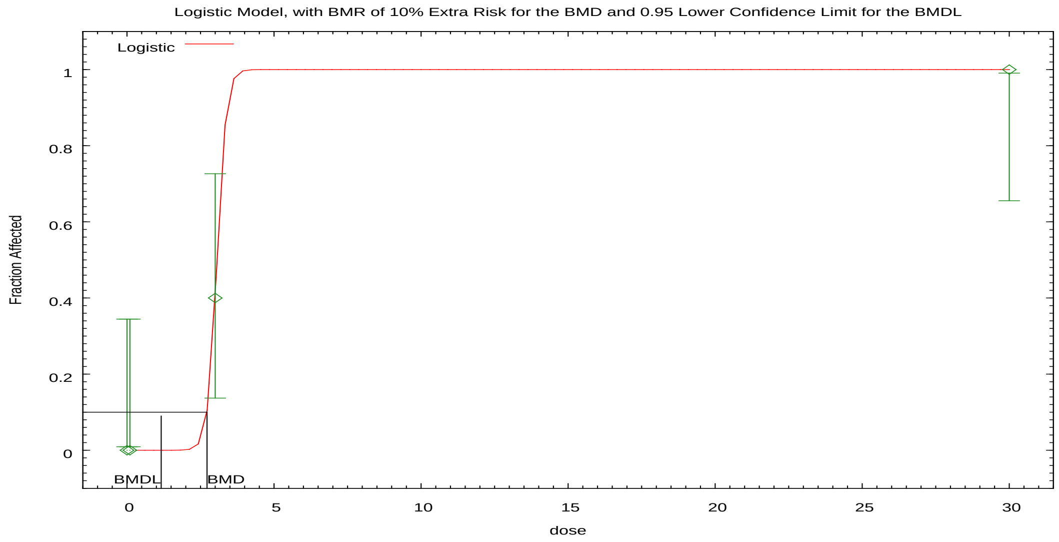

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Figure 220. Plot of incidence rate by dose with fitted curve for Logistic model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = 1/[1+EXP(-intercept-slope*dose)]

Slope parameter is not restricted

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Warning: BMDU computation is at best imprecise for these data

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.72165

BMDL at the 95% confidence level = 1.16321

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-1.9717E+01	-2.3927E+00
slope	6.43701	0.186054

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.0000001589 26	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4602

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0 d.f = 2 P-value = 1

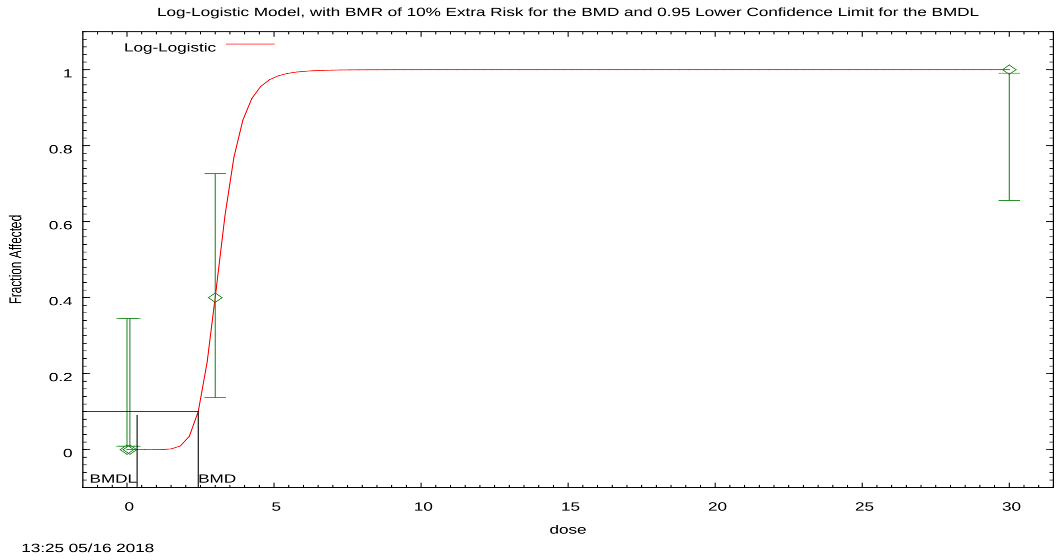

Figure 221. Plot of incidence rate by dose with fitted curve for LogLogistic model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.42169

BMDL at the 95% confidence level = 0.343163

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-9.5975E+00	-9.0088E-01
slope	8.36697	1.04549

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.000000128876	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4602

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0   d.f = 2   P-value = 1

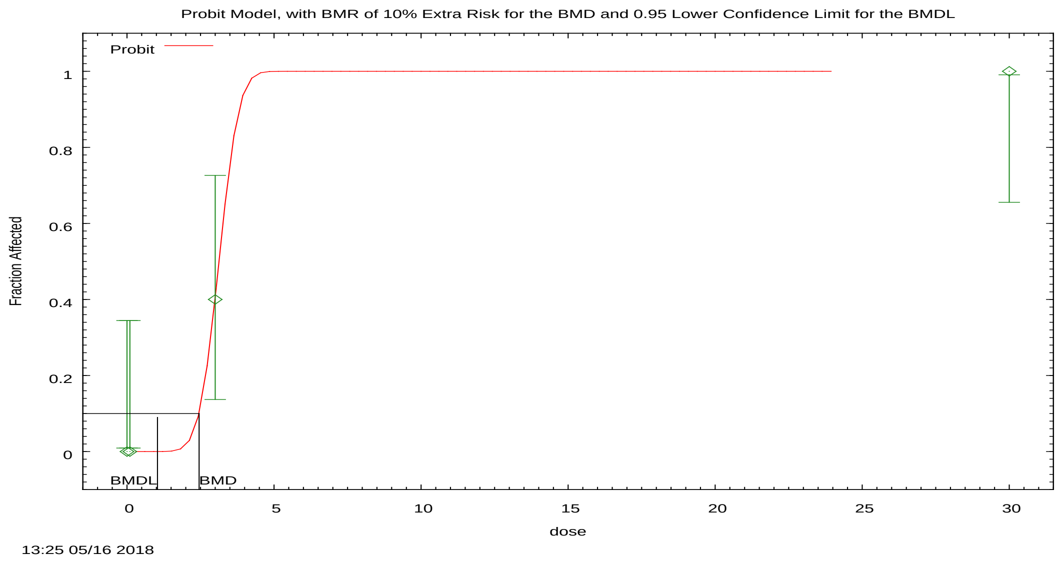

Figure 222. Plot of incidence rate by dose with fitted curve for Probit model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = CumNorm(Intercept+Slope*Dose), where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Warning: BMDU computation is at best imprecise for these data

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.45186

BMDL at the 95% confidence level = 1.03642

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-5.8808E+00	-1.6482E+00

slope	1.87582	0.123523

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.000000165492	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4602

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0 d.f = 2 P-value = 1

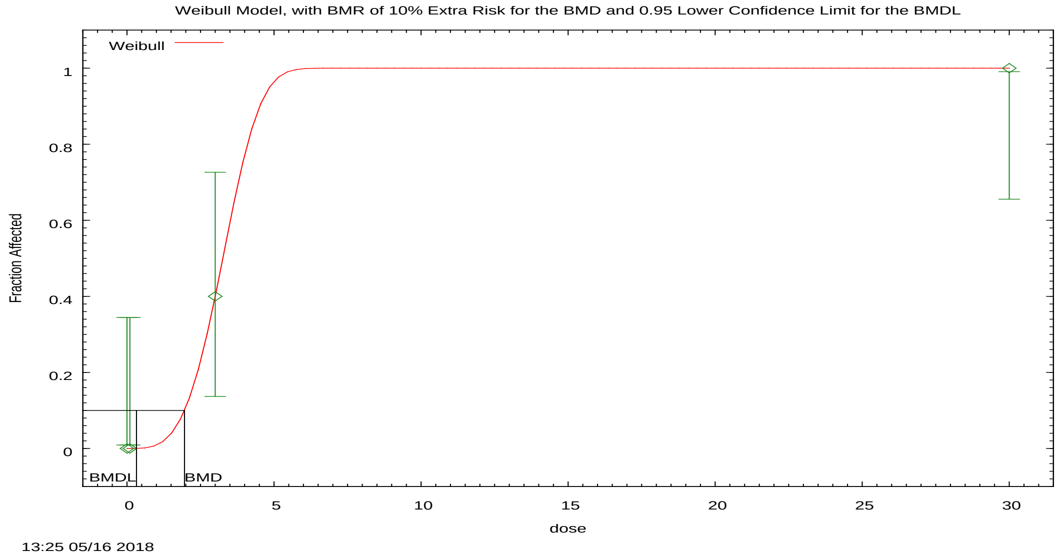

Figure 223. Plot of incidence rate by dose with fitted curve for Weibull model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Weibull Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]

Power parameter is restricted as power >=1

Warning: BMDU computation is at best imprecise for these data

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.95584

BMDL at the 95% confidence level = 0.323064

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	0.0088635	0.0799298
Power	3.69018	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.0000361794	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4603

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
3	0.4	4	4	10	0
30	1	10	10	10	0

Chi^2 = 0   d.f = 2   P-value = 1

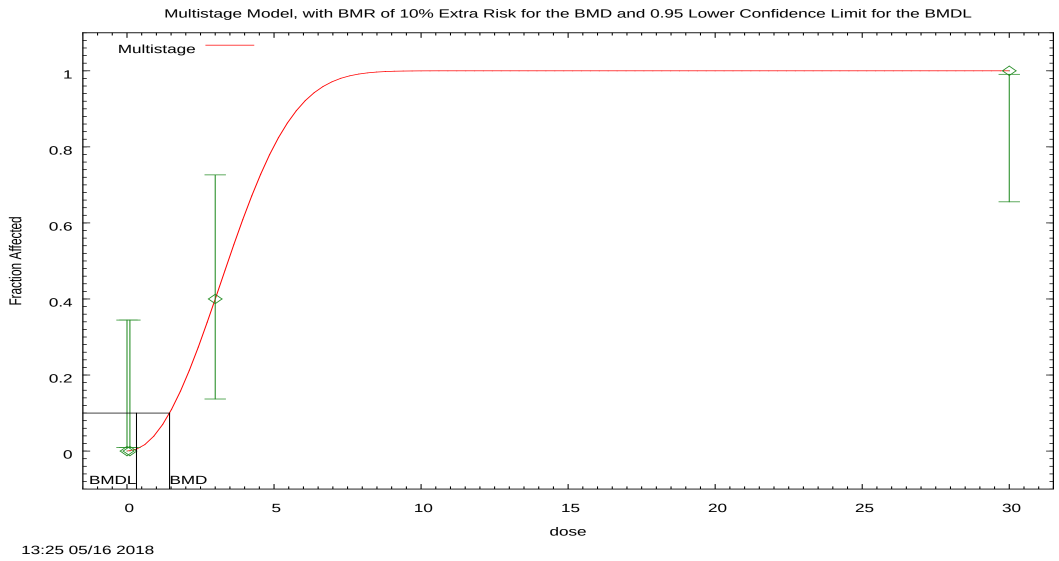

Figure 224. Plot of incidence rate by dose with fitted curve for Multistage 3° model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.44721

BMDL at the 95% confidence level = 0.322688

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0.0443672	0
Beta(3)	0.00410304	3.7049E+15

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.73	2	0.00896369	2	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 17.4692

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0.0004	0.004	0	10	-0.07
3	0.3996	3.996	4	10	0
30	1	10	10	10	0

Chi^2 = 0   d.f = 2   P-value = 0.9978

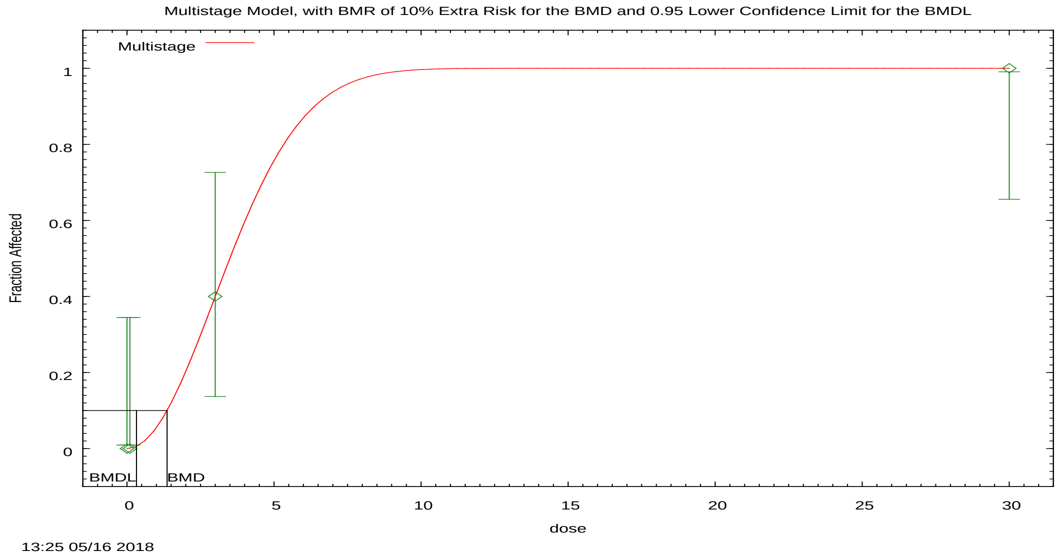

Figure 225. Plot of incidence rate by dose with fitted curve for Multistage 2° model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.36345

BMDL at the 95% confidence level = 0.322588

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0.0566762	1.1147E+17

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.74	1	0.0113435	3	1
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 15.4716

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0.0006	0.006	0	10	-0.08
3	0.3996	3.996	4	10	0
30	1	10	10	10	0

Chi^2 = 0.01 d.f = 3 P-value = 0.9999

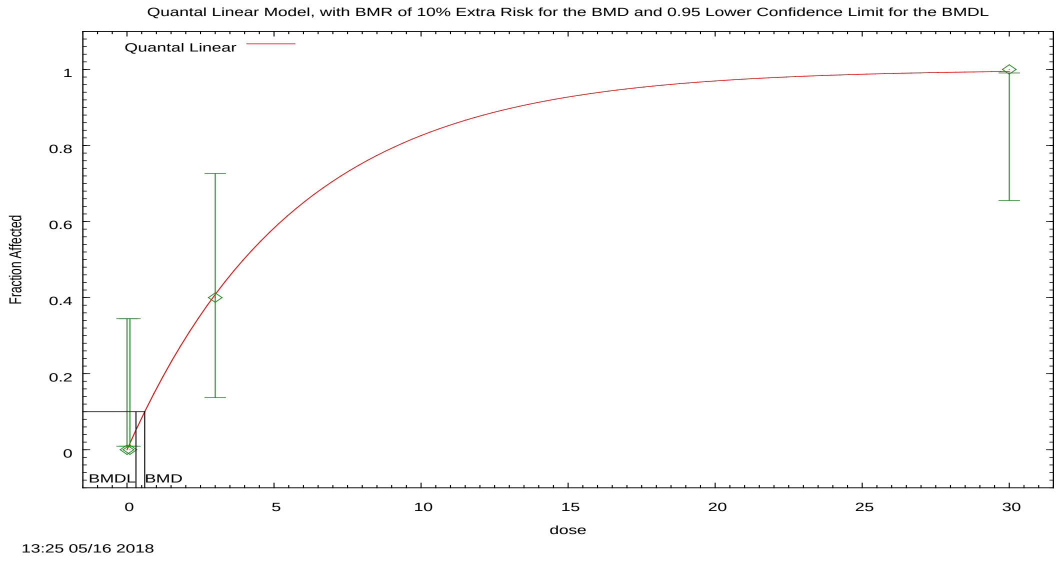

Figure 226. Plot of incidence rate by dose with fitted curve for Quantal-Linear model for Single Cell Hepatocellular Necrosis in Males (28-Day Mice); dose shown in mg/kg/day.

Quantal Linear Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.602799

BMDL at the 95% confidence level = 0.305305

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	0.174785	0.0799298
Power	n/a	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.73	4			
Fitted model	-6.96	1	0.458177	3	0.93
Reduced model	-25.9	1	38.3355	3	<.0001

AIC: = 15.9184

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid

0	0	0	0	10	0
0.1	0.0173	0.173	0	10	-0.42
3	0.4081	4.081	4	10	-0.05
30	0.9947	9.947	10	10	0.23

Chi^2 = 0.23   d.f = 3   P-value = 0.9722

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery – Hepatocellular Necrosis in Males

1.26. BMDS Summary of Hepatocellular Necrosis Males (28 Day Rats GenX)

Table 26. Summary of BMD Modeling Results for Hepatocellular Necrosis in Males (28-Day Rats)

Model[a]	Goodness of fit		BMD_{10Pct} (mg/kg/day)	$BMDL_{10Pct}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Gamma	1.000	16.217	22.8	4.89	4.67	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were not sufficiently close (> 3-fold difference), so the lowest BMDL was selected.
Dichotomous-Hill	1.000	18.217	24.9	2.72	9.14	
Logistic	1.000	16.217	28.0	14.6	1.91	
LogLogistic	1.000	16.217	25.3	4.05	6.25	
Probit	1.000	16.217	26.1	13.1	1.99	
LogProbit	**1.000**	**16.217**	**21.5**	**2.70**	**7.98**	
Weibull	1.000	16.217	25.7	4.89	5.25	
Multistage 3°	1.000	14.224	20.0	4.89	4.09	
Multistage 2°	0.998	14.289	16.4	4.84	3.39	
Quantal-Linear	0.941	14.954	10.0	4.39	2.28	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.3, 3, and 30 mg/kg/day were 0, 0, 0, 0, respectively.

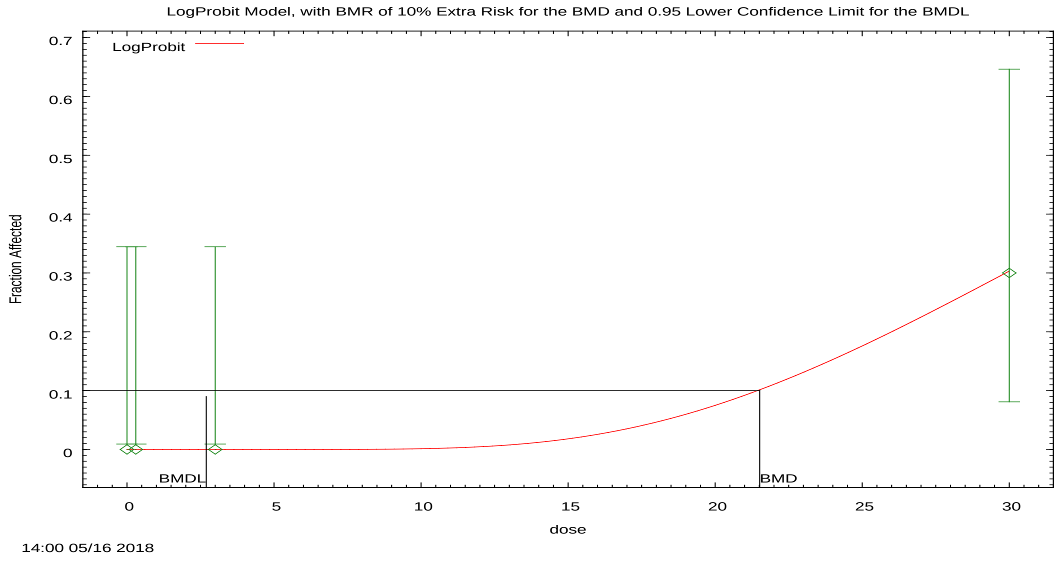

Figure 227. Plot of incidence rate by dose with fitted curve for LogProbit model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 21.5145

BMDL at the 95% confidence level = 2.69529

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-8.2701E+00	-1.5801E+00
slope	2.27735	0.253242

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	2	0.0000000801219	2	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 16.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid

0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0   d.f = 2   P-value = 1

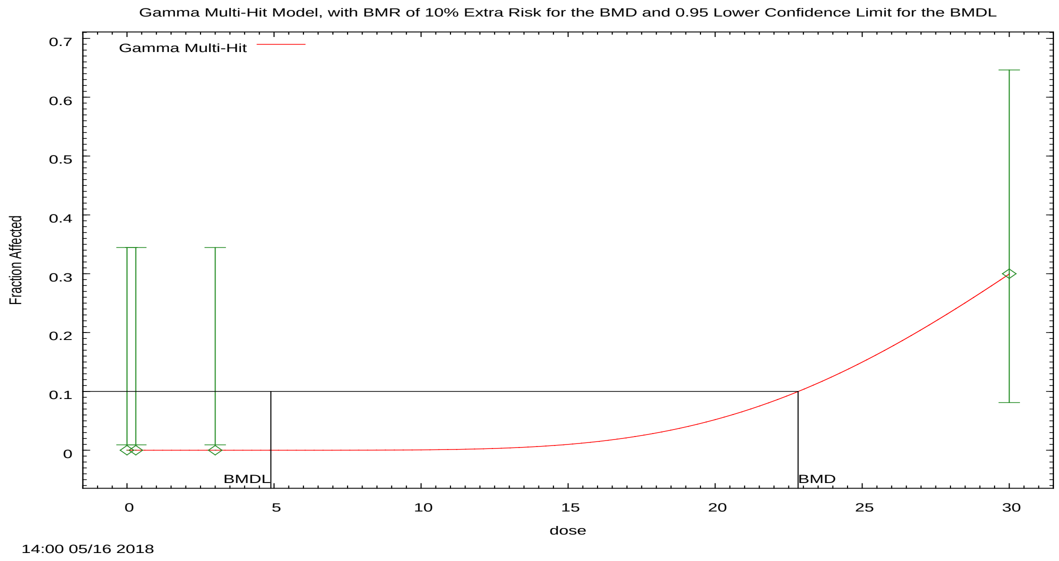

Figure 228. Plot of incidence rate by dose with fitted curve for Gamma model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Gamma Model. (Version: 2.17; Date: 6/22/2017)

The form of the probability function is: P[response]= background+(1-background)*CumGamma[slope*dose,power], where CumGamma(.) is the cumulative Gamma distribution function

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 22.8198

BMDL at the 95% confidence level = 4.89143

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	0.260092	0.0194895
Power	9.63903	1.40183

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	2	0.000000582716	2	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 16.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0   d.f = 2   P-value = 1

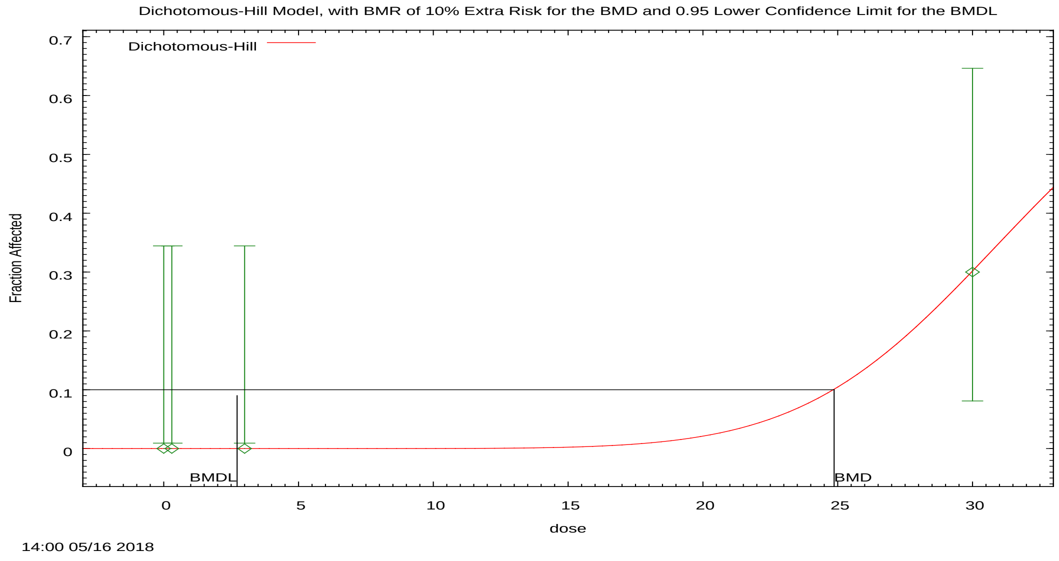

Figure 229. Plot of incidence rate by dose with fitted curve for Dichotomous-Hill model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Dichotomous Hill Model. (Version: 1.3; Date: 02/28/2013)

The form of the probability function is: P[response] = v*g +(v-v*g)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

Warning: BMDL computation is at best imprecise for these data

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 24.8662

BMDL at the 95% confidence level = 2.72083

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
v	0.789447	1
g	0	0

intercept	-2.6606E+01	-4.2523E+00
slope	7.67852	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	3	0.000000207435	1	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 18.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0   d.f = 1   P-value = 0.9997

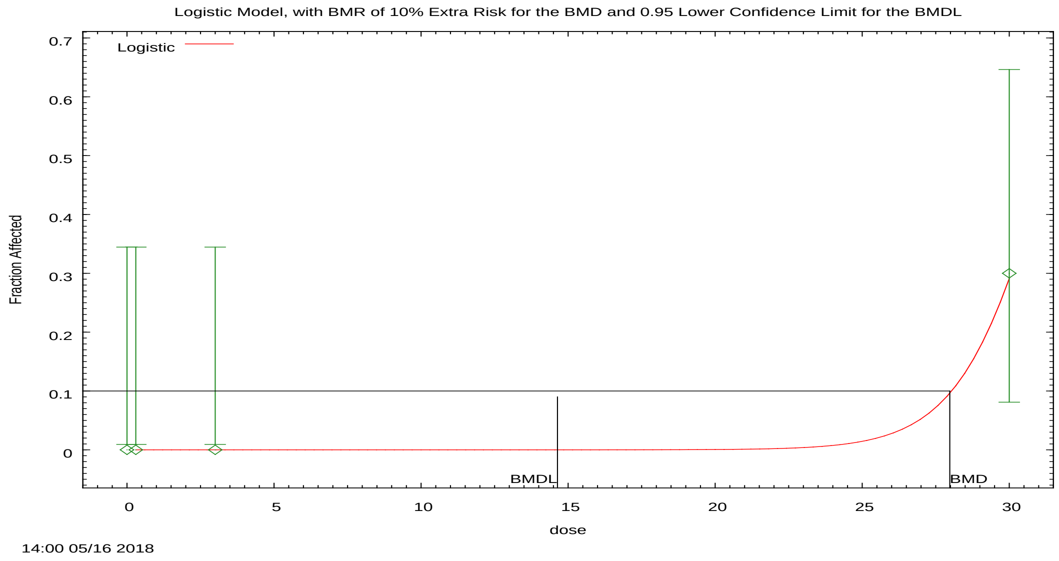

Figure 230. Plot of incidence rate by dose with fitted curve for Logistic model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = 1/[1+EXP(-intercept-slope*dose)]

Slope parameter is not restricted

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 27.9773

BMDL at the 95% confidence level = 14.6373

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-2.0869E+01	-3.1257E+00
slope	0.66738	0.0782927

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	2	0.000000166474	2	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 16.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0 d.f = 2 P-value = 1

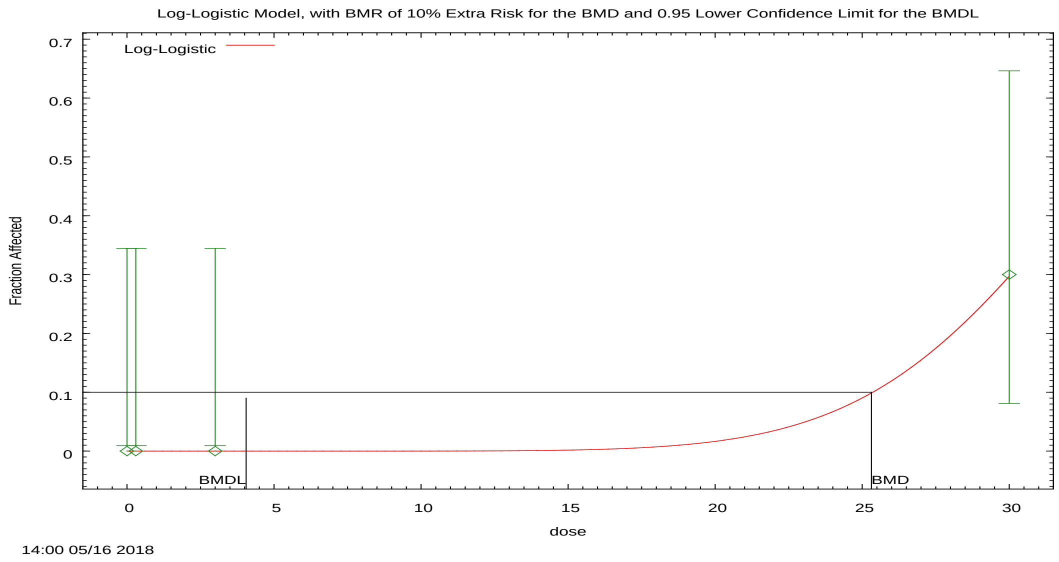

Figure 231. Plot of incidence rate by dose with fitted curve for LogLogistic model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 25.3124

BMDL at the 95% confidence level = 4.05137

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-2.7871E+01	-4.2523E+00
slope	7.94535	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	2	0.0000000972086	2	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 16.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0   d.f = 2   P-value = 1

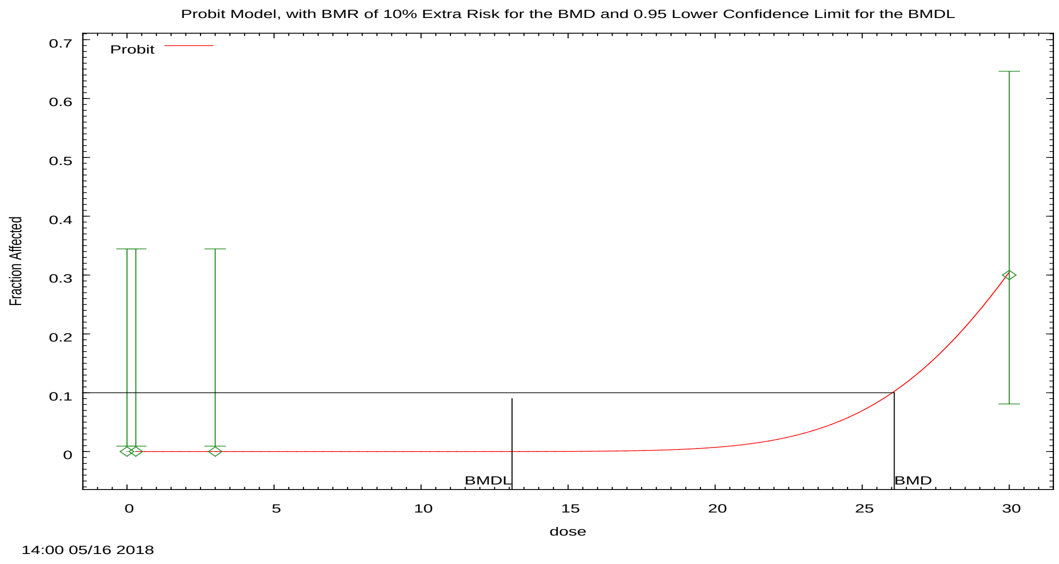

Figure 232. Plot of incidence rate by dose with fitted curve for Probit model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = CumNorm(Intercept+Slope*Dose), where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Warning: BMDU computation is at best imprecise for these data

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 26.0894

BMDL at the 95% confidence level = 13.0927

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0

intercept	-6.3329E+00	-2.1652E+00
slope	0.193616	0.0550069

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	2	0.0000000940851	2	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 16.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0 d.f = 2 P-value = 1

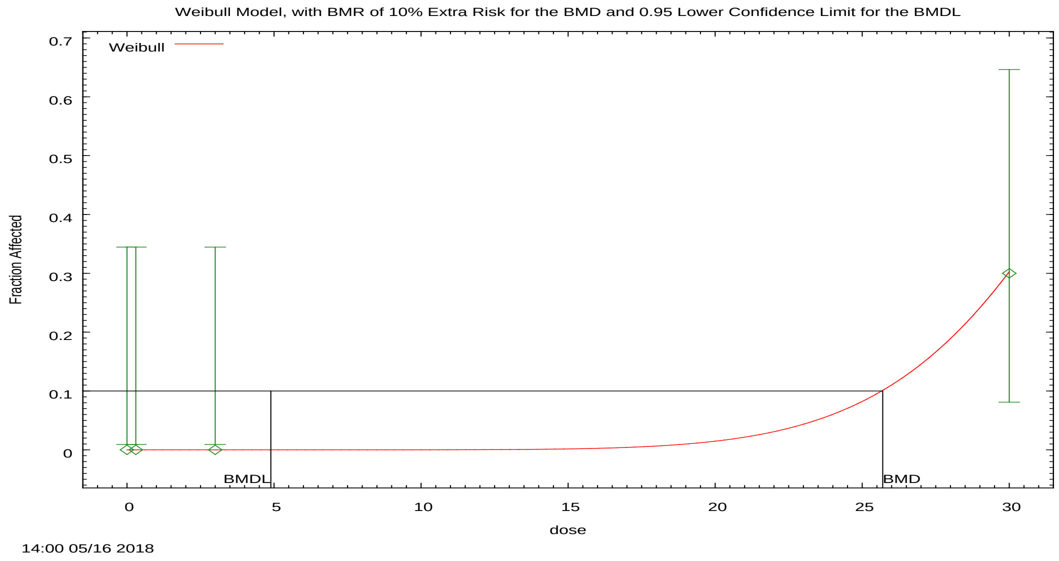

Figure 233. Plot of incidence rate by dose with fitted curve for Weibull model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Weibull Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]

Power parameter is restricted as power >=1

Warning: BMDU computation is at best imprecise for these data

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 25.6972

BMDL at the 95% confidence level = 4.89143

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	8.2683E-13	0.00385791
Power	7.87671	1.29759

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	2	0.0000000947531	2	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 16.2173

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0	0	0	10	0
30	0.3	3	3	10	0

Chi^2 = 0   d.f = 2   P-value = 1

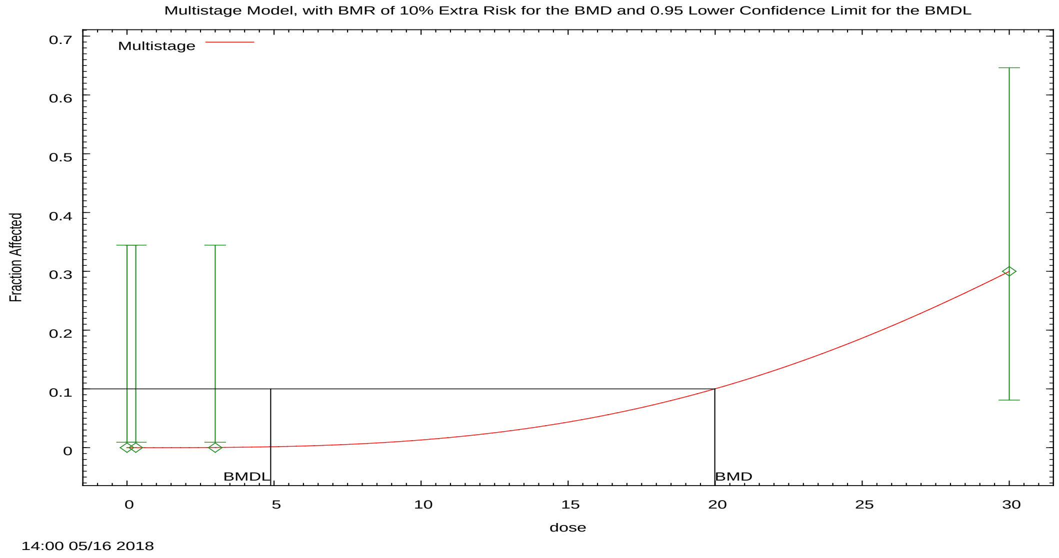

Figure 234. Plot of incidence rate by dose with fitted curve for Multistage 3° model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 19.9877

BMDL at the 95% confidence level = 4.88581

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0	0
Beta(3)	0.0000131943	0.0000132146

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.11	1	0.00713634	3	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 14.2244

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	0
3	0.0004	0.004	0	10	-0.06
30	0.2997	2.997	3	10	0

Chi^2 = 0   d.f = 3   P-value = 0.9999

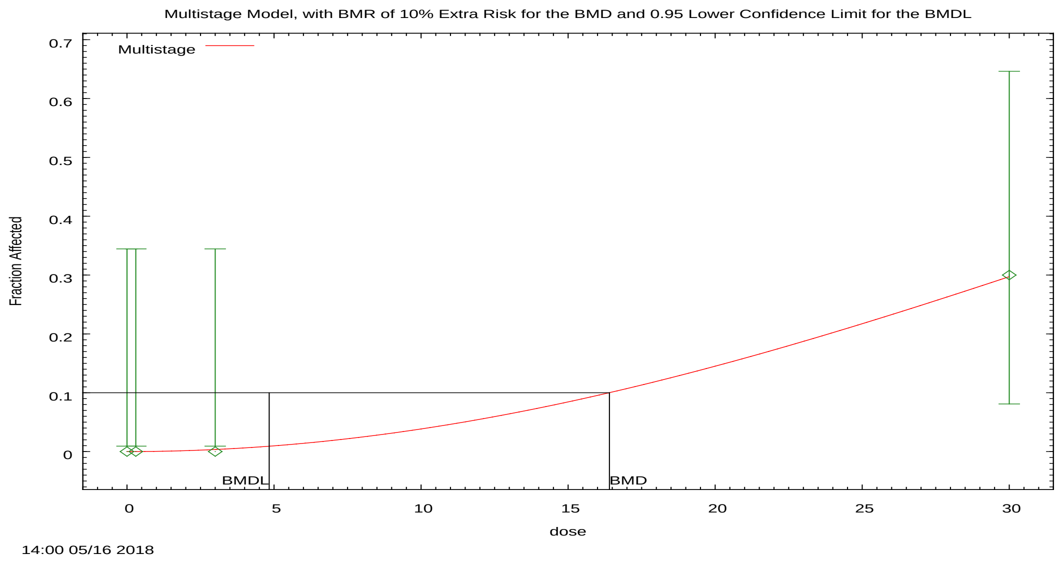

Figure 235. Plot of incidence rate by dose with fitted curve for Multistage 2° model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 16.4037

BMDL at the 95% confidence level = 4.83587

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0.000391555	0.000397609

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.14	1	0.0716147	3	1
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 14.2889

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.3	0	0	0	10	-0.02
3	0.0035	0.035	0	10	-0.19
30	0.297	2.97	3	10	0.02

Chi^2 = 0.04 d.f = 3 P-value = 0.9982

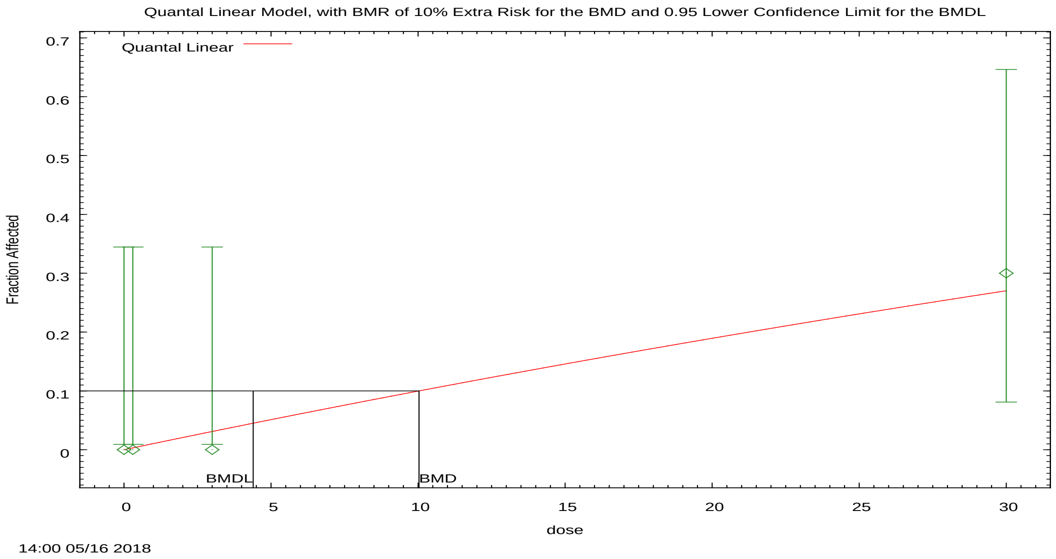

Figure 236. Plot of incidence rate by dose with fitted curve for Quantal-Linear model for Hepatocellular Necrosis in Males (28-Day Rats); dose shown in mg/kg/day.

Quantal Linear Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 10.0318

BMDL at the 95% confidence level = 4.39358

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	0.0105027	0.0106151
Power	n/a	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-6.11	4			
Fitted model	-6.48	1	0.737024	3	0.86
Reduced model	-10.66	1	9.09347	3	0.03

AIC: = 14.9543

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid

0	0	0	0	10	0
0.3	0.0031	0.031	0	10	-0.18
3	0.031	0.31	0	10	-0.57
30	0.2703	2.703	3	10	0.21

Chi^2 = 0.4 d.f = 3 P-value = 0.941

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Single Cell Hepatocellular Necrosis in Males

1.27. BMDS Summary of Single Cell Necrosis, Hepatocellular Male (90 Day Mice GenX)

Table 27. Summary of BMD Modeling Results for Single Cell Hepatocellular Necrosis in Males (90-Day Mice)

Model[a]	Goodness of fit		$\text{BMD}_{\text{10Pct}}$ (mg/kg/day)	$\text{BMDL}_{\text{10Pct}}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Gamma	1.000	2.0001	1.39	0.452	3.08	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were not sufficiently close (> 3-fold difference), so the lowest BMDL was selected. Note: visual inspection of the selected model shows that the fitted curve does not fit the data well, and a different model may be more appropriate.
Dichotomous-Hill[b]	1.000	2.00	1.40	0.466	3.00	
Logistic	1.000	4.00	2.64	0.477	5.53	
LogLogistic[c]	1.000	2.00	1.40	0.466	3.00	
Probit	1.000	4.00	2.34	0.470	4.98	
LogProbit	1.000	4.00	1.00	0.464	2.16	
Weibull	1.000	2.00	3.61	0.449	8.04	
Multistage 3°	0.994	2.1593	1.24	0.437	2.84	
Multistage 2°	0.899	3.1588	0.759	0.349	2.17	
Quantal-Linear	**0.245**	**9.6272**	**0.236**	**0.126**	**1.87**	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were 0, -0.68, -1.58, 1.1, respectively.

[b] The Dichotomous-Hill model may appear equivalent to the LogLogistic model, however differences exist in digits not displayed in the table.

[c] The LogLogistic model may appear equivalent to the Dichotomous-Hill model, however differences exist in digits not displayed in the table.

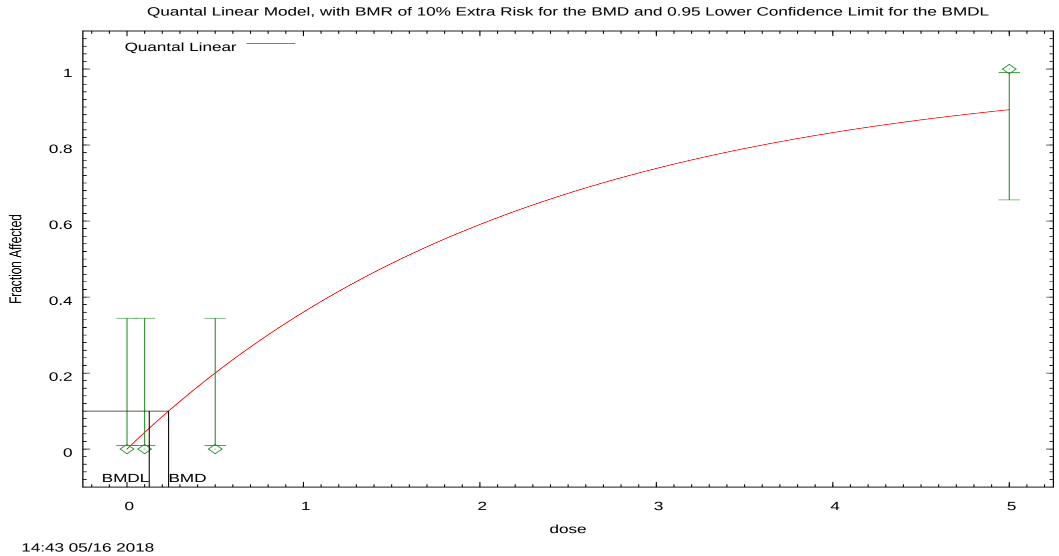

Figure 237. Plot of incidence rate by dose with fitted curve for Quantal-Linear model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Quantal Linear Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.235854

BMDL at the 95% confidence level = 0.126139

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	0.446718	0.479579
Power	n/a	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	-3.81	1	7.6272	3	0.05
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 9.6272

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0.0437	0.437	0	10	-0.68
0.5	0.2002	2.002	0	10	-1.58
5	0.8929	8.929	10	10	1.1

Chi^2 = 4.16   d.f = 3   P-value = 0.2447

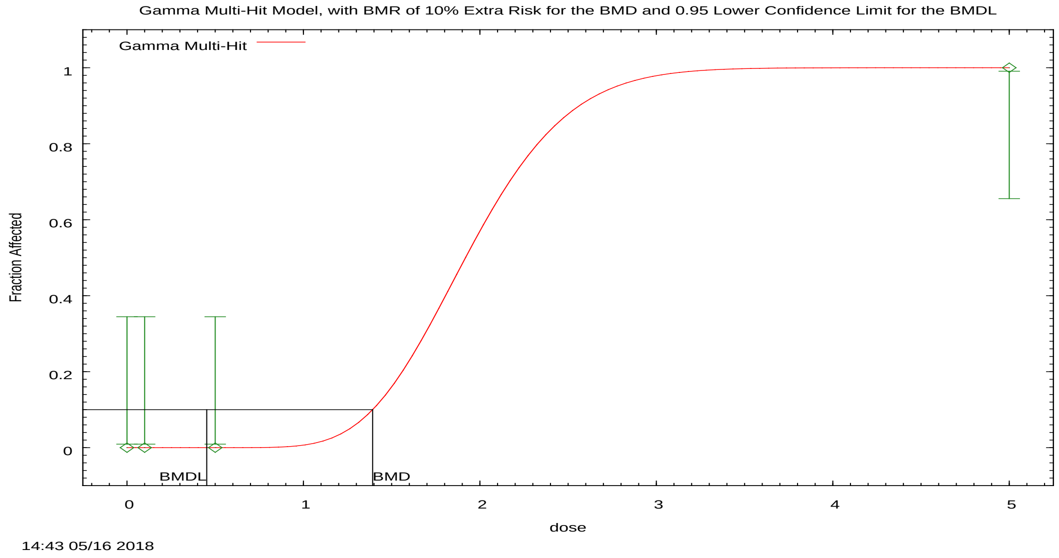

Figure 238. Plot of incidence rate by dose with fitted curve for Gamma model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Gamma Model. (Version: 2.17; Date: 6/22/2017)

The form of the probability function is: P[response]= background+(1-background)*CumGamma[slope*dose,power], where CumGamma(.) is the cumulative Gamma distribution function

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.39209

BMDL at the 95% confidence level = 0.45197

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	9.21034	1.6901
Power	18	5.22392

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	1	0.0000521053	3	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 2.00005

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0   d.f = 3   P-value = 1

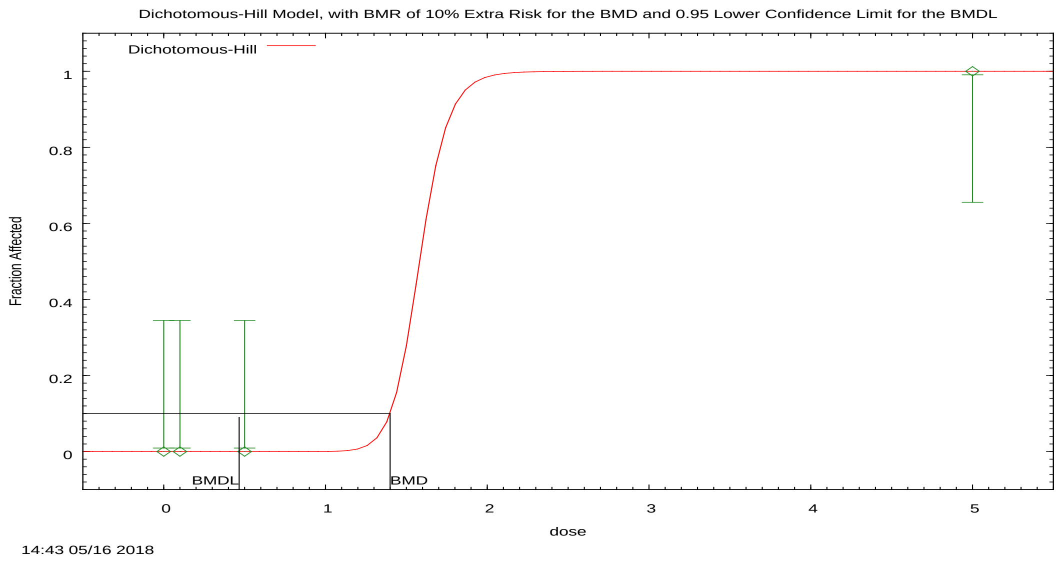

Figure 239. Plot of incidence rate by dose with fitted curve for Dichotomous-Hill model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Dichotomous Hill Model. (Version: 1.3; Date: 02/28/2013)

The form of the probability function is: P[response] = v*g +(v-v*g)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.39943

BMDL at the 95% confidence level = 0.466176

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
v	1	1
g	0	0

intercept	-8.2464E+00	-2.6100E-01
slope	18	1.63135

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	1	0.00000004	3	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 2

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0 d.f = 3 P-value = 1

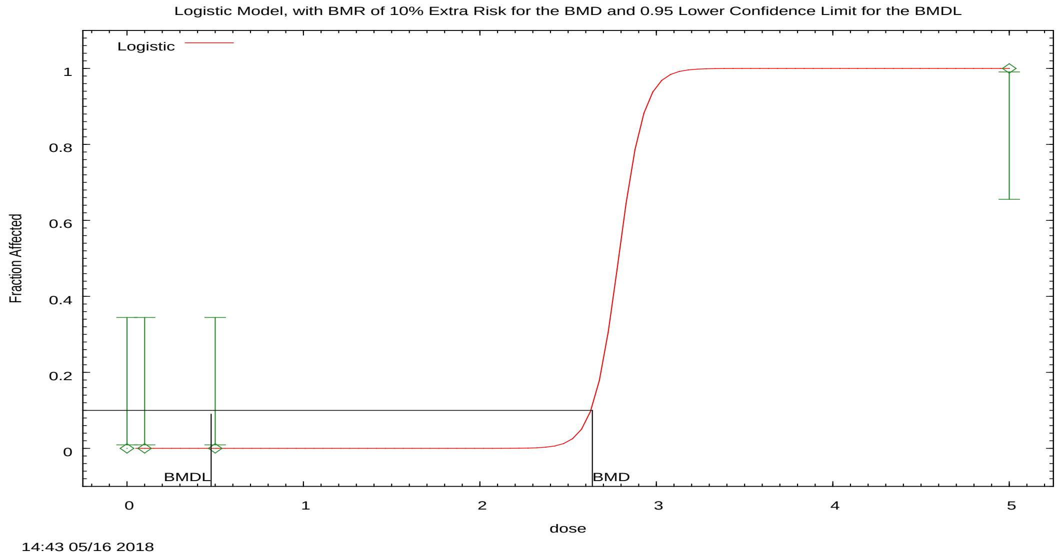

Figure 240. Plot of incidence rate by dose with fitted curve for Logistic model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = 1/[1+EXP(-intercept-slope*dose)]

Slope parameter is not restricted

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.63733

BMDL at the 95% confidence level = 0.476972

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-3.9049E+01	-3.2840E+00
slope	13.9732	1.25836

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	2	1.06359E-12	2	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 4

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid

0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0   d.f = 2   P-value = 1

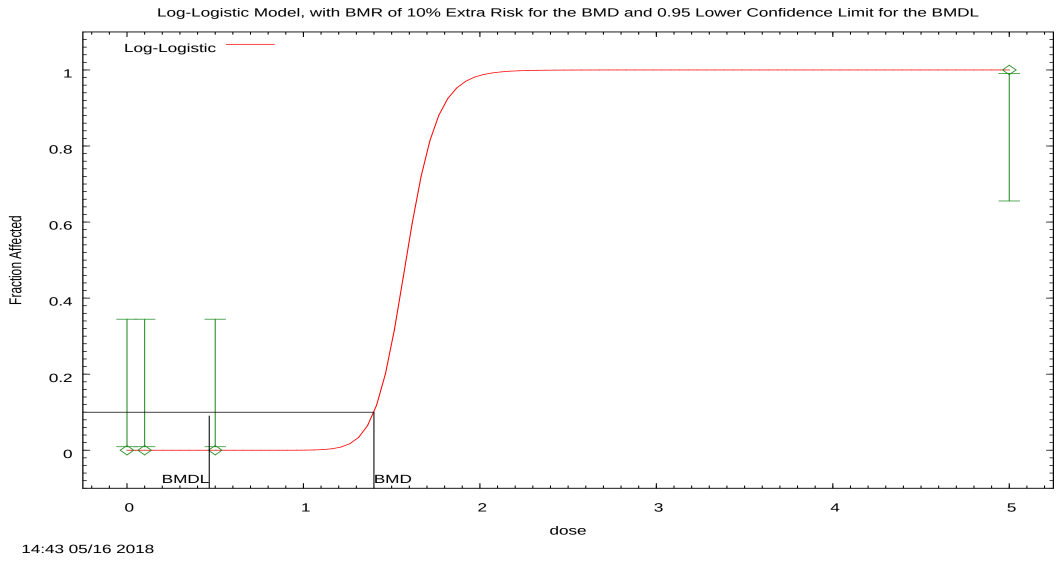

Figure 241. Plot of incidence rate by dose with fitted curve for LogLogistic model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.39944

BMDL at the 95% confidence level = 0.466176

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-8.2466E+00	-2.6100E-01
slope	18	1.63135

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	1	0.00000004	3	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 2

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0 d.f = 3 P-value = 1

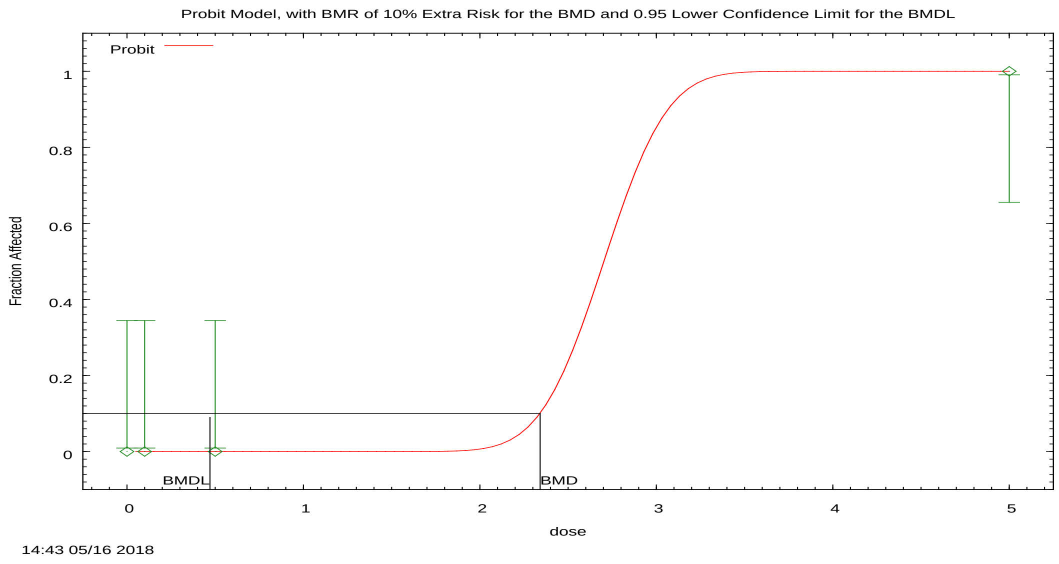

Figure 242. Plot of incidence rate by dose with fitted curve for Probit model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = CumNorm(Intercept+Slope*Dose), where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 2.34148

BMDL at the 95% confidence level = 0.470268

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-9.5416E+00	-2.2679E+00
slope	3.52773	0.839812

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	2	7.99361E-14	2	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 4

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0   d.f = 2   P-value = 1

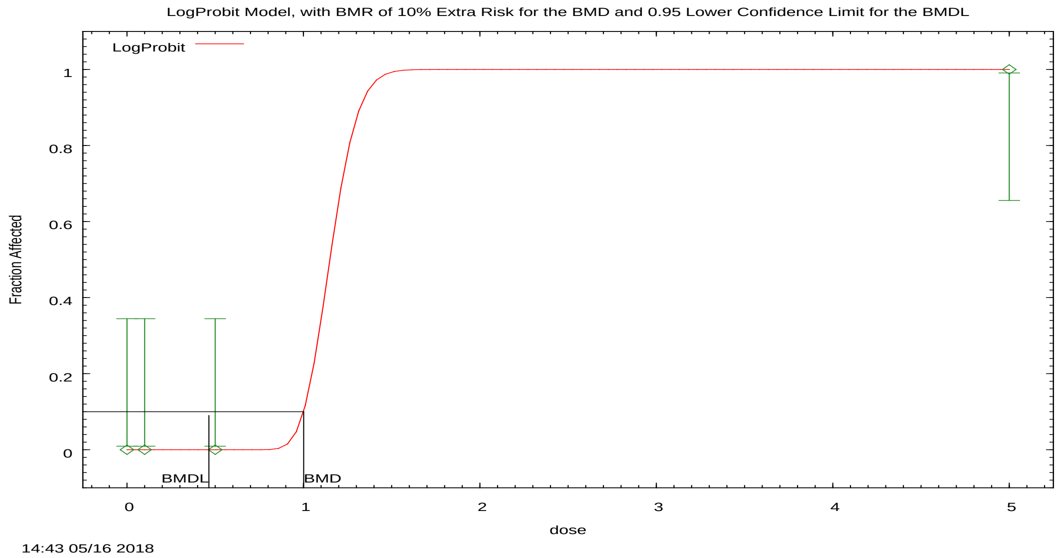

Figure 243. Plot of incidence rate by dose with fitted curve for LogProbit model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.00134

BMDL at the 95% confidence level = 0.464193

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-1.2939E+00	-1.4493E-01
slope	9.24923	0.905889

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	2	1.31006E-13	2	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 4

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0   d.f = 2   P-value = 1

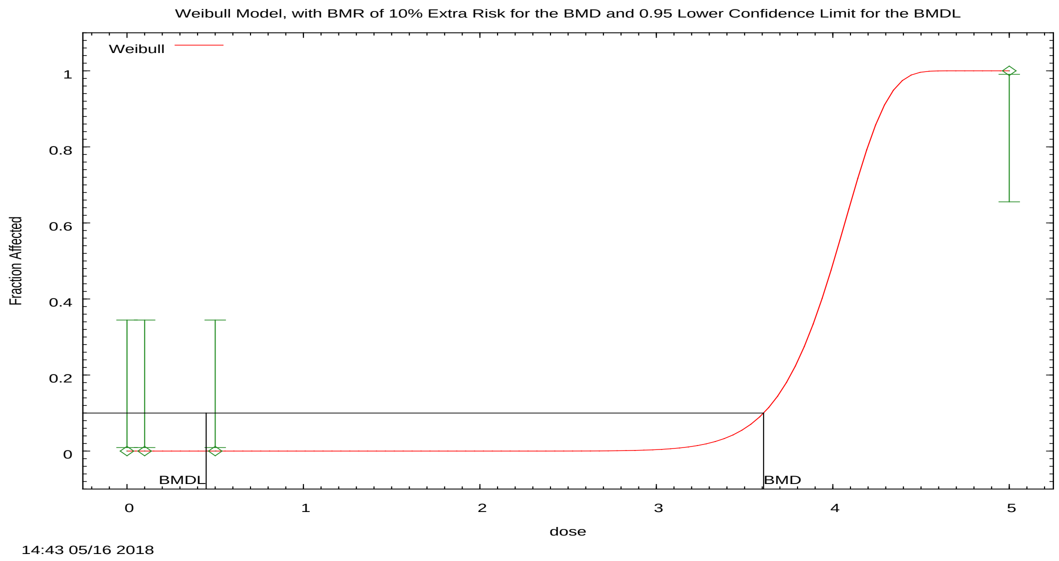

Figure 244. Plot of incidence rate by dose with fitted curve for Weibull model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Weibull Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 3.60768

BMDL at the 95% confidence level = 0.448866

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0833333
Slope	9.8305E-12	0.0591487
Power	18	2.30036

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	0	1	0	3	1
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 2

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0	0	0	10	0
0.5	0	0	0	10	0
5	1	10	10	10	0

Chi^2 = 0 d.f = 3 P-value = 1

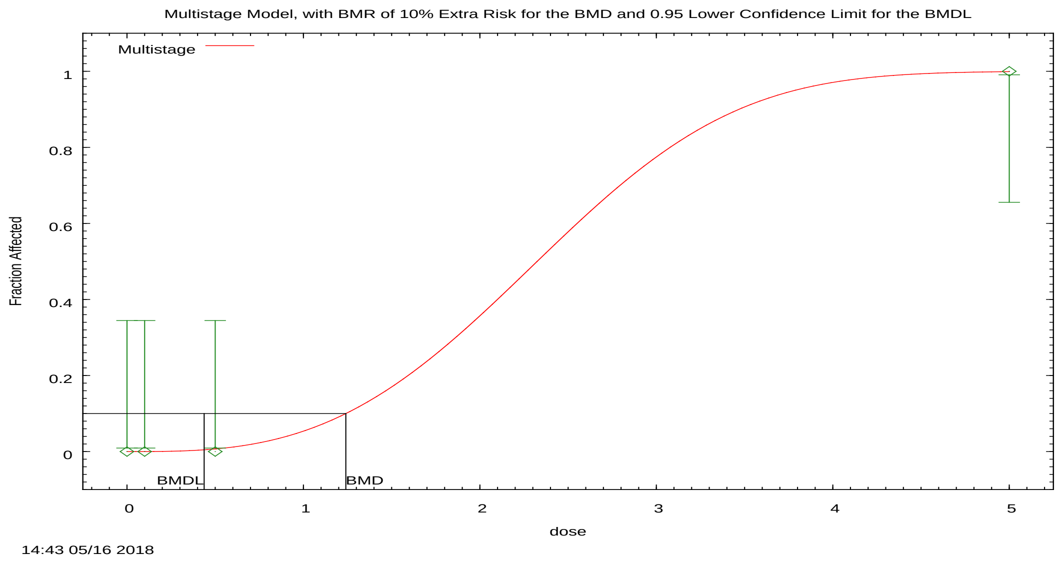

Figure 245. Plot of incidence rate by dose with fitted curve for Multistage 3° model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1.24024

BMDL at the 95% confidence level = 0.437315

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0	0

Beta(3)	0.0552283	8.0027E+17

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	-0.08	1	0.15927	3	0.98
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 2.15927

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	10	0
0.1	0.0001	0.001	0	10	-0.02
0.5	0.0069	0.069	0	10	-0.26
5	0.999	9.99	10	10	0.1

Chi^2 = 0.08 d.f = 3 P-value = 0.9941

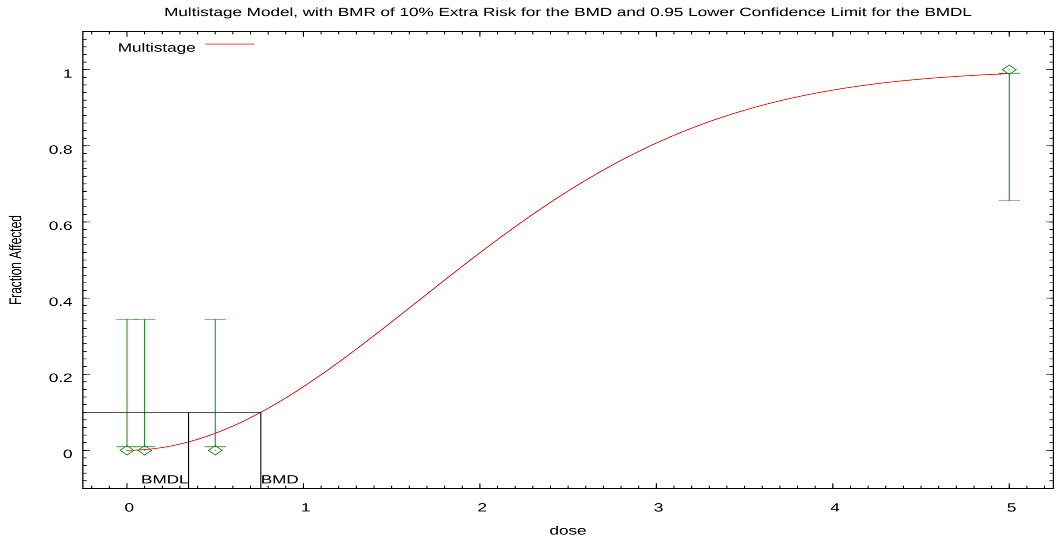

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Figure 246. Plot of incidence rate by dose with fitted curve for Multistage 2° model for Single Cell Hepatocellular Necrosis in Males (90-Day Mice); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.758655

BMDL at the 95% confidence level = 0.349241

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0.183058	4.0136E+18

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	0	4			
Fitted model	-0.58	1	1.1588	3	0.76
Reduced model	-22.49	1	44.9868	3	<.0001

AIC: = 3.1588

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid

0	0	0	0	10	0
0.1	0.0018	0.018	0	10	-0.14
0.5	0.0447	0.447	0	10	-0.68
5	0.9897	9.897	10	10	0.32

Chi^2 = 0.59 d.f = 3 P-value = 0.8986

BMDS WIZARD OUTPUT REPORT

BMDS Summary for Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice – Single Cell Hepatocellular Necrosis in Males

1.28. BMDS Summary of Liver - necrosis, single cell Males (Reproductive Mice GenX)

Table 28. Summary of BMD Modeling Results for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice)

Model[a]	Goodness of fit		BMD_{10Pct} (mg/kg/day)	$BMDL_{10Pct}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Gamma	0.992	47.275	0.399	0.172	2.32	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Dichotomous-Hill LogLogistic	0.977	47.275	0.464	0.253	1.83	
Logistic	0.969	45.337	0.362	0.253	1.43	
Probit	0.960	45.358	0.349	0.236	1.48	
LogProbit	0.977	47.275	0.443	0.248	1.79	
Weibull	1.000	47.275	0.407	0.166	2.45	
Multistage 3°	1.000	47.275	0.408	0.145	2.81	
Multistage 2°	**0.995**	**45.285**	**0.368**	**0.151**	**2.43**	
Quantal-Linear	0.261	48.991	0.162	0.106	1.53	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were 0.07, -0.08, 0.01, 0, respectively.

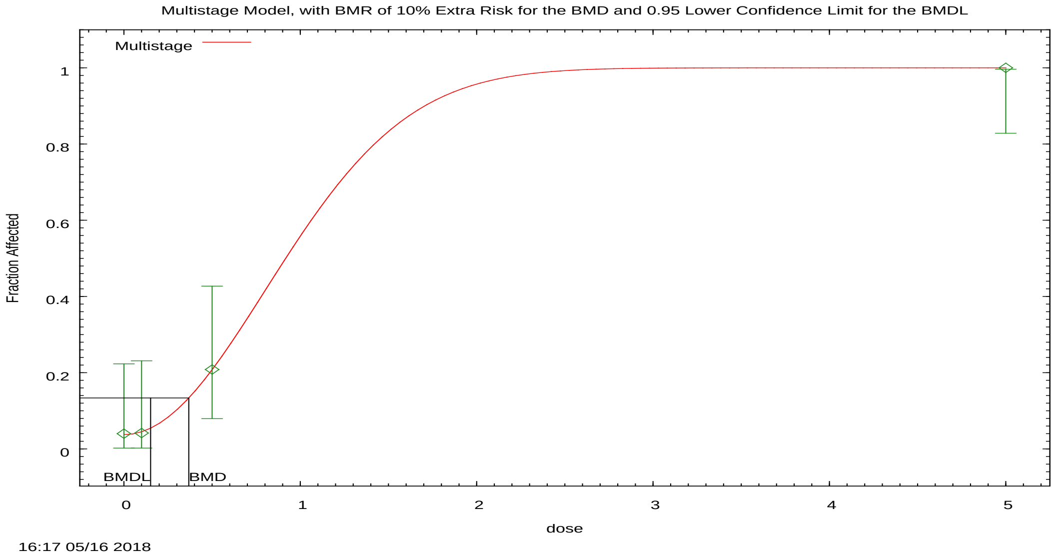

Figure 247. Plot of incidence rate by dose with fitted curve for Multistage 2° model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.36786

BMDL at the 95% confidence level = 0.151378

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0374803	0
Beta(1)	0	0
Beta(2)	0.778596	4.0136E+18

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	2	0.0105166	2	0.99
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 45.2851

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0375	0.937	1	25	0.07
0.1	0.0449	1.079	1	24	-0.08
0.5	0.2077	4.985	5	24	0.01

5	1	24	24	24	0

Chi^2 = 0.01 d.f = 2 P-value = 0.9948

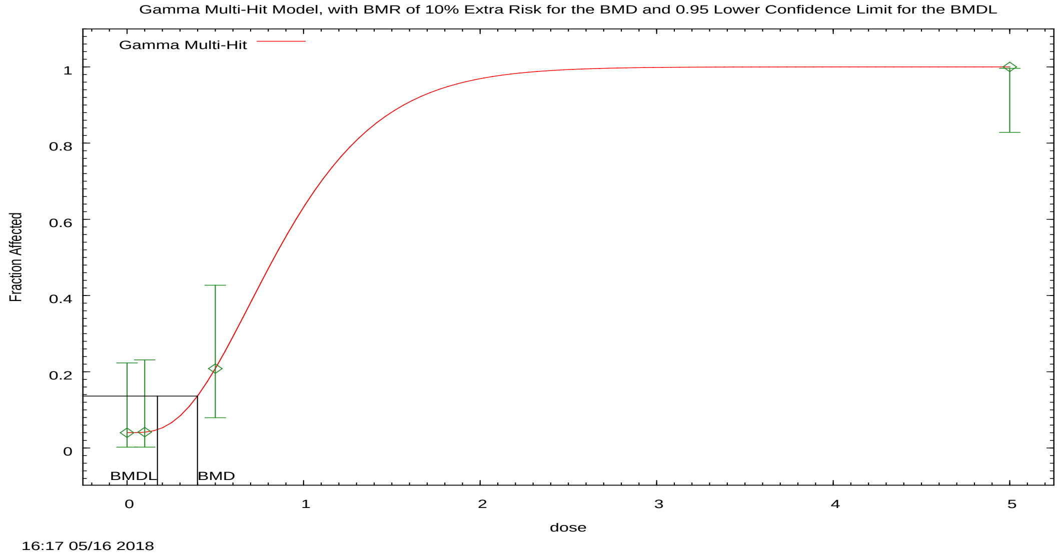

Figure 248. Plot of incidence rate by dose with fitted curve for Gamma model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Gamma Model. (Version: 2.17; Date: 6/22/2017)

The form of the probability function is: P[response]= background+(1-background)*CumGamma[slope*dose,power], where CumGamma(.) is the cumulative Gamma distribution function

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.398912

BMDL at the 95% confidence level = 0.172112

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0402031	0.0740741
Slope	4.06483	1.66473
Power	3.81438	4.20395

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	3	0.000137835	1	0.99
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 47.2747

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0402	1.005	1	25	0
0.1	0.0414	0.995	1	24	0.01
0.5	0.2084	5	5	24	0
5	1	24	24	24	0.01

Chi^2 = 0   d.f = 1   P-value = 0.9921

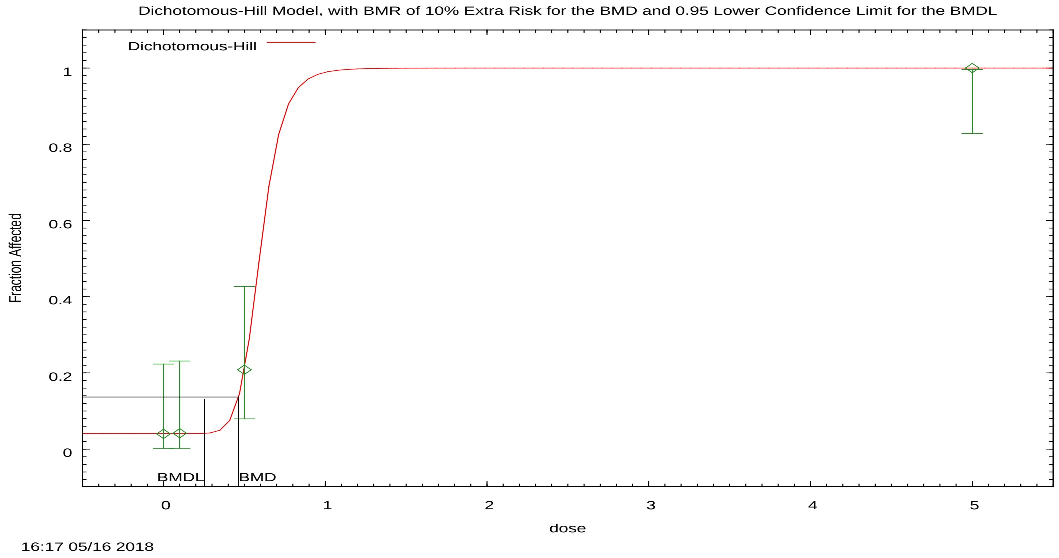

Figure 249. Plot of incidence rate by dose with fitted curve for Dichotomous-Hill model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Dichotomous Hill Model. (Version: 1.3; Date: 02/28/2013)

The form of the probability function is: P[response] = v*g +(v-v*g)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.464183

BMDL at the 95% confidence level = 0.253434

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
v	1	1
g	0.0408163	0.04
intercept	4.45404	-1.3477E-01
slope	8.66641	2.6015

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	3	0.000868905	1	0.98
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 47.2754

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0408	1.02	1	25	-0.02
0.1	0.0408	0.98	1	24	0.02
0.5	0.2083	5	5	24	0
5	1	24	24	24	0

Chi^2 = 0 d.f = 1 P-value = 0.9765

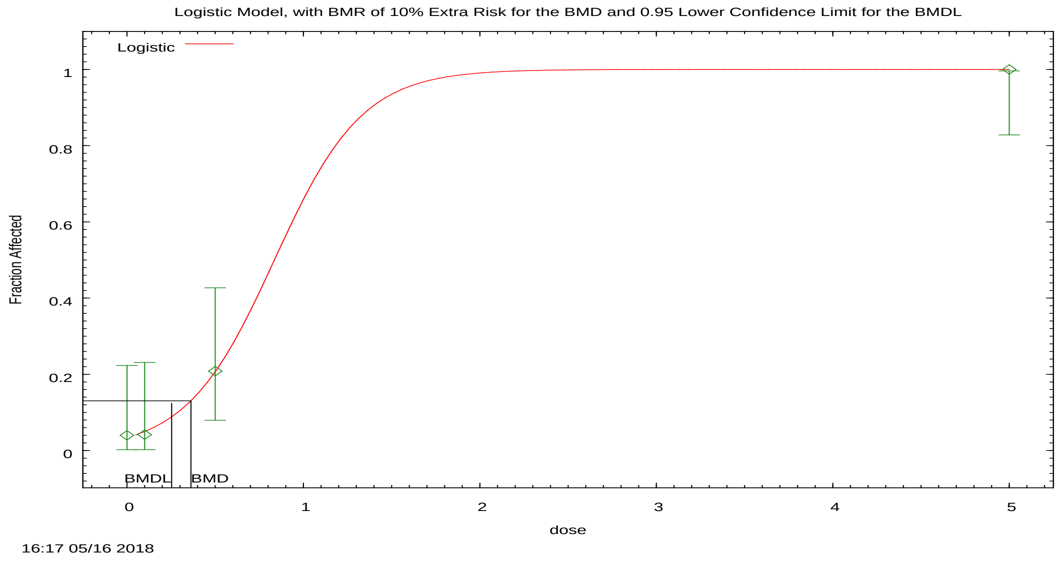

Figure 250. Plot of incidence rate by dose with fitted curve for Logistic model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = 1/[1+EXP(-intercept-slope*dose)]

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.362437

BMDL at the 95% confidence level = 0.253091

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-3.3521E+00	-2.5489E+00
slope	4.01471	1.29949

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.67	2	0.062635	2	0.97
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 45.3372

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0338	0.846	1	25	0.17

0.1	0.0497	1.193	1	24	-0.18
0.5	0.2067	4.961	5	24	0.02
5	1	24	24	24	0

Chi^2 = 0.06   d.f = 2   P-value = 0.9693

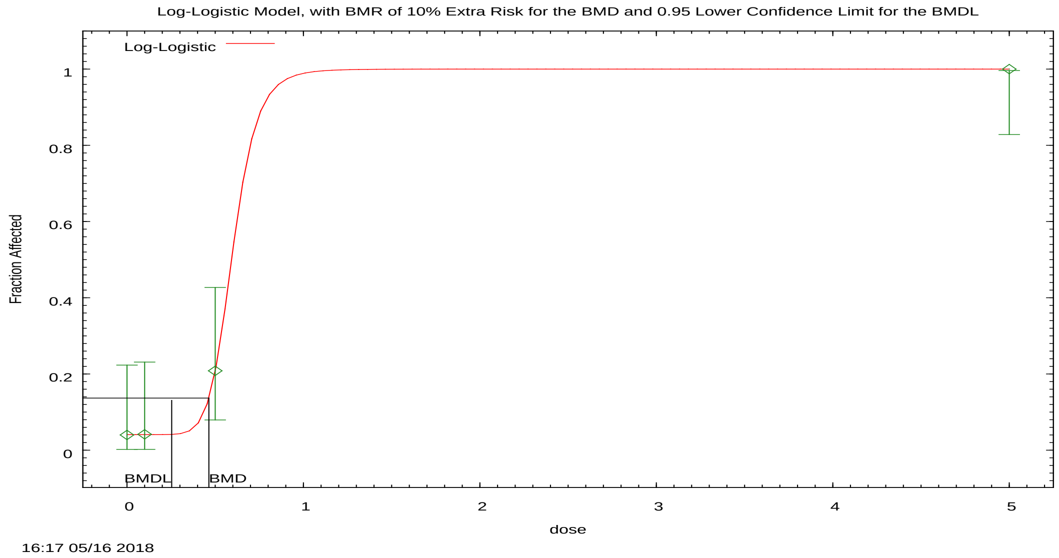

Figure 251. Plot of incidence rate by dose with fitted curve for LogLogistic model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Logistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.464183

BMDL at the 95% confidence level = 0.253434

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0.0408163	0.04
intercept	4.45403	-1.3477E-01
slope	8.66639	2.6015

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	3	0.000868905	1	0.98
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 47.2754

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0408	1.02	1	25	-0.02
0.1	0.0408	0.98	1	24	0.02
0.5	0.2083	5	5	24	0
5	1	24	24	24	0

Chi^2 = 0 d.f = 1 P-value = 0.9765

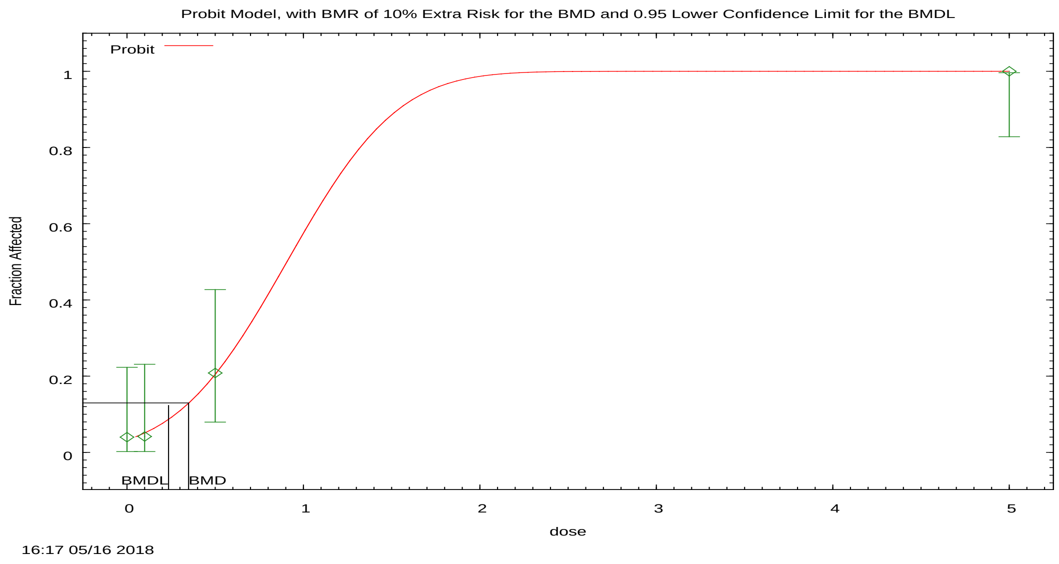

Figure 252. Plot of incidence rate by dose with fitted curve for Probit model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = CumNorm(Intercept+Slope*Dose), where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.34906

BMDL at the 95% confidence level = 0.235626

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-1.8366E+00	-1.5650E+00
slope	2.03222	0.78084

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.68	2	0.0831399	2	0.96
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 45.3577

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0331	0.828	1	25	0.19
0.1	0.0512	1.229	1	24	-0.21
0.5	0.206	4.943	5	24	0.03
5	1	24	24	24	0

Chi^2 = 0.08 d.f = 2 P-value = 0.9596

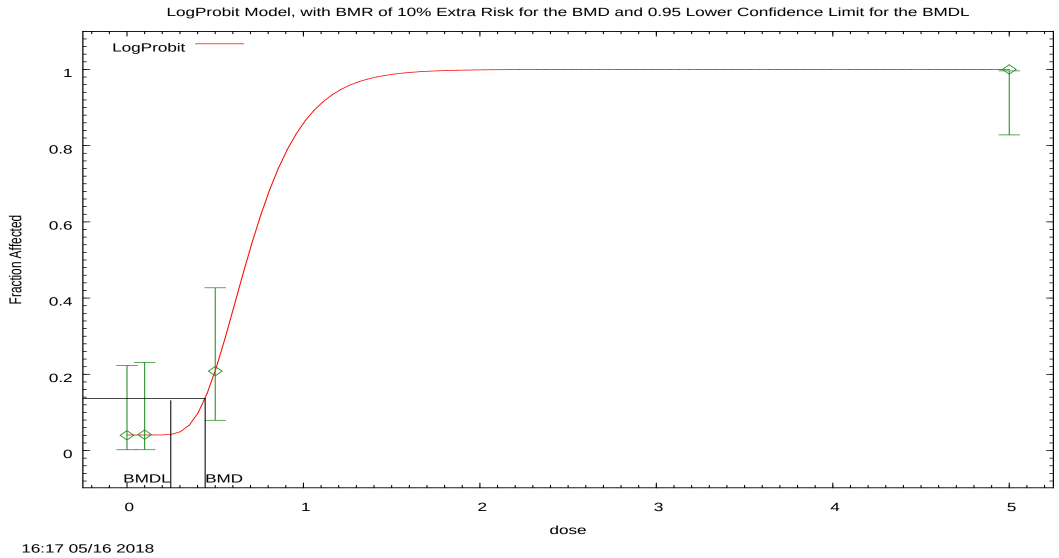

Figure 253. Plot of incidence rate by dose with fitted curve for LogProbit model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Probit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),where CumNorm(.) is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.44311

BMDL at the 95% confidence level = 0.248138

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0.0408136	0.04
intercept	1.04702	-1.2059E-02
slope	2.86087	1.27378

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	3	0.000868989	1	0.98
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 47.2754

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0408	1.02	1	25	-0.02
0.1	0.0408	0.98	1	24	0.02
0.5	0.2083	5	5	24	0
5	1	24	24	24	0

Chi^2 = 0   d.f = 1   P-value = 0.9765

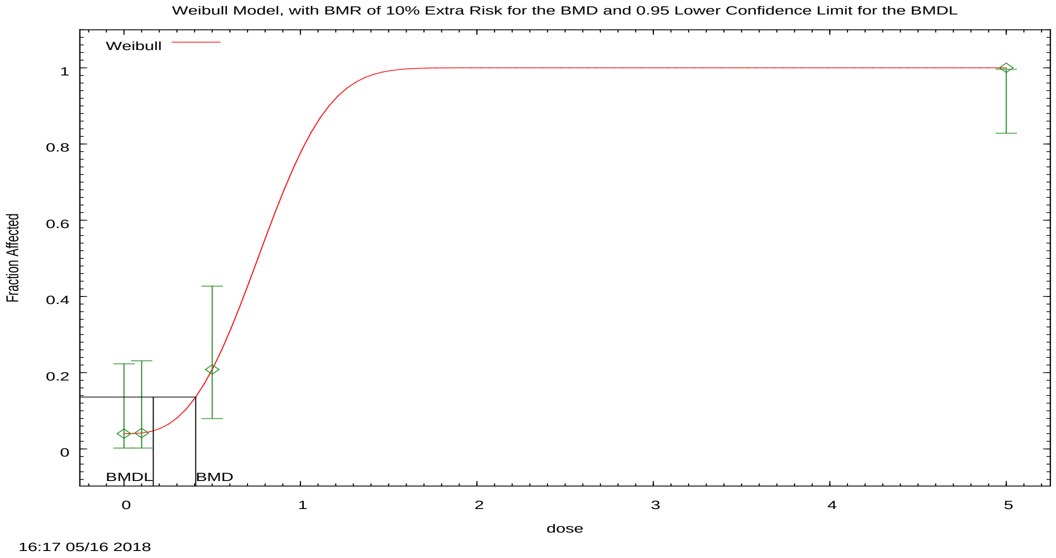

Figure 254. Plot of incidence rate by dose with fitted curve for Weibull model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Weibull Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]

Power parameter is restricted as power >=1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.406554

BMDL at the 95% confidence level = 0.166046

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0399917	0.0740741
Slope	1.45834	0.126527
Power	2.9195	2.00352

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	3	0.000000310824	1	1
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 47.2746

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.04	1	1	25	0
0.1	0.0417	1	1	24	0
0.5	0.2083	4.999	5	24	0
5	1	24	24	24	0

Chi^2 = 0 d.f = 1 P-value = 0.9996

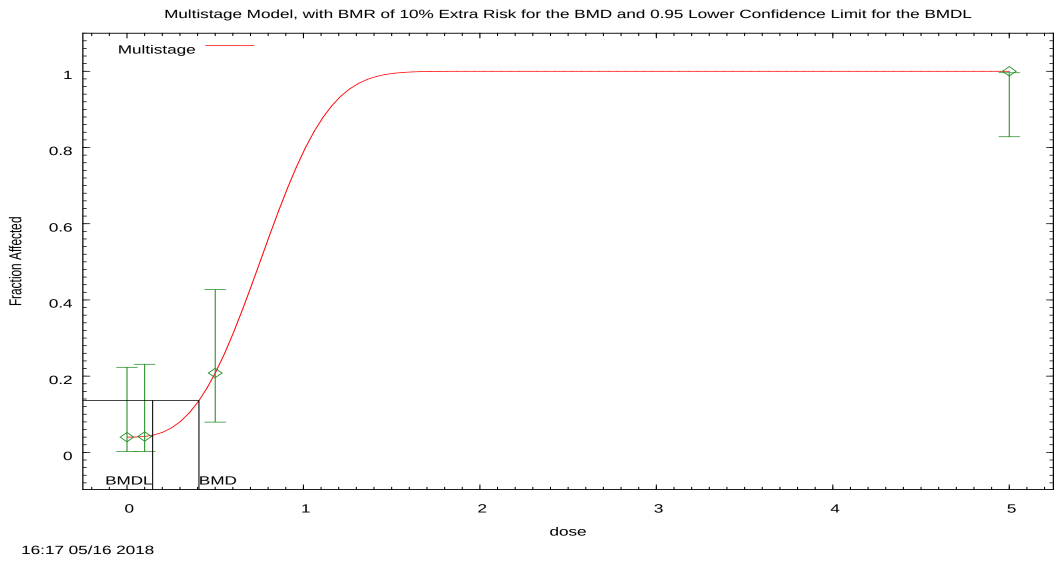

Figure 255. Plot of incidence rate by dose with fitted curve for Multistage 3° model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.407818

BMDL at the 95% confidence level = 0.14537

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.04	0
Beta(1)	0	0
Beta(2)	0.0244097	0

Beta(3)	1.49352	8.0027E+17

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-20.64	3	1.42109E-14	1	1
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 47.2746

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.04	1	1	25	0
0.1	0.0417	1	1	24	0
0.5	0.2083	5	5	24	0
5	1	24	24	24	0

Chi^2 = 0 d.f = 1 P-value = 1

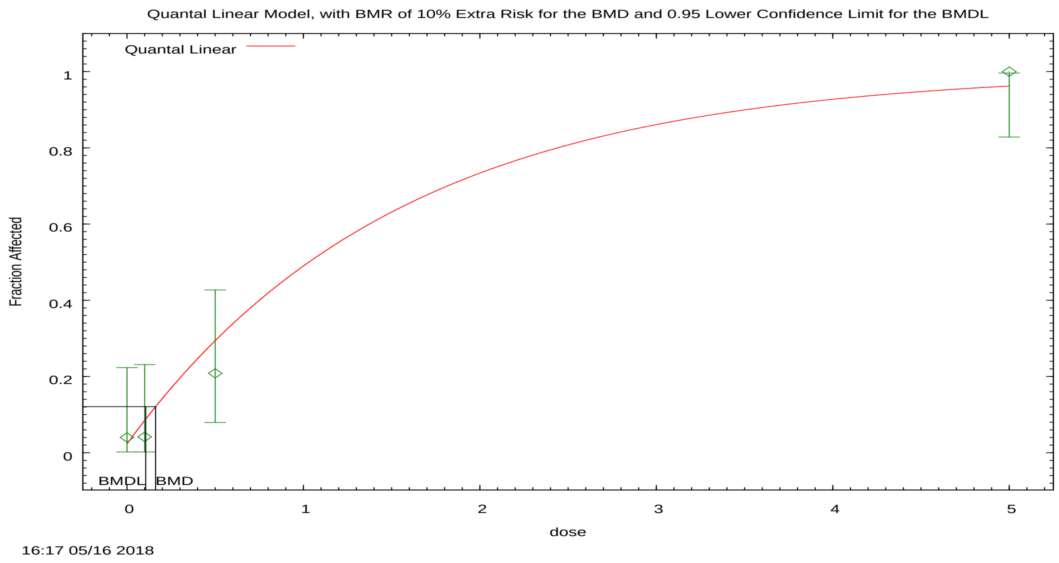

Figure 256. Plot of incidence rate by dose with fitted curve for Quantal-Linear model for Single Cell Hepatocellular Necrosis in Males (Reproductive Mice); dose shown in mg/kg/day.

Quantal Linear Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-slope*dose)]

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 0.162062

BMDL at the 95% confidence level = 0.106106

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0231249	0.0740741
Slope	0.650123	0.636227
Power	n/a	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.64	4			
Fitted model	-22.5	2	3.71609	2	0.16
Reduced model	-60.78	1	80.2777	3	<.0001

AIC: = 48.9907

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid

0	0.0231	0.578	1	25	0.56
0.1	0.0846	2.031	1	24	-0.76
0.5	0.2942	7.061	5	24	-0.92
5	0.9621	23.091	24	24	0.97

Chi^2 = 2.68 d.f = 2 P-value = 0.2614

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Liver Weight to Brain Weight (g/100g) in Males

1.29. BMDS Summary of Liver weight to brain weight (g/100g brain) Males (28 Day Mice GenX)

Table 29. Summary of BMD Modeling Results for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	<0.0001	442.40	8.93	6.93	1.29	Only one model met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from this model.
Exponential (M4) **Exponential (M5)[c]**	**0.726**	**392.82**	**0.296**	**0.194**	**1.53**	
Hill	0.871	392.73	0.238	error[d]	error	
Power[e] Linear	<0.0001	437.54	5.13	2.88	1.78	
Polynomial 3°[f] Polynomial 2°	<0.0001	435.43	0.554	0.368	1.50	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were -0.21, 0.31, -0.31, 0.23, respectively.
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.
[d] BMD or BMDL computation failed for this model.
[e] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model.

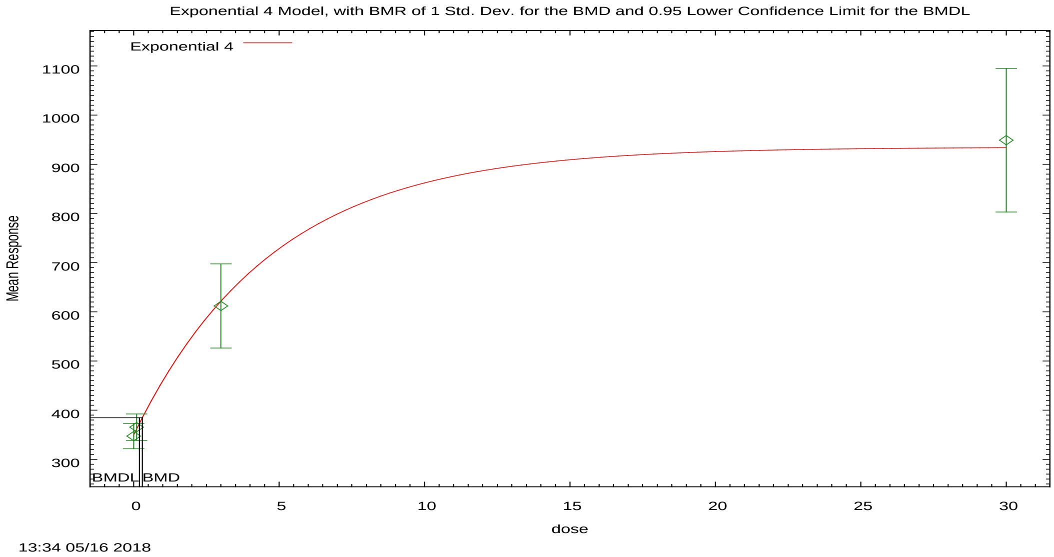

Figure 257. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.295612

BMDL at the 95% confidence level = 0.193746

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-14.3917	-13.9147
rho	3.67106	3.60787
a	349.675	329.948
b	0.208529	0.0890268
c	2.67347	3.01988
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347.3	349.7	35.93	34.98	-0.2134
0.1	10	365.4	361.8	37.57	37.23	0.3138
3	10	612	621.8	119.7	100.6	-0.3098
30	10	949	933.7	204.1	212.2	0.227

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.757	5	429.5139
A2	-191.0033	8	398.0066
A3	-191.3498	6	394.6996
R	-243.798	2	491.596
4	-191.4114	5	392.8228

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.6	6	<0.0001
Test 2	37.51	3	<0.0001
Test 3	0.693	2	0.7072
Test 6a	0.1232	1	0.7256

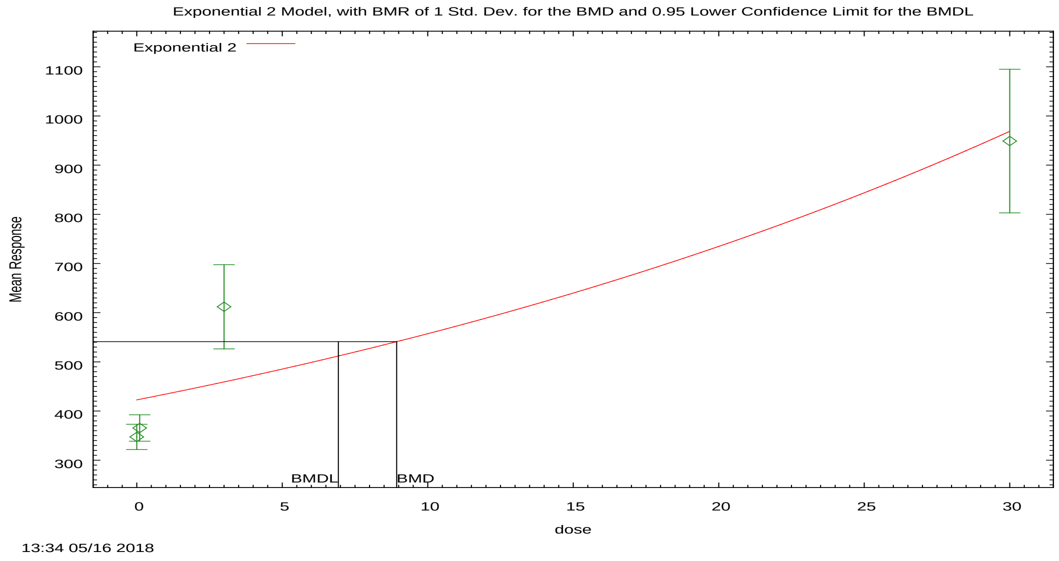

Figure 258. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 8.93061

BMDL at the 95% confidence level = 6.92769

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.29827	-13.9147
rho	1.36434	3.60787
a	422.623	409.803
b	0.0276507	0.0290228
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347.3	422.6	35.93	118.4	-2.012
0.1	10	365.4	423.8	37.57	118.6	-1.556
3	10	612	459.2	119.7	125.3	3.857
30	10	949	968.7	204.1	208.5	-0.3002

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.757	5	429.5139
A2	-191.0033	8	398.0066
A3	-191.3498	6	394.6996
R	-243.798	2	491.596
2	-217.1983	4	442.3966

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.6	6	<0.0001
Test 2	37.51	3	<0.0001
Test 3	0.693	2	0.7072
Test 4	51.7	2	<0.0001

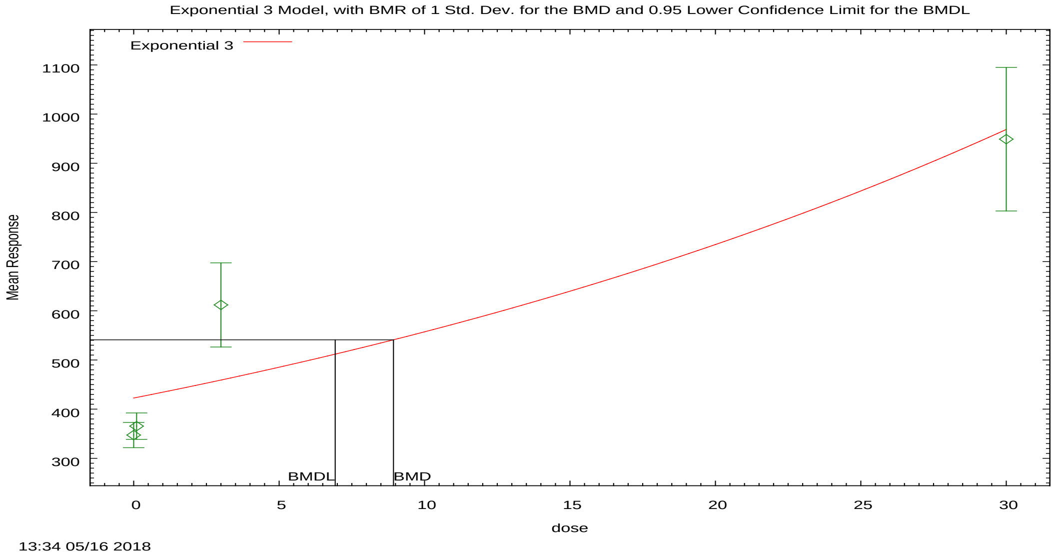

Figure 259. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 8.93061

BMDL at the 95% confidence level = 6.92769

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.29827	-13.9147
rho	1.36434	3.60787
a	422.623	409.803
b	0.0276507	0.0290228
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347.3	422.6	35.93	118.4	-2.012
0.1	10	365.4	423.8	37.57	118.6	-1.556
3	10	612	459.2	119.7	125.3	3.857
30	10	949	968.7	204.1	208.5	-0.3002

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.757	5	429.5139
A2	-191.0033	8	398.0066
A3	-191.3498	6	394.6996
R	-243.798	2	491.596
3	-217.1983	4	442.3966

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.6	6	<0.0001
Test 2	37.51	3	<0.0001
Test 3	0.693	2	0.7072
Test 5a	51.7	2	<0.0001

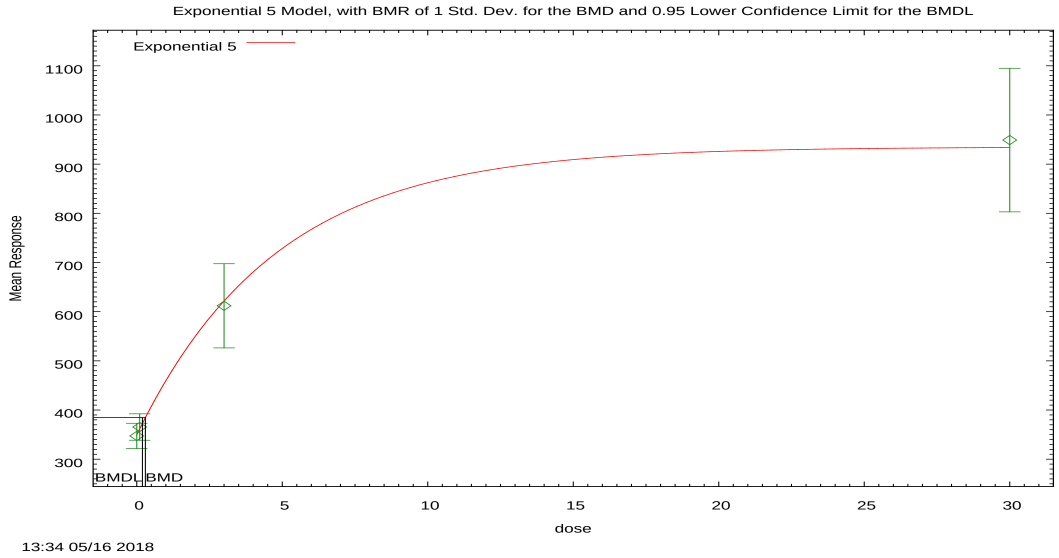

Figure 260. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.295612

BMDL at the 95% confidence level = 0.193746

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-14.3917	-13.9147
rho	3.67106	3.60787
a	349.675	329.948
b	0.208529	0.0890268

c	2.67347	3.01988
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347.3	349.7	35.93	34.98	-0.2134
0.1	10	365.4	361.8	37.57	37.23	0.3138
3	10	612	621.8	119.7	100.6	-0.3098
30	10	949	933.7	204.1	212.2	0.227

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.757	5	429.5139
A2	-191.0033	8	398.0066
A3	-191.3498	6	394.6996
R	-243.798	2	491.596
5	-191.4114	5	392.8228

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.6	6	<0.0001
Test 2	37.51	3	<0.0001
Test 3	0.693	2	0.7072
Test 7a	0.1232	1	0.7256

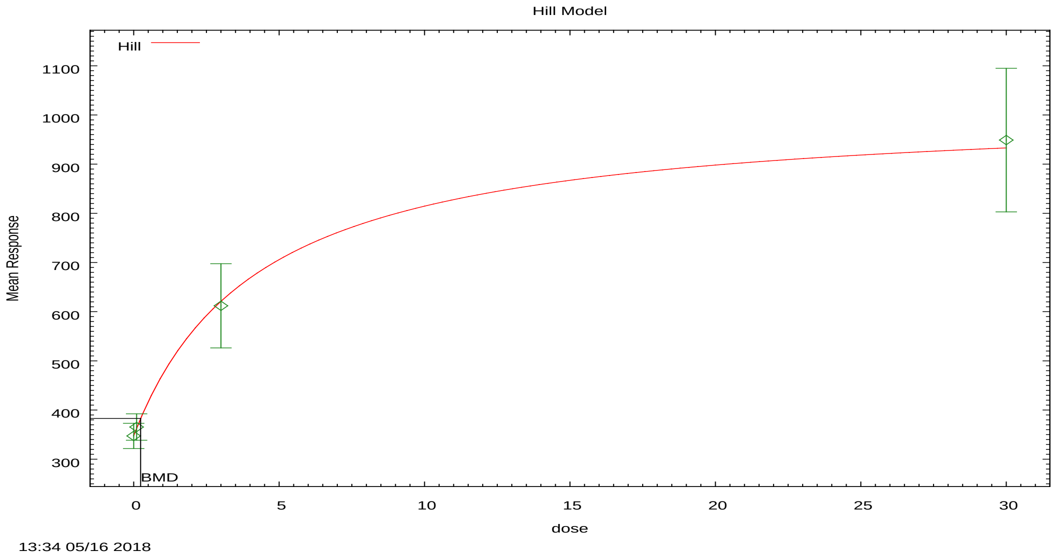

Figure 261. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.237536

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-14.4381	9.59321
rho	3.67815	0
intercept	348.287	347.314
v	670.126	601.642
n	1	0.211723

k	4.35726	54.101

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347	348	35.9	34.6	-0.0888
0.1	10	365	363	37.6	37.4	0.179
3	10	612	622	120	101	-0.302
30	10	949	933	204	212	0.231

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.756967	5	429.513934
A2	-191.003314	8	398.006627
A3	-191.349795	6	394.699591
fitted	-191.362956	5	392.725912
R	-243.798014	2	491.596028

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.589	6	<0.0001
Test 2	37.5073	3	<0.0001
Test 3	0.692963	2	0.7072
Test 4	0.0263214	1	0.8711

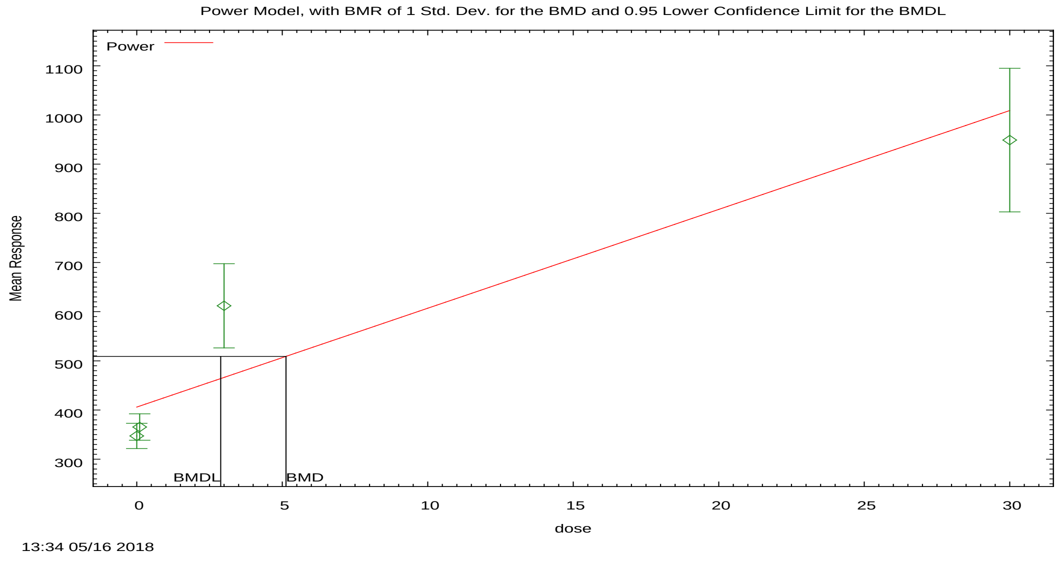

Figure 262. Plot of mean response by dose with fitted curve for Power model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 5.12748

BMDL at the 95% confidence level = 2.884

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-1.3227	9.59321
rho	1.7642	0
control	405.867	347.314
slope	20.125	71.279
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347	406	35.9	103	-1.79
0.1	10	365	408	37.6	104	-1.29
3	10	612	466	120	117	3.95
30	10	949	1010	204	231	-0.832

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.756967	5	429.513934
A2	-191.003314	8	398.006627
A3	-191.349795	6	394.699591
fitted	-214.768715	4	437.537431
R	-243.798014	2	491.596028

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.589	6	<0.0001
Test 2	37.5073	3	<0.0001
Test 3	0.692963	2	0.7072
Test 4	46.8378	2	<0.0001

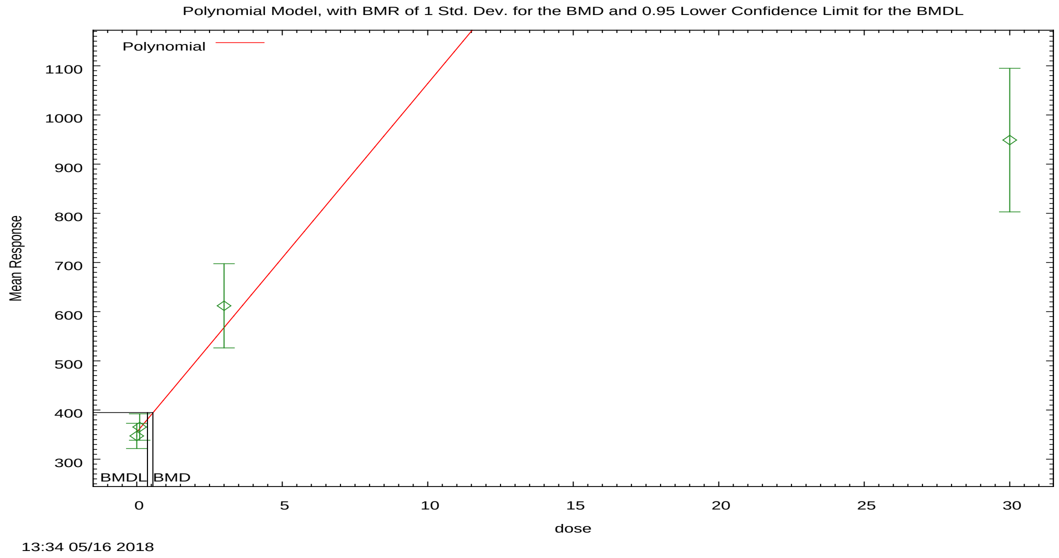

Figure 263. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.554052

BMDL at the 95% confidence level = 0.368145

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-15.2937	9.59321
rho	3.85388	0
beta_0	355.495	347.314
beta_1	70.9191	184.827

beta_2	0	0
beta_3	0	0.989356

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347	355	35.9	39.3	-0.658
0.1	10	365	363	37.6	40.8	0.222
3	10	612	568	120	97	1.42
30	10	949	2480	204	1660	-2.92

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.756967	5	429.513934
A2	-191.003314	8	398.006627
A3	-191.349795	6	394.699591
fitted	-213.715421	4	435.430842
R	-243.798014	2	491.596028

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.589	6	<0.0001
Test 2	37.5073	3	<0.0001
Test 3	0.692963	2	0.7072
Test 4	44.7313	2	<0.0001

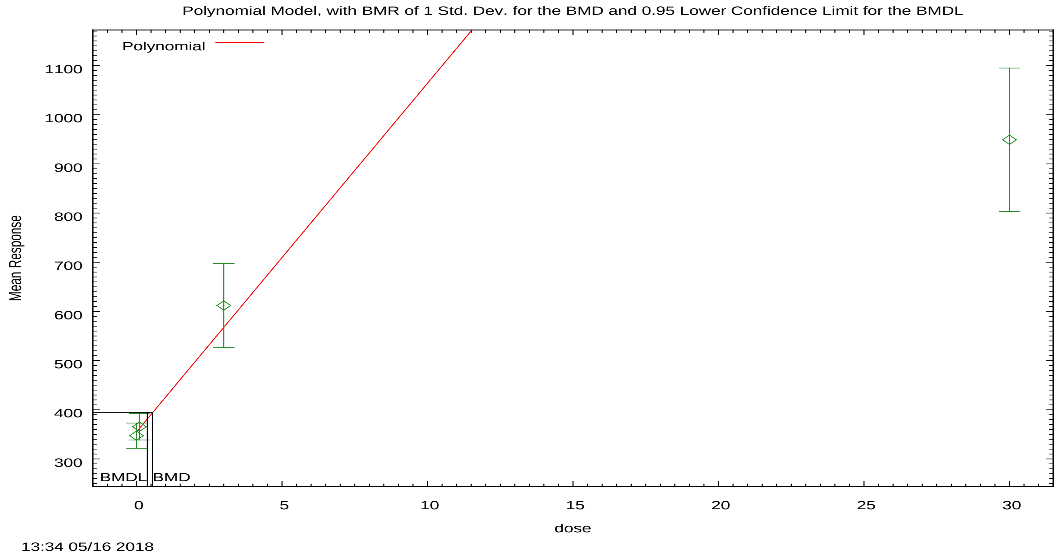

Figure 264. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.554052

BMDL at the 95% confidence level = 0.368145

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-15.2937	9.59321
rho	3.85388	0
beta_0	355.495	351.597
beta_1	70.9191	94.2756

beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347	355	35.9	39.3	-0.658
0.1	10	365	363	37.6	40.8	0.222
3	10	612	568	120	97	1.42
30	10	949	2480	204	1660	-2.92

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.756967	5	429.513934
A2	-191.003314	8	398.006627
A3	-191.349795	6	394.699591
fitted	-213.715421	4	435.430842
R	-243.798014	2	491.596028

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.589	6	<0.0001
Test 2	37.5073	3	<0.0001
Test 3	0.692963	2	0.7072
Test 4	44.7313	2	<0.0001

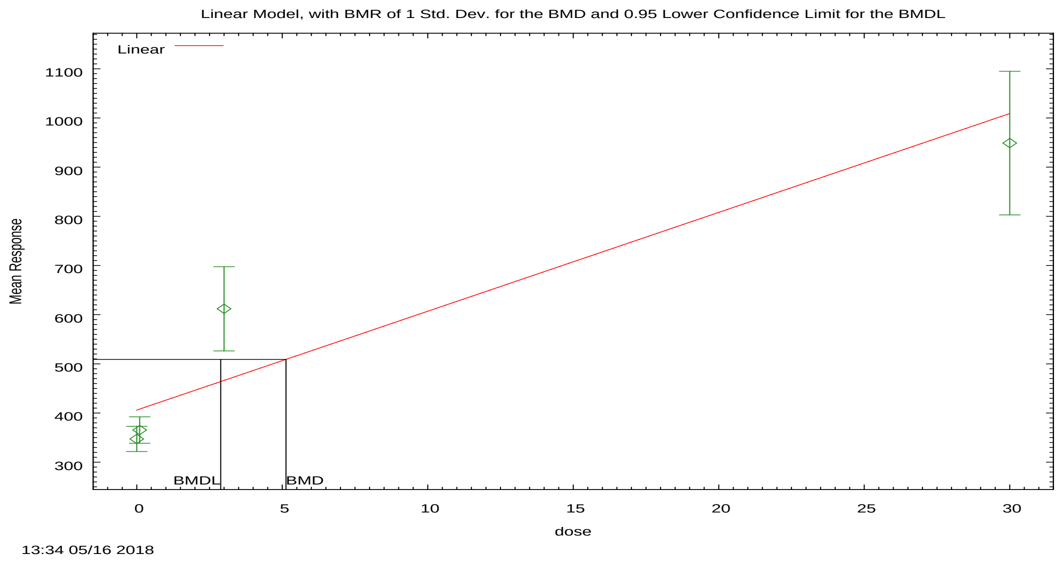

Figure 265. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 5.12748

BMDL at the 95% confidence level = 2.884

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-1.3227	9.59321
rho	1.76421	0
beta_0	405.867	418.235
beta_1	20.125	18.1489

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	347	406	35.9	103	-1.79
0.1	10	365	408	37.6	104	-1.29
3	10	612	466	120	117	3.95
30	10	949	1010	204	231	-0.832

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-209.756967	5	429.513934
A2	-191.003314	8	398.006627
A3	-191.349795	6	394.699591
fitted	-214.768715	4	437.537431
R	-243.798014	2	491.596028

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.589	6	<0.0001
Test 2	37.5073	3	<0.0001
Test 3	0.692963	2	0.7072
Test 4	46.8378	2	<0.0001

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery – Liver Weight to Brain Weight (g/100g brain) in Females

1.30. BMDS Summary of Liver weight to brain weight (g/100g brain) females (28 Day Mice GenX)

Table 30. Summary of BMD Modeling Results for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	9.00E-04	351.80	5.78	4.59	1.26	Only one model met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from this model.
Exponential (M4) **Exponential (M5)[c]**	**0.381**	**340.54**	**1.14**	**0.751**	**1.52**	
Hill	0.387	340.52	1.10	error[d]	error	
Power[e]	0.00434	348.65	3.99	3.02	1.32	
Polynomial 3°[f] Polynomial 2°[g] Linear[h]	0.00434	348.65	3.99	3.02	1.32	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.035), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 3, and 30 mg/kg/day were -0.64, 0.66, -0.02, 0, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[d] BMD or BMDL computation failed for this model.

[e] The Power model may appear equivalent to the Polynomial 3° model, however differences exist in digits not displayed in the table. This also applies to the Polynomial 2° model. This also applies to the Linear model.

[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[g] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[h] The Linear model may appear equivalent to the Power model, however differences exist in digits not displayed in the table.

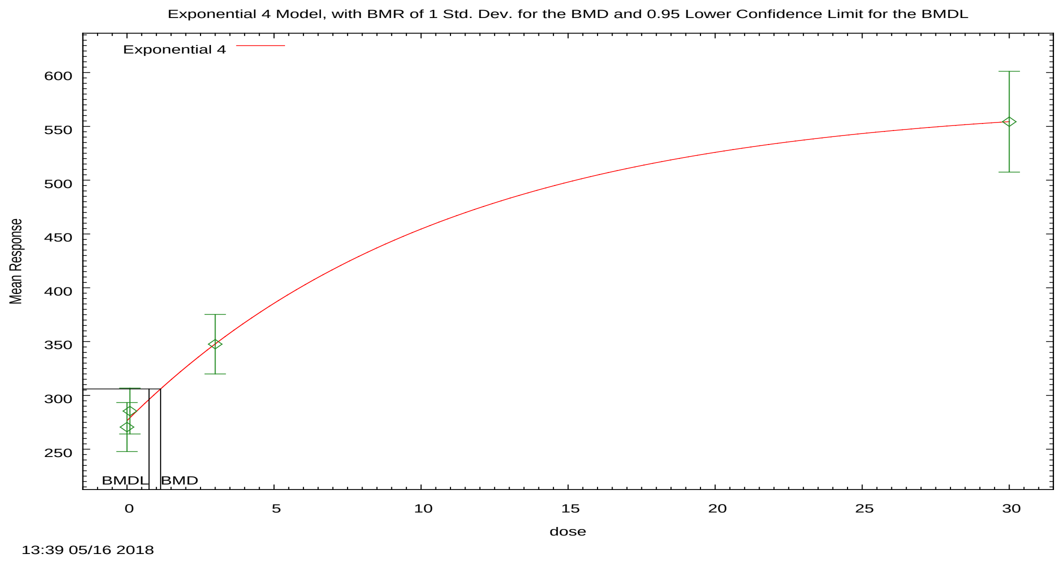

Figure 266. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.14268

BMDL at the 95% confidence level = 0.75065

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.14733	-5.34291
rho	2.11933	2.16682
a	276.535	257.053
b	0.0915598	0.0823334
c	2.07363	2.26425
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	270.6	276.5	31.83	29.49	-0.6383
0.1	10	285.5	279.2	29.77	29.8	0.6611
3	10	347.6	347.8	38.68	37.61	-0.01903
30	10	554.3	554.4	65.5	61.63	-0.003785

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.1109	5	348.2218
A2	-164.8074	8	345.6148
A3	-164.886	6	341.772
R	-211.7408	2	427.4817
4	-165.2698	5	340.5397

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.87	6	<0.0001
Test 2	8.607	3	0.035
Test 3	0.1572	2	0.9244
Test 6a	0.7677	1	0.3809

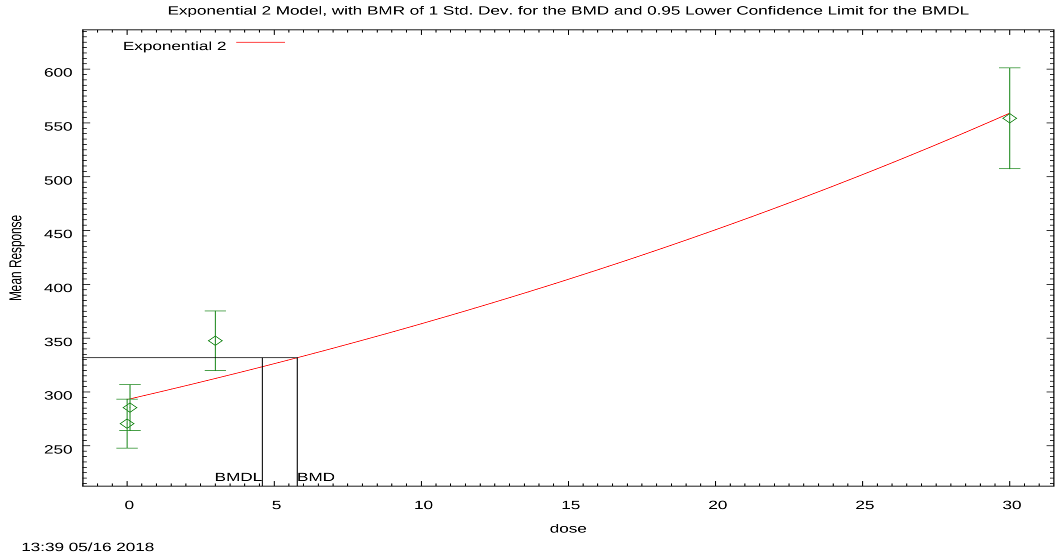

Figure 267. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 5.77952

BMDL at the 95% confidence level = 4.59476

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.47223	-5.34291
rho	1.54775	2.16682
a	292.97	291.725
b	0.0215421	0.0217614
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	270.6	293	31.83	38.84	-1.823
0.1	10	285.5	293.6	29.77	38.91	-0.6609
3	10	347.6	312.5	38.68	40.84	2.717
30	10	554.3	559.1	65.5	64.05	-0.2363

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.1109	5	348.2218
A2	-164.8074	8	345.6148
A3	-164.886	6	341.772
R	-211.7408	2	427.4817
2	-171.8997	4	351.7993

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.87	6	<0.0001
Test 2	8.607	3	0.035
Test 3	0.1572	2	0.9244
Test 4	14.03	2	0.0008995

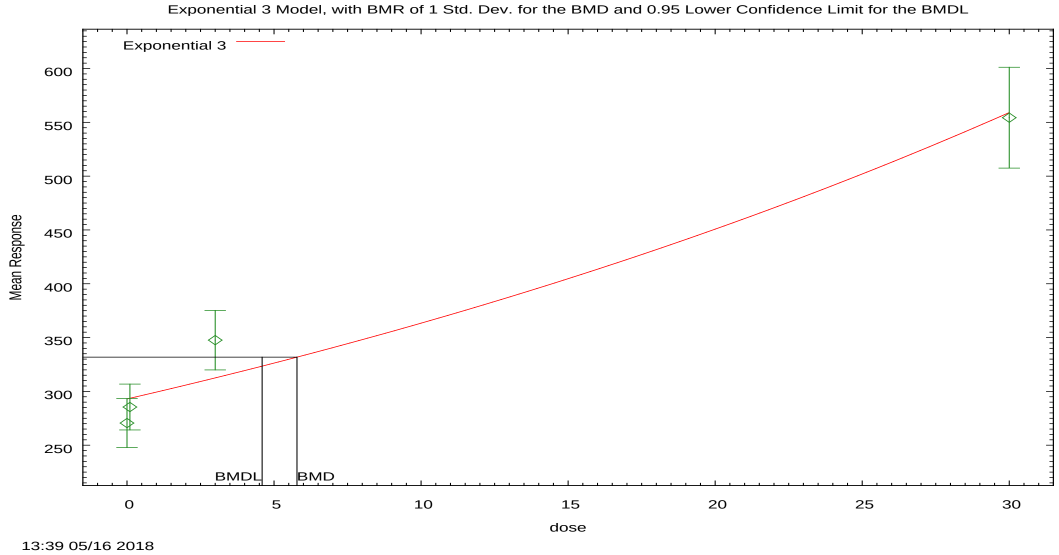

Figure 268. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 5.77952

BMDL at the 95% confidence level = 4.59476

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-1.47222	-5.34291
rho	1.54775	2.16682
a	292.97	291.725

b	0.0215421	0.0217614
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	270.6	293	31.83	38.84	-1.823
0.1	10	285.5	293.6	29.77	38.91	-0.6609
3	10	347.6	312.5	38.68	40.84	2.717
30	10	554.3	559.1	65.5	64.05	-0.2363

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.1109	5	348.2218
A2	-164.8074	8	345.6148
A3	-164.886	6	341.772
R	-211.7408	2	427.4817
3	-171.8997	4	351.7993

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.87	6	<0.0001
Test 2	8.607	3	0.035
Test 3	0.1572	2	0.9244
Test 5a	14.03	2	0.0008995

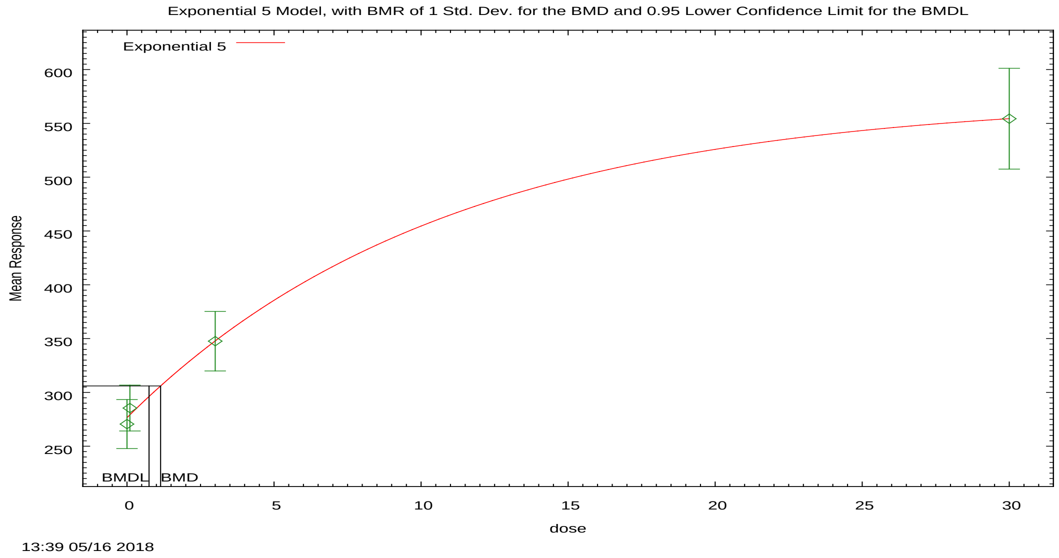

Figure 269. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.14268

BMDL at the 95% confidence level = 0.75065

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.14729	-5.34291
rho	2.11933	2.16682
a	276.535	257.053
b	0.0915596	0.0823334

c	2.07363	2.26425
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	270.6	276.5	31.83	29.49	-0.6383
0.1	10	285.5	279.2	29.77	29.8	0.6611
3	10	347.6	347.8	38.68	37.61	-0.01902
30	10	554.3	554.4	65.5	61.63	-0.003788

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.1109	5	348.2218
A2	-164.8074	8	345.6148
A3	-164.886	6	341.772
R	-211.7408	2	427.4817
5	-165.2698	5	340.5397

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.87	6	<0.0001
Test 2	8.607	3	0.035
Test 3	0.1572	2	0.9244
Test 7a	0.7677	1	0.3809

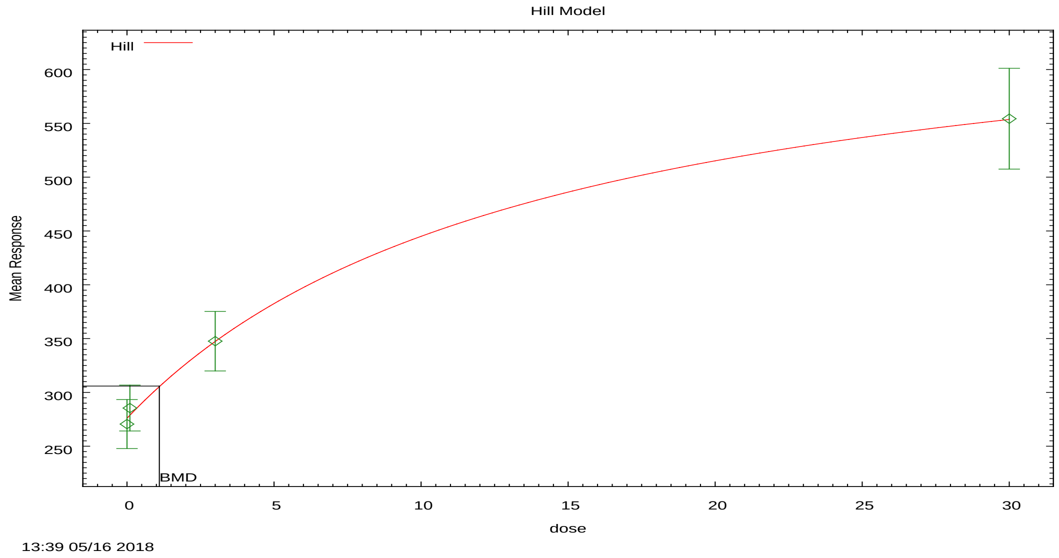

Figure 270. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.09982

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-5.15539	7.56091
rho	2.12062	0
intercept	276.432	270.582
v	409.207	283.733
n	1	0.411212

k	14.1723	48.5315

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	271	276	31.8	29.5	-0.628
0.1	10	285	279	29.8	29.8	0.655
3	10	348	348	38.7	37.6	-0.0254
30	10	554	554	65.5	61.6	-0.00171

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.110923	5	348.221846
A2	-164.807379	8	345.614758
A3	-164.885988	6	341.771976
fitted	-165.259533	5	340.519065
R	-211.740842	2	427.481684

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.8669	6	<0.0001
Test 2	8.60709	3	0.035
Test 3	0.157219	2	0.9244
Test 4	0.747089	1	0.3874

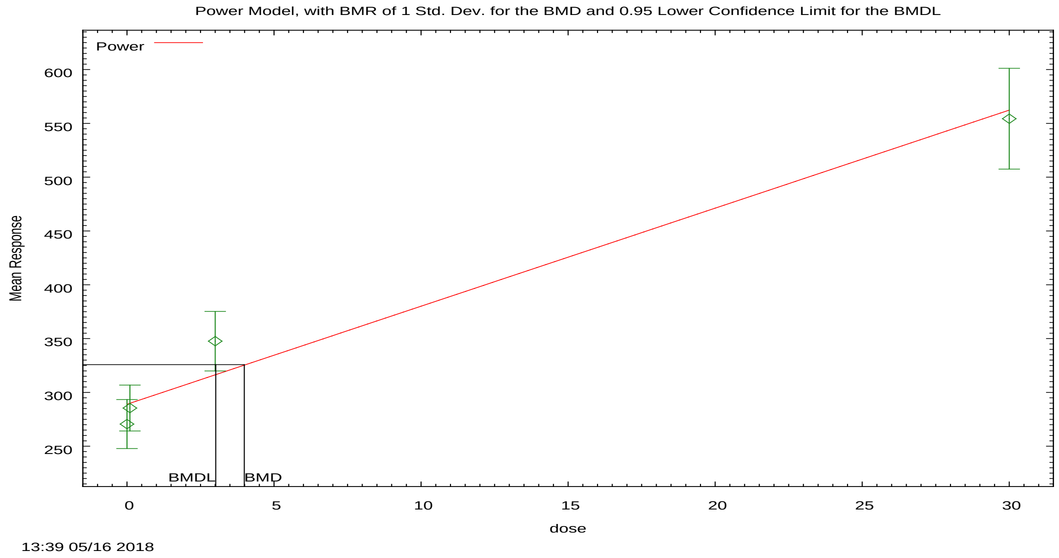

Figure 271. Plot of mean response by dose with fitted curve for Power model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.98904

BMDL at the 95% confidence level = 3.01743

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.67787	7.56091
rho	1.74036	0
control	289.421	270.582
slope	9.11208	49.3555
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	271	289	31.8	36.3	-1.64
0.1	10	285	290	29.8	36.4	-0.422
3	10	348	317	38.7	39.3	2.48
30	10	554	563	65.5	64.8	-0.413

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.110923	5	348.221846
A2	-164.807379	8	345.614758
A3	-164.885988	6	341.771976
fitted	-170.325497	4	348.650994
R	-211.740842	2	427.481684

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.8669	6	<0.0001
Test 2	8.60709	3	0.035
Test 3	0.157219	2	0.9244
Test 4	10.879	2	0.004342

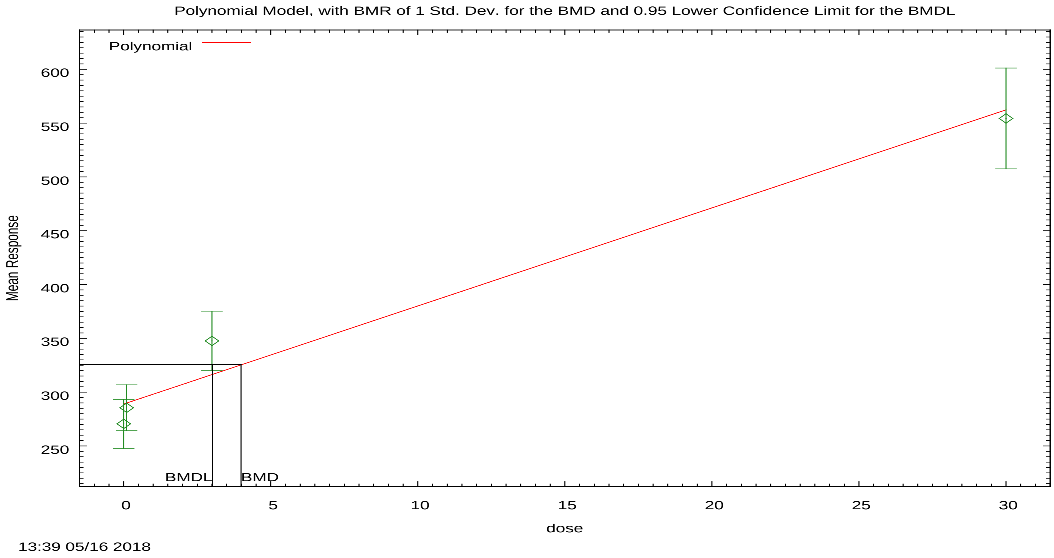

Figure 272. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.98903

BMDL at the 95% confidence level = 3.01743

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.67789	7.56091
rho	1.74037	0
beta_0	289.421	270.582
beta_1	9.11208	153.549

beta_2	0	0
beta_3	0	1.40075

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	271	289	31.8	36.3	-1.64
0.1	10	285	290	29.8	36.4	-0.422
3	10	348	317	38.7	39.3	2.48
30	10	554	563	65.5	64.8	-0.413

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.110923	5	348.221846
A2	-164.807379	8	345.614758
A3	-164.885988	6	341.771976
fitted	-170.325497	4	348.650994
R	-211.740842	2	427.481684

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.8669	6	<0.0001
Test 2	8.60709	3	0.035
Test 3	0.157219	2	0.9244
Test 4	10.879	2	0.004342

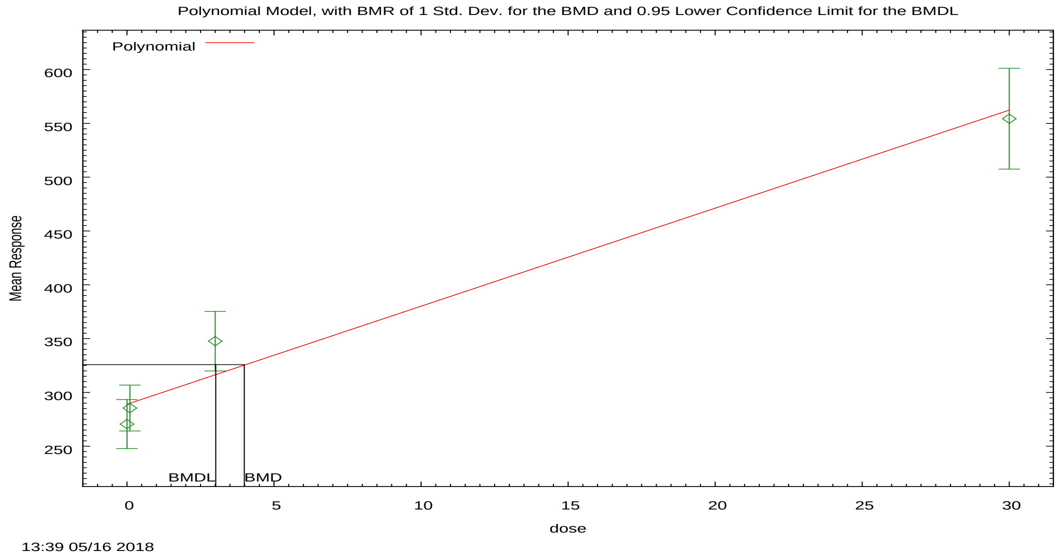

Figure 273. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.98903

BMDL at the 95% confidence level = 3.01743

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.67789	7.56091
rho	1.74037	0
beta_0	289.421	276.646
beta_1	9.11208	25.3434

beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	271	289	31.8	36.3	-1.64
0.1	10	285	290	29.8	36.4	-0.422
3	10	348	317	38.7	39.3	2.48
30	10	554	563	65.5	64.8	-0.413

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.110923	5	348.221846
A2	-164.807379	8	345.614758
A3	-164.885988	6	341.771976
fitted	-170.325497	4	348.650994
R	-211.740842	2	427.481684

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.8669	6	<0.0001
Test 2	8.60709	3	0.035
Test 3	0.157219	2	0.9244
Test 4	10.879	2	0.004342

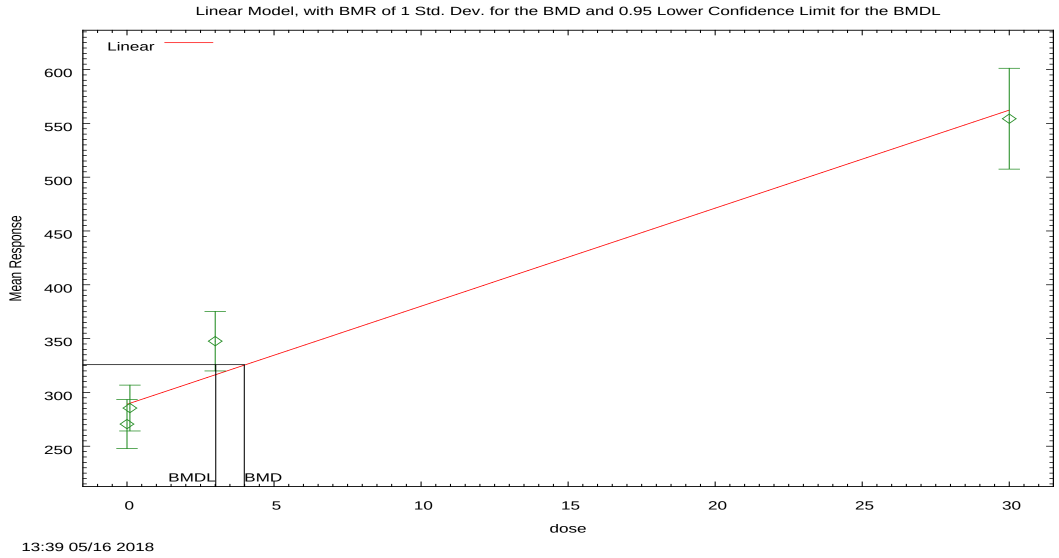

Figure 274. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Liver Weight to Brain Weight in Females (28-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.98903

BMDL at the 95% confidence level = 3.01743

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-2.67788	7.56091
rho	1.74036	0
beta_0	289.421	291.063
beta_1	9.11208	8.87413

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	271	289	31.8	36.3	-1.64
0.1	10	285	290	29.8	36.4	-0.422
3	10	348	317	38.7	39.3	2.48
30	10	554	563	65.5	64.8	-0.413

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-169.110923	5	348.221846
A2	-164.807379	8	345.614758
A3	-164.885988	6	341.771976
fitted	-170.325497	4	348.650994
R	-211.740842	2	427.481684

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	93.8669	6	<0.0001
Test 2	8.60709	3	0.035
Test 3	0.157219	2	0.9244
Test 4	10.879	2	0.004342

BMDS WIZARD OUTPUT REPORT

BMDS Summary of 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-day Recovery – Liver Weight to Brain Weight (g/100g brain) in Males

1.31. BMDS Summary of Liver weight to brain weight (g/100g brain) Males (28 Day Rats GenX)

Table 31. Summary of BMD Modeling Results for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	3.82E-04	403.18	8.78	6.58	1.33	Only one model met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from this model.
Exponential (M4)	**0.762**	**389.53**	**1.01**	**0.611**	**1.65**	
Exponential (M5)	N/A[c]	391.44	1.27	0.616	2.06	
Hill	N/A[c]	391.44	1.20	error[d]	error	
Power[e]	7.43E-04	401.85	7.09	4.98	1.42	
Polynomial 3°[f] Polynomial 2°[g] Linear[h]	7.43E-04	401.85	7.09	4.98	1.42	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0263), selected model in bold; scaled residuals for selected model for doses 0, 0.3, 3, and 30 mg/kg/day were 0.05, -0.1, 0.1, -0.04, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] No available degrees of freedom to calculate a goodness of fit value.

[d] BMD or BMDL computation failed for this model.

[e] The Power model may appear equivalent to the Polynomial 3° model, however differences exist in digits not displayed in the table. This also applies to the Polynomial 2° model. This also applies to the Linear model.

[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[g] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[h] The Linear model may appear equivalent to the Power model, however differences exist in digits not displayed in the table.

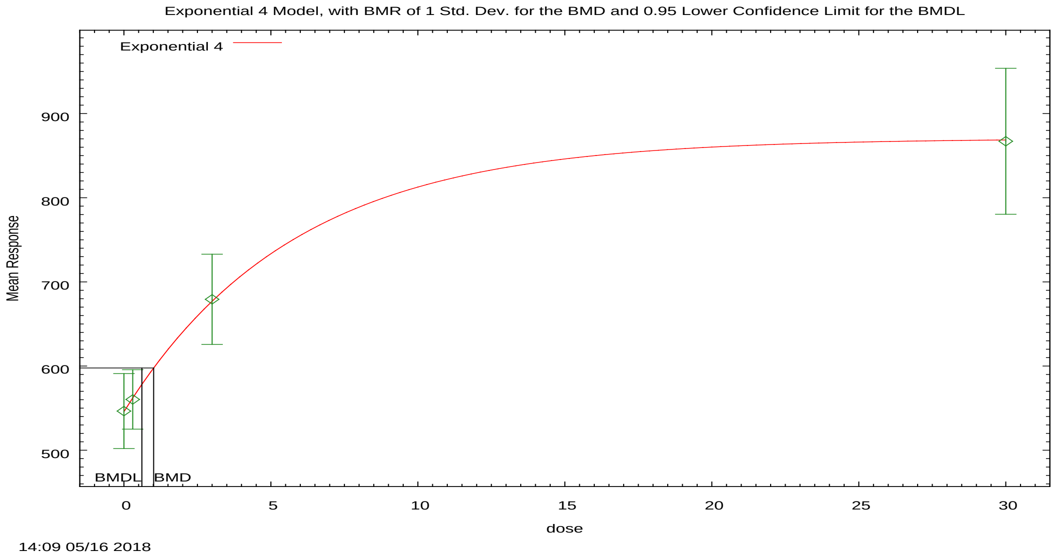

Figure 275. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.01078

BMDL at the 95% confidence level = 0.610799

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-12.9002	-13.4573
rho	3.30092	3.39985
a	545.71	519.162

b	0.172629	0.074374
c	1.59511	1.75365
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	546.5	545.7	62.27	52	0.04719
0.3	10	560.3	562.1	49.37	54.6	-0.1024
3	10	679.3	677	74.89	74.22	0.09887
30	10	867.1	868.6	121.2	112	-0.04414

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.9575	5	397.915
A2	-189.3381	8	394.6761
A3	-189.7208	6	391.4416
R	-220.4231	2	444.8461
4	-189.7667	5	389.5334

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.17	6	<0.0001
Test 2	9.239	3	0.02628
Test 3	0.7655	2	0.682
Test 6a	0.09174	1	0.762

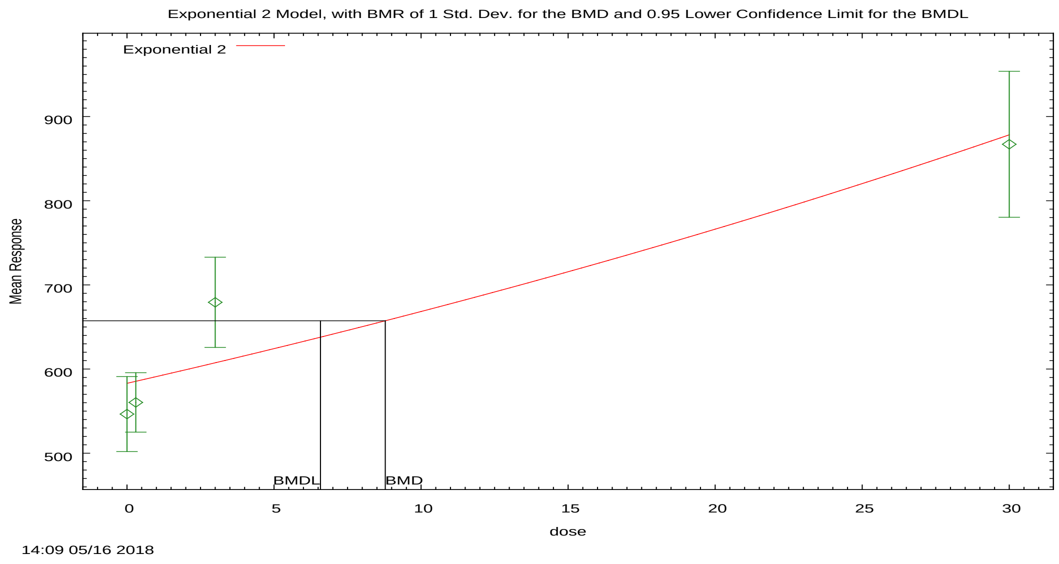

Figure 276. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 8.782

BMDL at the 95% confidence level = 6.57964

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-6.13218	-13.4573
rho	2.31593	3.39985
a	583.048	581.518
b	0.0136582	0.0136837

c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	546.5	583	62.27	74.3	-1.556
0.3	10	560.3	585.4	49.37	74.65	-1.064
3	10	679.3	607.4	74.89	77.91	2.917
30	10	867.1	878.3	121.2	119.4	-0.2979

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.9575	5	397.915
A2	-189.3381	8	394.6761
A3	-189.7208	6	391.4416
R	-220.4231	2	444.8461
2	-197.5918	4	403.1836

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.17	6	<0.0001
Test 2	9.239	3	0.02628
Test 3	0.7655	2	0.682
Test 4	15.74	2	0.0003816

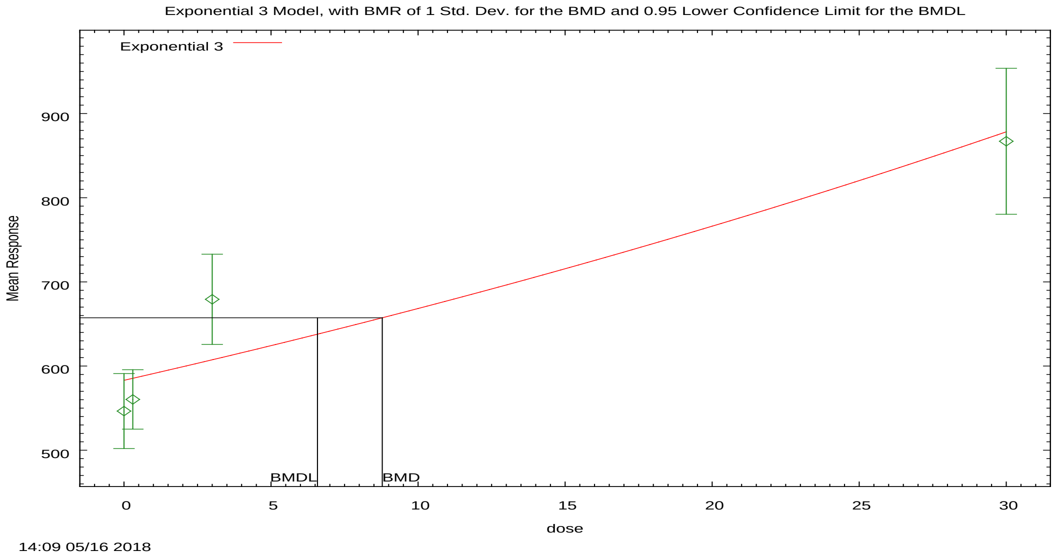

Figure 277. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 8.782

BMDL at the 95% confidence level = 6.57964

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-6.13218	-13.4573
rho	2.31593	3.39985
a	583.048	581.518
b	0.0136582	0.0136837

c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	546.5	583	62.27	74.3	-1.556
0.3	10	560.3	585.4	49.37	74.65	-1.064
3	10	679.3	607.4	74.89	77.91	2.917
30	10	867.1	878.3	121.2	119.4	-0.2979

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.9575	5	397.915
A2	-189.3381	8	394.6761
A3	-189.7208	6	391.4416
R	-220.4231	2	444.8461
3	-197.5918	4	403.1836

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.17	6	<0.0001
Test 2	9.239	3	0.02628
Test 3	0.7655	2	0.682
Test 5a	15.74	2	0.0003816

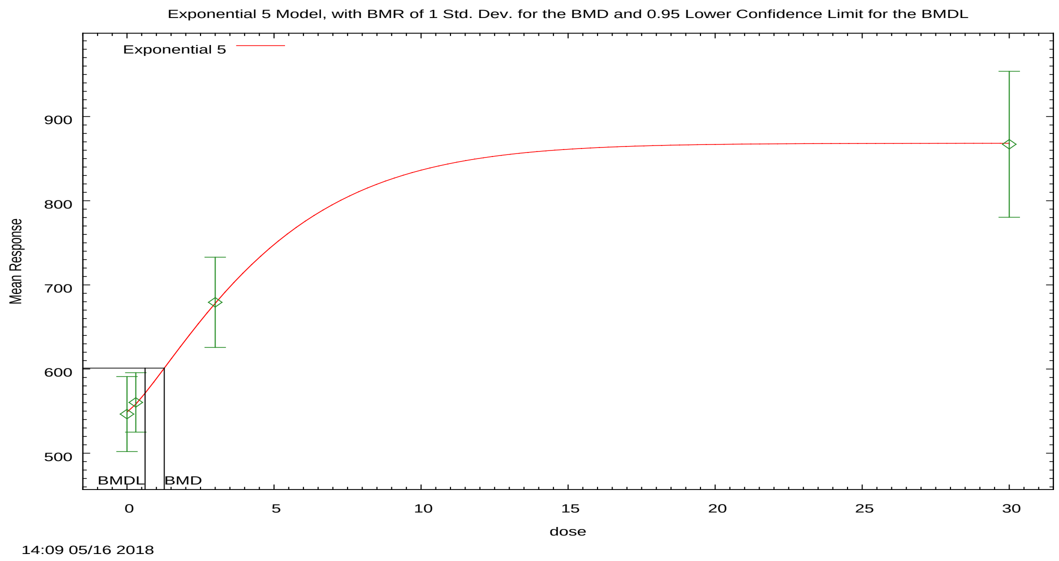

Figure 278. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.26762

BMDL at the 95% confidence level = 0.615908

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-13.1092	-13.4573
rho	3.33281	3.39985
a	548.799	519.162
b	0.196101	0.074374

c	1.5822	1.75365
d	1.23719	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	546.5	548.8	62.27	52.28	-0.1399
0.3	10	560.3	558.3	49.37	53.79	0.1221
3	10	679.3	678.1	74.89	74.38	0.05058
30	10	867.1	868.3	121.2	112.3	-0.03361

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.9575	5	397.915
A2	-189.3381	8	394.6761
A3	-189.7208	6	391.4416
R	-220.4231	2	444.8461
5	-189.7208	6	391.4416

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.17	6	<0.0001
Test 2	9.239	3	0.02628
Test 3	0.7655	2	0.682
Test 7a	-9.663E-13	0	N/A

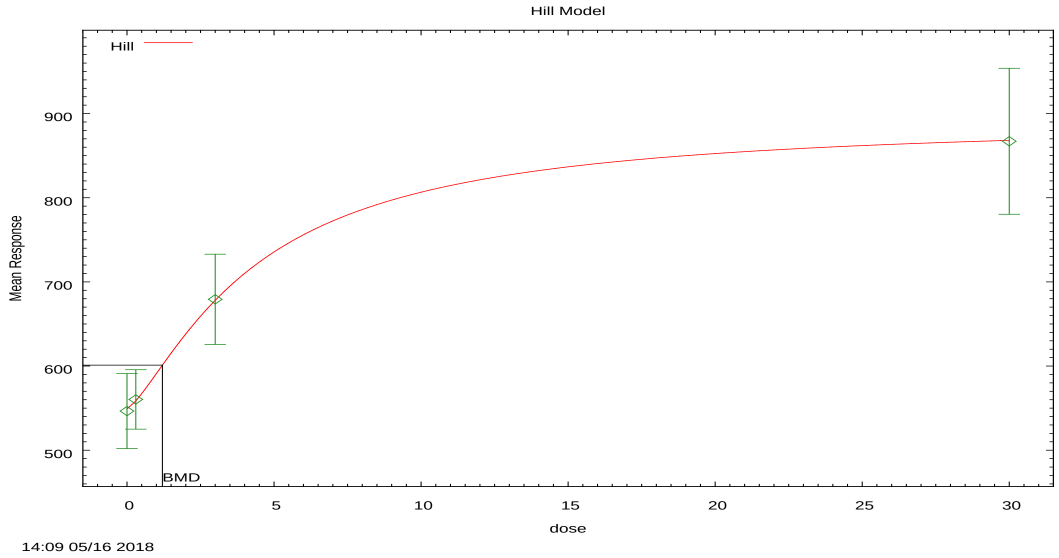

Figure 279. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.20483

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-13.1092	8.80324
rho	3.33281	0
intercept	548.799	546.486
v	344.427	320.59
n	1.32826	0.359579

k	4.40059	53.0492

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	546	549	62.3	52.3	-0.14
0.3	10	560	558	49.4	53.8	0.122
3	10	679	678	74.9	74.4	0.0506
30	10	867	868	121	112	-0.0336

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.957517	5	397.915035
A2	-189.338063	8	394.676127
A3	-189.72081	6	391.441621
fitted	-189.72081	6	391.441621
R	-220.423064	2	444.846129

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.17	6	<0.0001
Test 2	9.23891	3	0.02628
Test 3	0.765494	2	0.682
Test 4	1.63709E-11	0	N/A

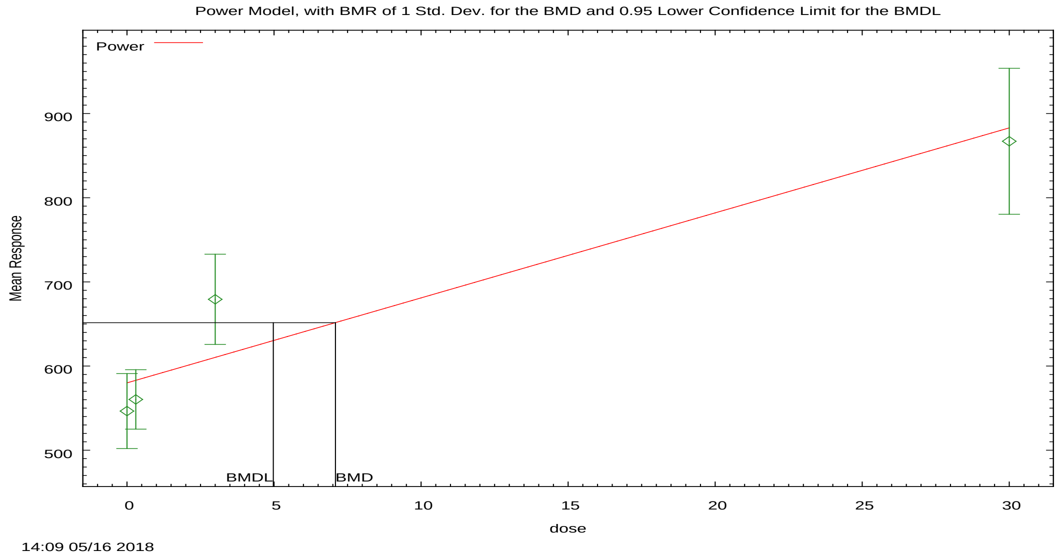

Figure 280. Plot of mean response by dose with fitted curve for Power model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 7.08863

BMDL at the 95% confidence level = 4.97533

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.10734	8.80324
rho	2.46125	0
control	579.553	546.486
slope	10.1491	31.4841
power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	546	580	62.3	71.9	-1.45
0.3	10	560	583	49.4	72.4	-0.972
3	10	679	610	74.9	76.6	2.86
30	10	867	884	121	121	-0.443

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.957517	5	397.915035
A2	-189.338063	8	394.676127
A3	-189.72081	6	391.441621
fitted	-196.925841	4	401.851681
R	-220.423064	2	444.846129

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.17	6	<0.0001
Test 2	9.23891	3	0.02628
Test 3	0.765494	2	0.682
Test 4	14.4101	2	0.0007428

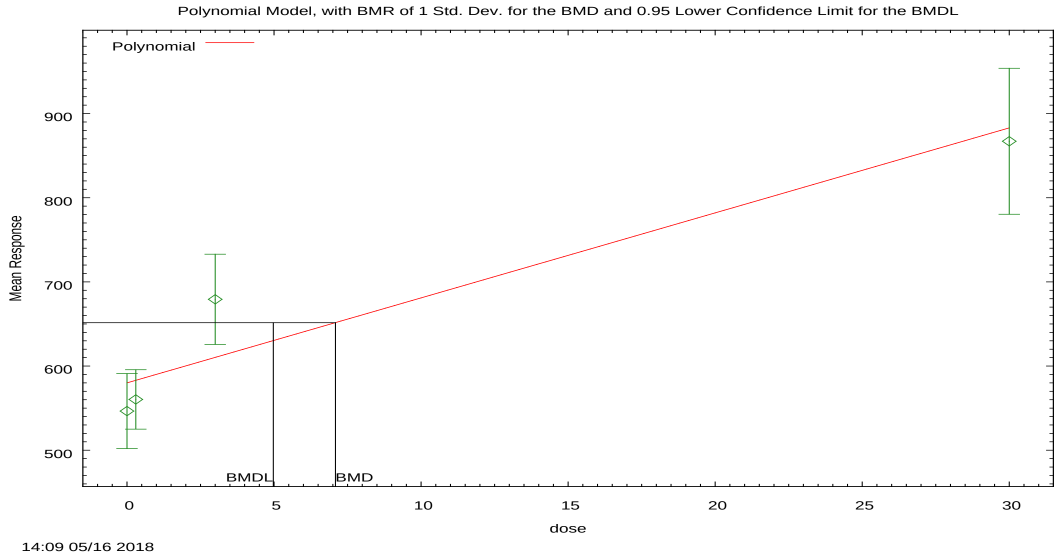

Figure 281. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 7.08864

BMDL at the 95% confidence level = 4.97533

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.10731	8.80324
rho	2.46124	0
beta_0	579.553	546.486
beta_1	10.1491	46.3457

beta_2	0	0
beta_3	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	546	580	62.3	71.9	-1.45
0.3	10	560	583	49.4	72.4	-0.972
3	10	679	610	74.9	76.6	2.86
30	10	867	884	121	121	-0.443

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.957517	5	397.915035
A2	-189.338063	8	394.676127
A3	-189.72081	6	391.441621
fitted	-196.925841	4	401.851681
R	-220.423064	2	444.846129

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.17	6	<0.0001
Test 2	9.23891	3	0.02628
Test 3	0.765494	2	0.682
Test 4	14.4101	2	0.0007428

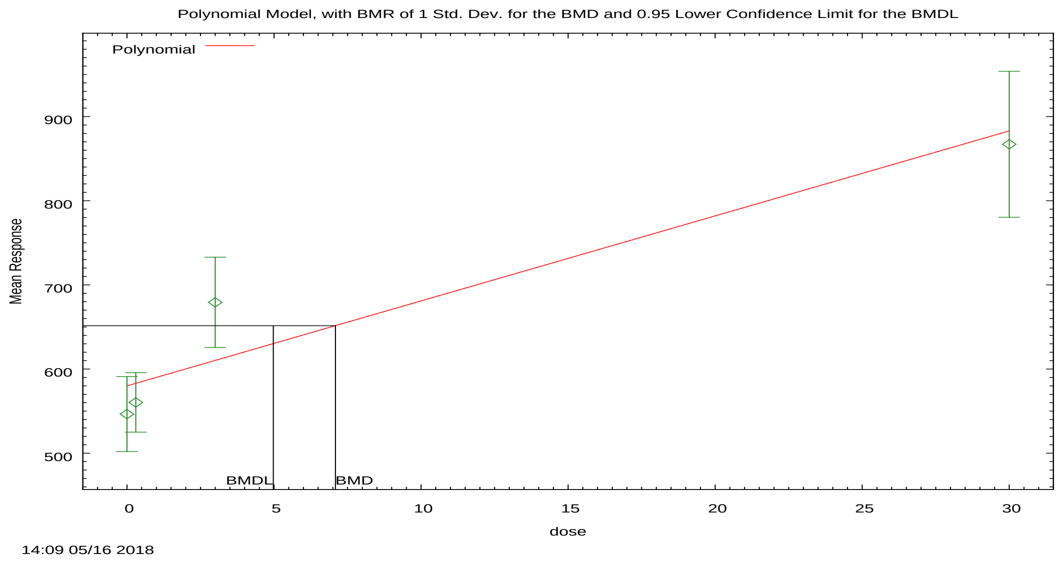

Figure 282. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 7.08864

BMDL at the 95% confidence level = 4.97533

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.10735	8.80324
rho	2.46125	0
beta_0	579.553	546.267
beta_1	10.1491	48.0751

beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	546	580	62.3	71.9	-1.45
0.3	10	560	583	49.4	72.4	-0.972
3	10	679	610	74.9	76.6	2.86
30	10	867	884	121	121	-0.443

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.957517	5	397.915035
A2	-189.338063	8	394.676127
A3	-189.72081	6	391.441621
fitted	-196.925841	4	401.851681
R	-220.423064	2	444.846129

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.17	6	<0.0001
Test 2	9.23891	3	0.02628
Test 3	0.765494	2	0.682
Test 4	14.4101	2	0.0007428

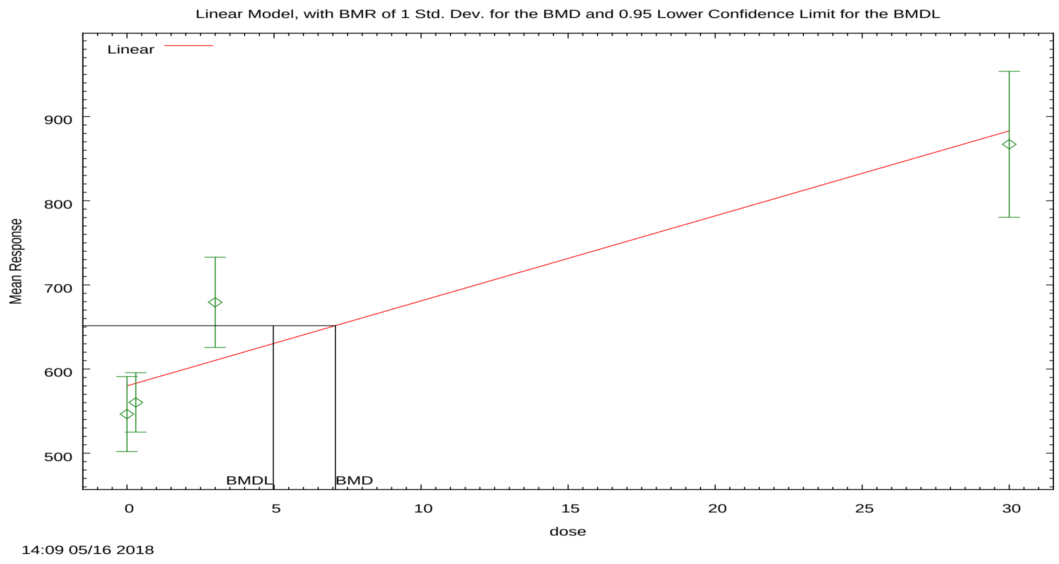

Figure 283. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Liver Weight to Brain Weight in Males (28-Day Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 7.08864

BMDL at the 95% confidence level = 4.97533

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-7.10734	8.80324
rho	2.46125	0
beta_0	579.553	582.53
beta_1	10.1491	9.70205

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	546	580	62.3	71.9	-1.45
0.3	10	560	583	49.4	72.4	-0.972
3	10	679	610	74.9	76.6	2.86
30	10	867	884	121	121	-0.443

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.957517	5	397.915035
A2	-189.338063	8	394.676127
A3	-189.72081	6	391.441621
fitted	-196.925841	4	401.851681
R	-220.423064	2	444.846129

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	62.17	6	<0.0001
Test 2	9.23891	3	0.02628
Test 3	0.765494	2	0.682
Test 4	14.4101	2	0.0007428

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Liver Weight to Brain Weight (%) in Males

1.32. BMDS Summary of Liver weight to brain weight (%) Males (90 Day Mice GenX)

Table 32. Summary of BMD Modeling Results for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	0.619	373.81	0.630	0.496	1.27	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M4)[c]	0.747	374.96	0.395	0.210	1.88	
Exponential (M5)[d]	0.747	374.96	0.395	0.210	1.88	
Hill	0.747	374.96	0.398	error[e]	error	
Power[f] **Polynomial 3°[g]** **Polynomial 2°[h]** **Linear**	**0.949**	**372.96**	**0.400**	**0.300**	**1.34**	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.19, 0.5, -0.36, 0.06, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] The Exponential (M4) model may appear equivalent to the Exponential (M5) model, however differences exist in digits not displayed in the table.

[d] The Exponential (M5) model may appear equivalent to the Exponential (M4) model, however differences exist in digits not displayed in the table.

[e] BMD or BMDL computation failed for this model.

[f] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[g] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[h] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

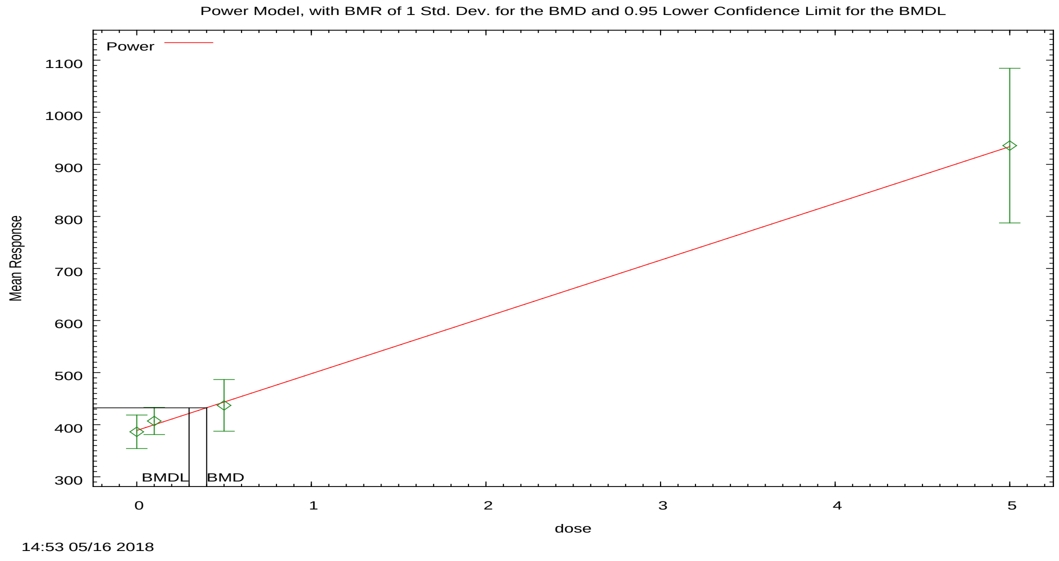

Figure 284. Plot of mean response by dose with fitted curve for Power model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.400252

BMDL at the 95% confidence level = 0.299666

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-12.4949	9.2714
rho	3.3602	0
control	389.017	386.366
slope	108.602	139.636

power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386	389	45	43.5	-0.193
0.1	10	407	400	36.4	45.5	0.502
0.5	10	437	443	69.4	54.1	-0.363
5	9	936	932	193	189	0.0626

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.182127	5	406.364254
A2	-181.17551	8	378.351021
A3	-182.426362	6	376.852725
fitted	-182.47882	4	372.957641
R	-233.69519	2	471.39038

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.039	6	<0.0001
Test 2	34.0132	3	<0.0001
Test 3	2.5017	2	0.2863
Test 4	0.104916	2	0.9489

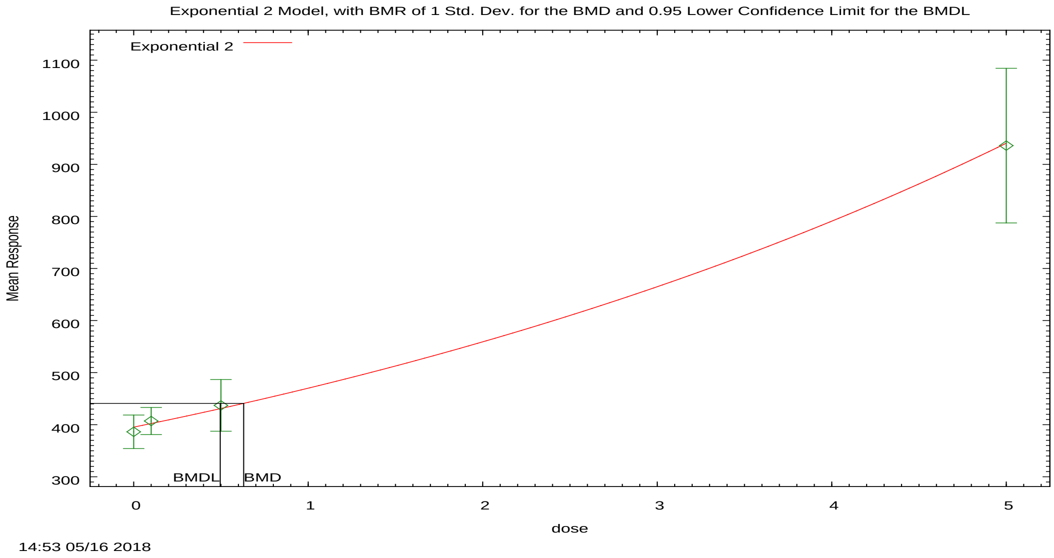

Figure 285. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.630028

BMDL at the 95% confidence level = 0.495699

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-11.8538	-12.7752
rho	3.26009	3.41177
a	395.343	395.553
b	0.173345	0.172612

c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386.4	395.3	45.01	45.62	-0.6223
0.1	10	407.1	402.3	36.41	46.93	0.3265
0.5	10	437.1	431.1	69.39	52.55	0.3588
5	9	936	940.6	193.2	187.4	-0.07359

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.1821	5	406.3643
A2	-181.1755	8	378.351
A3	-182.4264	6	376.8527
R	-233.6952	2	471.3904
2	-182.9059	4	373.8117

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105	6	<0.0001
Test 2	34.01	3	<0.0001
Test 3	2.502	2	0.2863
Test 4	0.959	2	0.6191

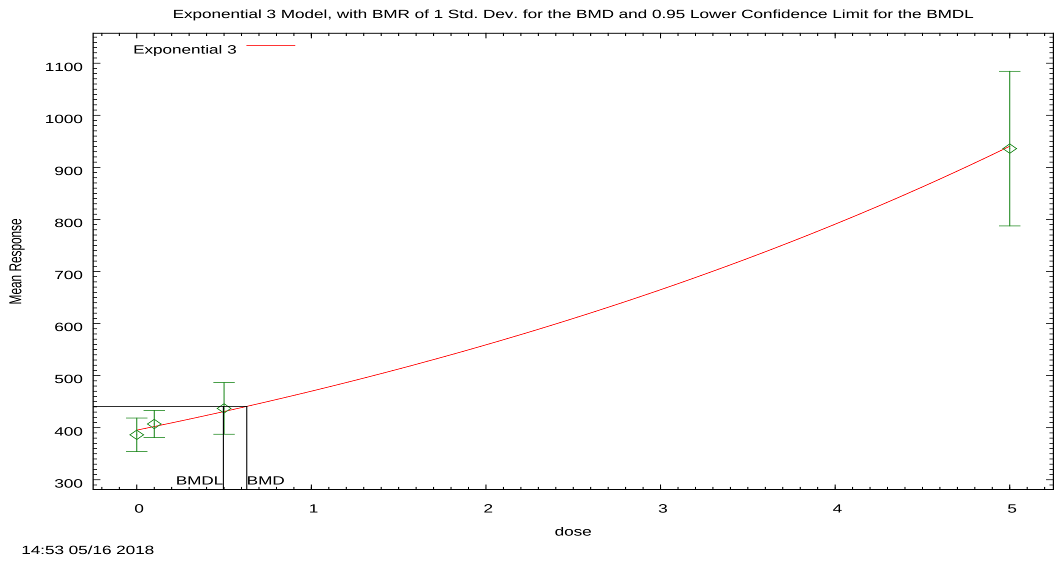

Figure 286. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.630028

BMDL at the 95% confidence level = 0.495699

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-11.8538	-12.7752
rho	3.26009	3.41177
a	395.343	395.553
b	0.173345	0.172612

c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386.4	395.3	45.01	45.62	-0.6223
0.1	10	407.1	402.3	36.41	46.93	0.3265
0.5	10	437.1	431.1	69.39	52.55	0.3588
5	9	936	940.6	193.2	187.4	-0.07359

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.1821	5	406.3643
A2	-181.1755	8	378.351
A3	-182.4264	6	376.8527
R	-233.6952	2	471.3904
3	-182.9059	4	373.8117

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105	6	<0.0001
Test 2	34.01	3	<0.0001
Test 3	2.502	2	0.2863
Test 5a	0.959	2	0.6191

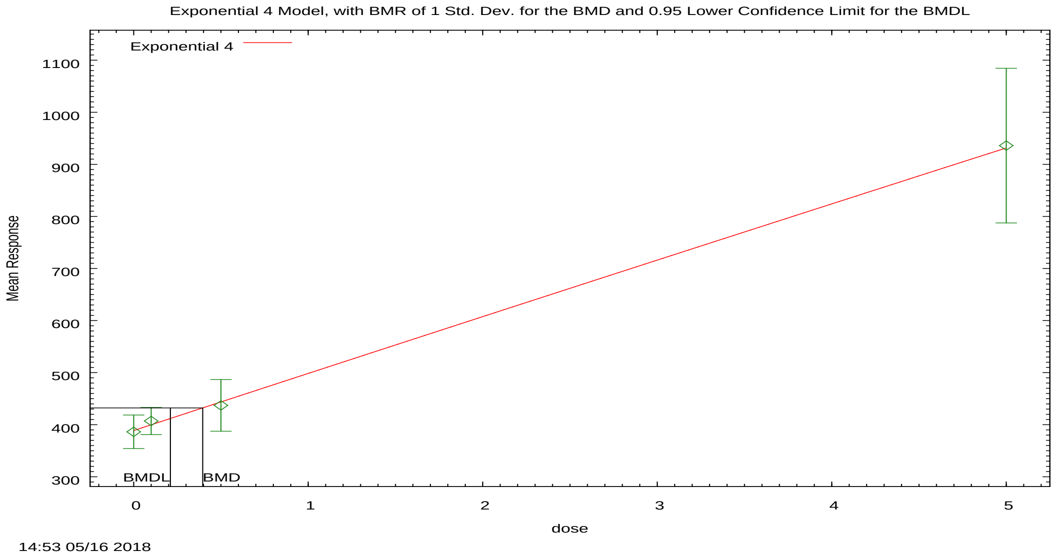

Figure 287. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.395422

BMDL at the 95% confidence level = 0.210227

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-12.5182	-12.7752
rho	3.36398	3.41177
a	388.84	367.048
b	0.00509897	0.0950512

c	56.4368	5.09997
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386.4	388.8	45.01	43.42	-0.1802
0.1	10	407.1	399.8	36.41	45.5	0.5054
0.5	10	437.1	443.7	69.39	54.22	-0.3865
5	9	936	931.5	193.2	188.7	0.07162

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.1821	5	406.3643
A2	-181.1755	8	378.351
A3	-182.4264	6	376.8527
R	-233.6952	2	471.3904
4	-182.4784	5	374.9568

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105	6	<0.0001
Test 2	34.01	3	<0.0001
Test 3	2.502	2	0.2863
Test 6a	0.1041	1	0.747

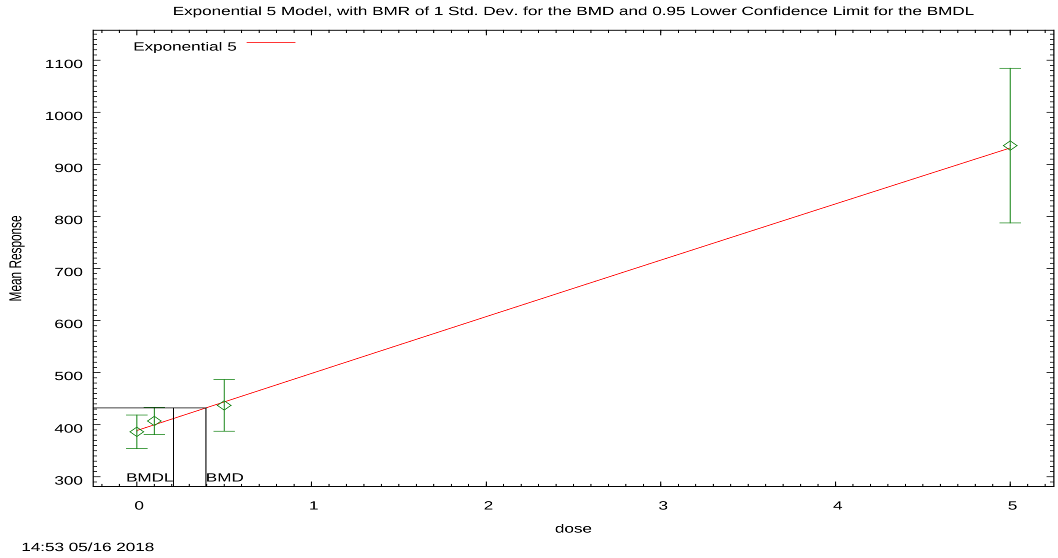

Figure 288. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.395425

BMDL at the 95% confidence level = 0.210227

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-12.5182	-12.7752
rho	3.36397	3.41177
a	388.84	367.048
b	0.00509556	0.0950512

c	56.4734	5.09997
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386.4	388.8	45.01	43.42	-0.1802
0.1	10	407.1	399.8	36.41	45.5	0.5054
0.5	10	437.1	443.7	69.39	54.22	-0.3865
5	9	936	931.5	193.2	188.7	0.07161

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.1821	5	406.3643
A2	-181.1755	8	378.351
A3	-182.4264	6	376.8527
R	-233.6952	2	471.3904
5	-182.4784	5	374.9568

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105	6	<0.0001
Test 2	34.01	3	<0.0001
Test 3	2.502	2	0.2863
Test 7a	0.1041	1	0.747

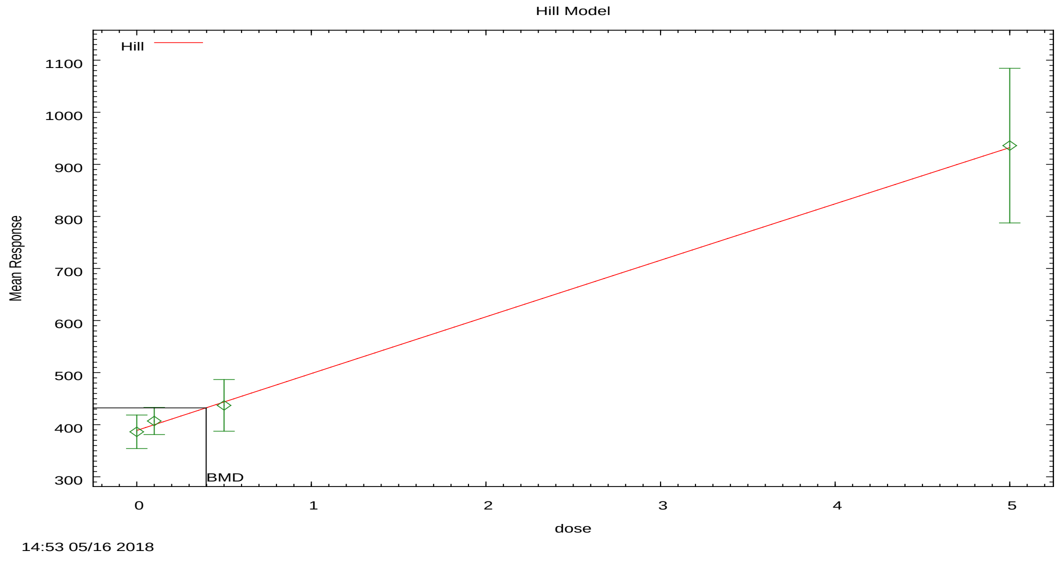

Figure 289. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.397504

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-12.5081	9.2714
rho	3.36233	0
intercept	388.917	386.366
v	75472.5	549.6

n	1	0.797806
k	690.226	7.47882

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386	389	45	43.4	-0.186
0.1	10	407	400	36.4	45.5	0.504
0.5	10	437	444	69.4	54.2	-0.376
5	9	936	932	193	189	0.0677

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.182127	5	406.364254
A2	-181.17551	8	378.351021
A3	-182.426362	6	376.852725
fitted	-182.478479	5	374.956959
R	-233.69519	2	471.39038

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.039	6	<0.0001
Test 2	34.0132	3	<0.0001
Test 3	2.5017	2	0.2863
Test 4	0.104234	1	0.7468

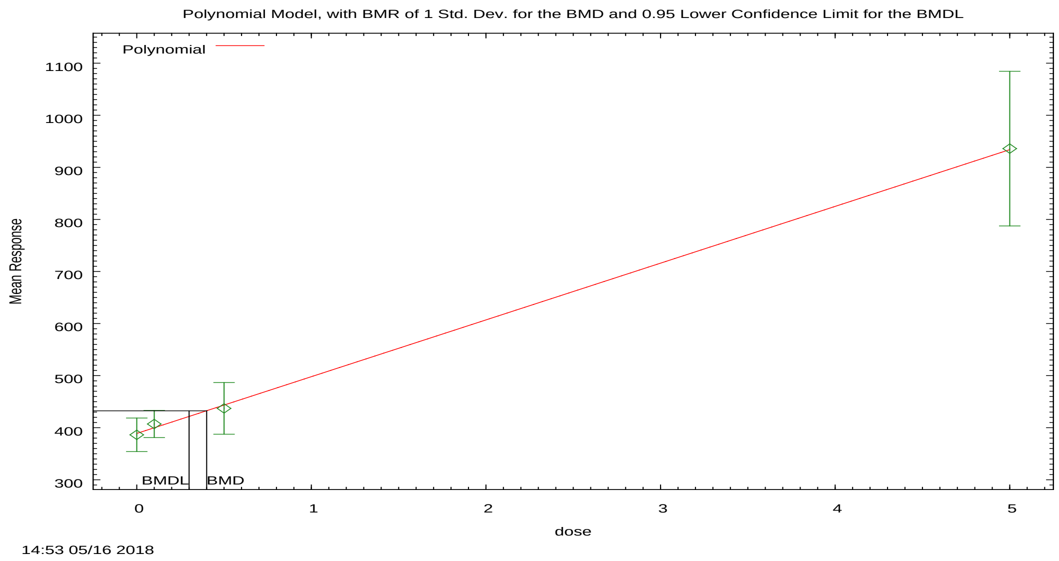

Figure 290. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.400252

BMDL at the 95% confidence level = 0.299666

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-12.4949	9.2714
rho	3.3602	0
beta_0	389.017	386.366
beta_1	108.602	236.541

beta_2	0	0
beta_3	2.57962E-84	54.4047

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386	389	45	43.5	-0.193
0.1	10	407	400	36.4	45.5	0.502
0.5	10	437	443	69.4	54.1	-0.363
5	9	936	932	193	189	0.0626

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.182127	5	406.364254
A2	-181.17551	8	378.351021
A3	-182.426362	6	376.852725
fitted	-182.47882	4	372.957641
R	-233.69519	2	471.39038

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.039	6	<0.0001
Test 2	34.0132	3	<0.0001
Test 3	2.5017	2	0.2863
Test 4	0.104916	2	0.9489

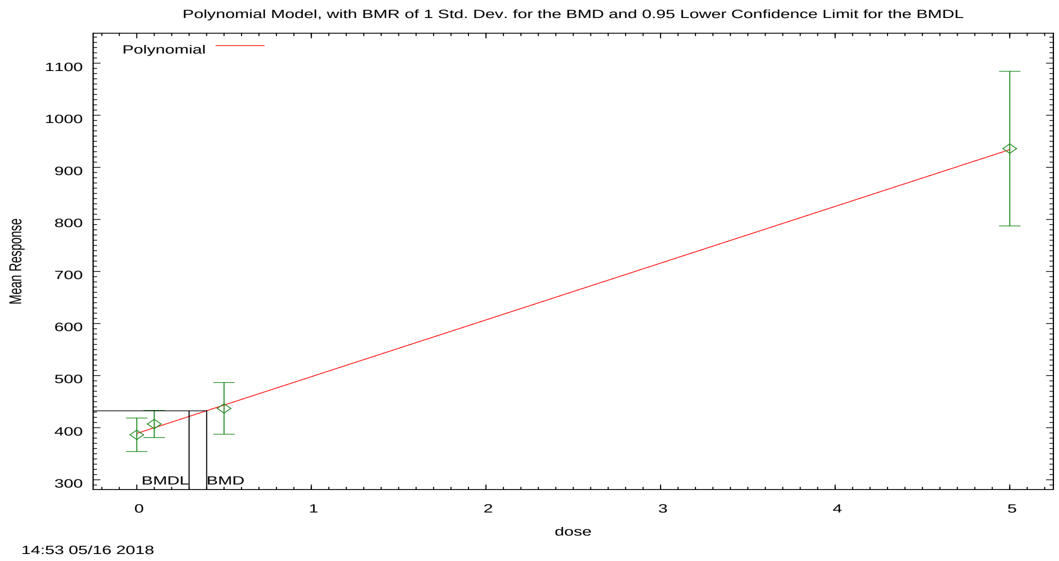

Figure 291. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.400252

BMDL at the 95% confidence level = 0.299666

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-12.4949	9.2714
rho	3.3602	0
beta_0	389.017	391.396
beta_1	108.602	92.5683

beta_2	0	3.26869

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386	389	45	43.5	-0.193
0.1	10	407	400	36.4	45.5	0.502
0.5	10	437	443	69.4	54.1	-0.363
5	9	936	932	193	189	0.0626

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.182127	5	406.364254
A2	-181.17551	8	378.351021
A3	-182.426362	6	376.852725
fitted	-182.47882	4	372.957641
R	-233.69519	2	471.39038

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.039	6	<0.0001
Test 2	34.0132	3	<0.0001
Test 3	2.5017	2	0.2863
Test 4	0.104916	2	0.9489

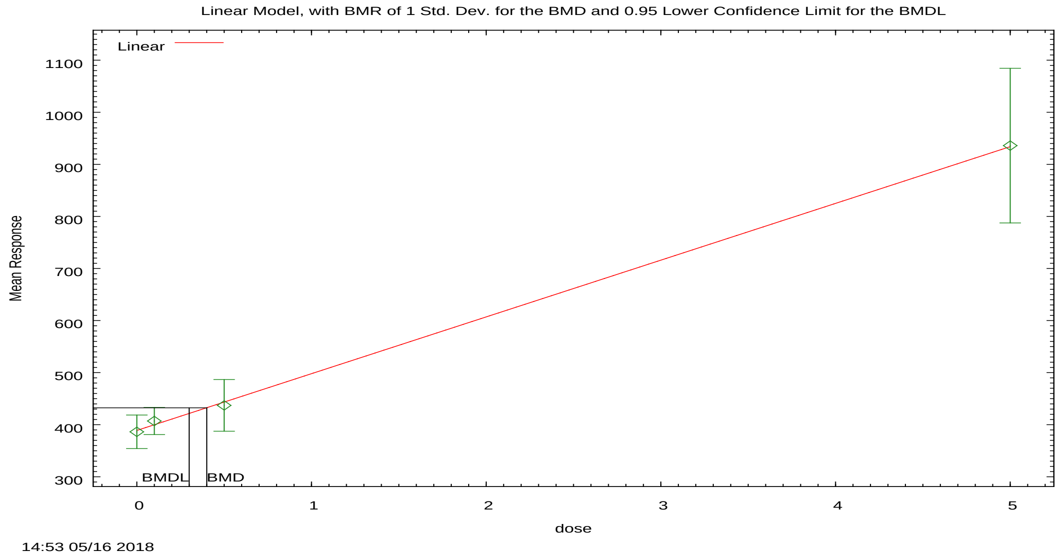

Figure 292. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Liver Weight to Brain Weight in Males (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.400252

BMDL at the 95% confidence level = 0.299666

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-12.4949	9.2714
rho	3.3602	0
beta_0	389.017	388.458
beta_1	108.602	109.411

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	386	389	45	43.5	-0.193
0.1	10	407	400	36.4	45.5	0.502
0.5	10	437	443	69.4	54.1	-0.363
5	9	936	932	193	189	0.0626

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-198.182127	5	406.364254
A2	-181.17551	8	378.351021
A3	-182.426362	6	376.852725
fitted	-182.47882	4	372.957641
R	-233.69519	2	471.39038

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	105.039	6	<0.0001
Test 2	34.0132	3	<0.0001
Test 3	2.5017	2	0.2863
Test 4	0.104916	2	0.9489

BMDS WIZARD OUTPUT REPORT

BMDS Summary of H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice – Liver Weight to Brain Weight (%) in Females

1.33. BMDS Summary of Liver weight to brain weight (%) Females (90 Day Mice GenX)

Table 33. Summary of BMD Modeling Results for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	**0.520**	**368.12**	**1.34**	**0.929**	1.44	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.268	370.04	1.59	0.933	1.70	
Exponential (M4)	0.227	370.28	1.10	0.449	2.45	
Exponential (M5)	N/A[b]	371.77	0.555	0.469	1.18	
Hill	N/A[b]	371.77	0.564	error[c]	error	
Power	0.275	370.01	1.47	0.714	2.05	
Polynomial 3°[d] Polynomial 2°	0.261	370.08	1.57	0.709	2.21	
Linear	0.483	368.27	1.10	0.699	1.57	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were 0.05, -0.08, 0.03, 0, respectively.
[b] No available degrees of freedom to calculate a goodness of fit value.
[c] BMD or BMDL computation failed for this model.
[d] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model.

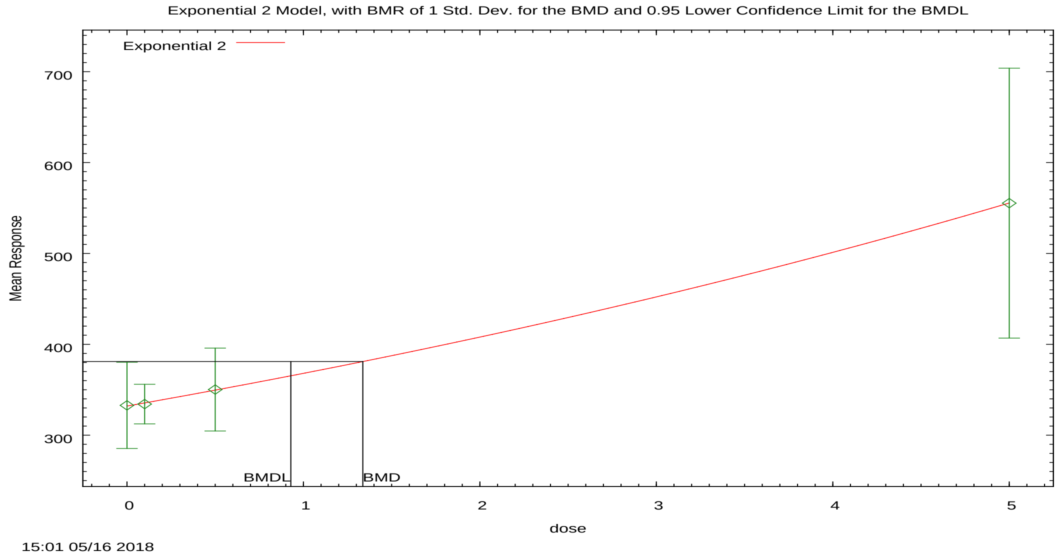

Figure 293. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Liver Weight to Brain Weight in

Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.33655

BMDL at the 95% confidence level = 0.928594

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-21.701	-24.6464
rho	5.07868	5.5678
a	332.061	332.075
b	0.102919	0.102859
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	332.8	332.1	66.34	48.97	0.04942
0.1	10	334.2	335.5	30.44	50.26	-0.07851
0.5	9	350.2	349.6	59.32	55.8	0.03335
5	9	555.3	555.5	193.2	180.9	-0.003207

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.7363	5	397.4727

A2	-177.1145	8	370.229
A3	-179.4087	6	370.8173
R	-205.5727	2	415.1453
2	-180.062	4	368.124

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.92	6	<0.0001
Test 2	33.24	3	<0.0001
Test 3	4.588	2	0.1008
Test 4	1.307	2	0.5203

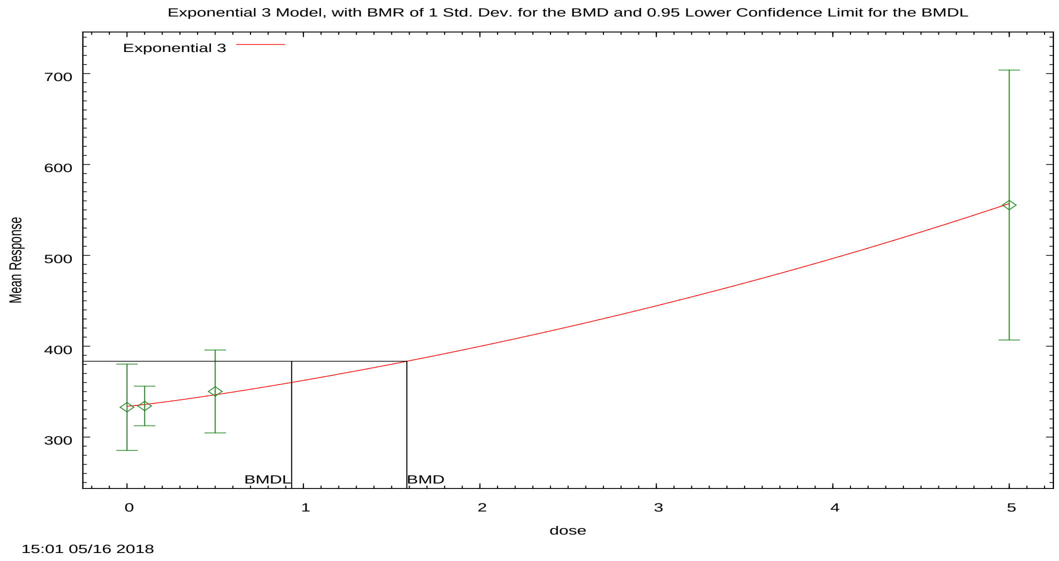

Figure 294. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.58582

BMDL at the 95% confidence level = 0.933248

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-21.7049	-24.6464
rho	5.07872	5.5678
a	333.889	332.075
b	0.111062	0.102859
c	n/a	0
d	1.13876	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	332.8	333.9	66.34	49.57	-0.06782
0.1	10	334.2	335.9	30.44	50.32	-0.1026
0.5	9	350.2	346.5	59.32	54.47	0.2026
5	9	555.3	557	193.2	181.8	-0.02782

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.7363	5	397.4727
A2	-177.1145	8	370.229
A3	-179.4087	6	370.8173
R	-205.5727	2	415.1453
3	-180.0222	5	370.0445

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value

Test 1	56.92	6	<0.0001
Test 2	33.24	3	<0.0001
Test 3	4.588	2	0.1008
Test 5a	1.227	1	0.268

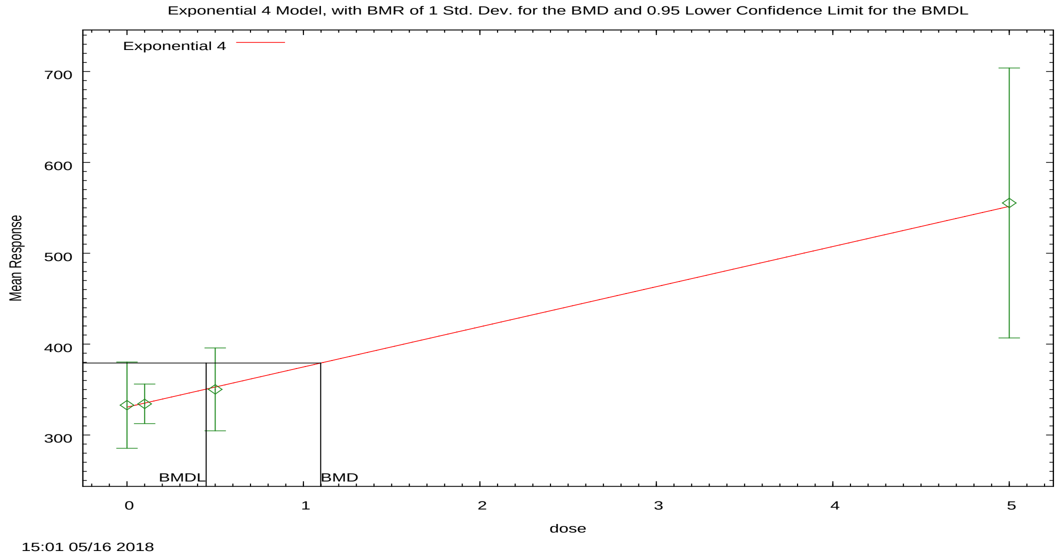

Figure 295. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 1.09769

BMDL at the 95% confidence level = 0.448825

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-21.9721	-24.6464
rho	5.1258	5.5678
a	330.674	316.185
b	0.0000741586	0.0718443
c	1803.04	3.51269
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	332.8	330.7	66.34	48.51	0.1403
0.1	10	334.2	335.1	30.44	50.18	-0.05327
0.5	9	350.2	352.8	59.32	57.25	-0.1338
5	9	555.3	551.6	193.2	180	0.06242

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.7363	5	397.4727
A2	-177.1145	8	370.229
A3	-179.4087	6	370.8173
R	-205.5727	2	415.1453
4	-180.1376	5	370.2751

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.92	6	<0.0001
Test 2	33.24	3	<0.0001
Test 3	4.588	2	0.1008
Test 6a	1.458	1	0.2273

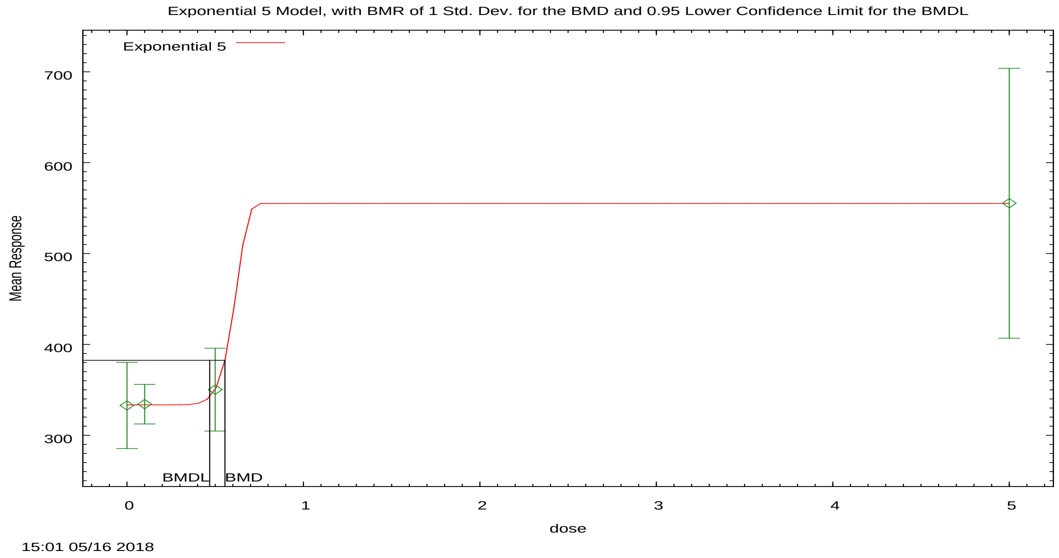

Figure 296. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.555118

BMDL at the 95% confidence level = 0.468614

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-22.1329	-24.6464
rho	5.14986	5.5678
a	333.478	316.185
b	1.58761	0.0718443

c	1.66492	3.51269
d	10.9725	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	332.8	333.5	66.34	49.05	-0.04202
0.1	10	334.2	333.5	30.44	49.05	0.04966
0.5	9	350.2	350.4	59.32	55.71	-0.009639
5	9	555.3	555.2	193.2	182.3	0.001931

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.7363	5	397.4727
A2	-177.1145	8	370.229
A3	-179.4087	6	370.8173
R	-205.5727	2	415.1453
5	-179.8862	6	371.7724

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.92	6	<0.0001
Test 2	33.24	3	<0.0001
Test 3	4.588	2	0.1008
Test 7a	0.9551	0	N/A

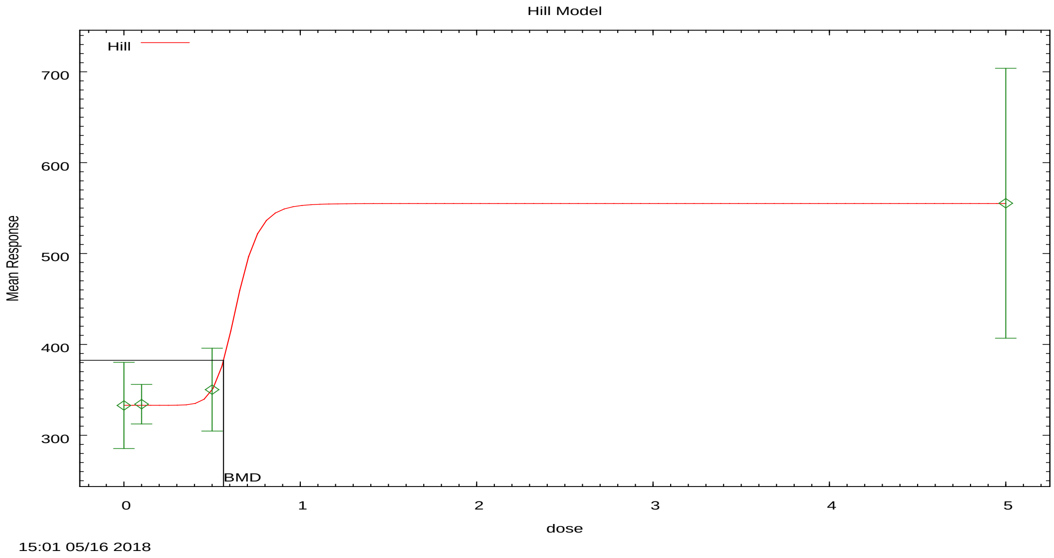

Figure 297. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.564491

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-22.133	9.30788
rho	5.14986	0
intercept	333.478	332.826
v	221.735	222.504
n	10.1808	1.04245

k	0.638779	7.44076

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	333	333	66.3	49	-0.042
0.1	10	334	333	30.4	49	0.0497
0.5	9	350	350	59.3	55.7	-0.00964
5	9	555	555	193	182	0.00193

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.736349	5	397.472698
A2	-177.114505	8	370.229011
A3	-179.408666	6	370.817331
fitted	-179.886216	6	371.772432
R	-205.572651	2	415.145302

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.9163	6	<0.0001
Test 2	33.2437	3	<0.0001
Test 3	4.58832	2	0.1008
Test 4	0.9551	0	N/A

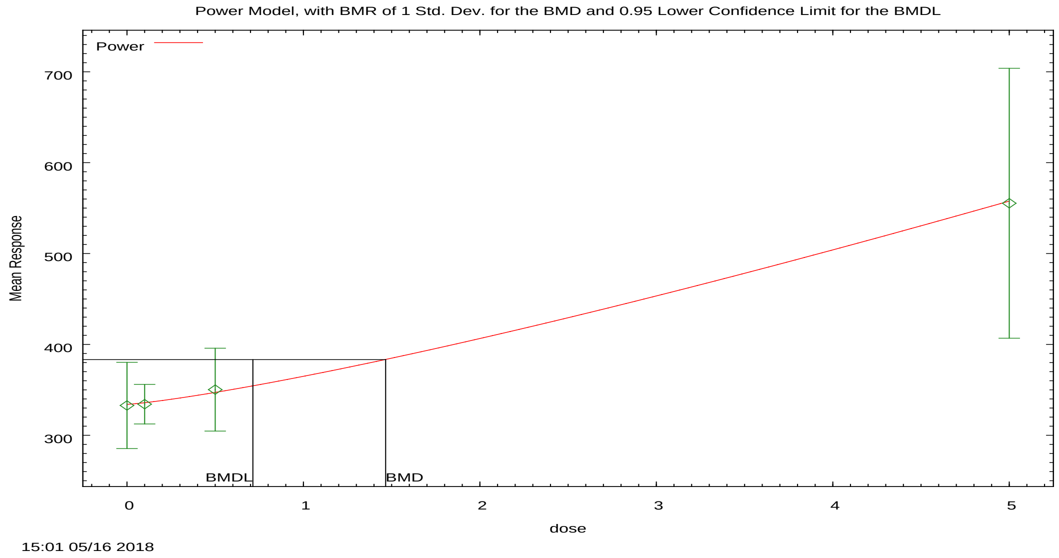

Figure 298. Plot of mean response by dose with fitted curve for Power model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.46578

BMDL at the 95% confidence level = 0.713574

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-21.717	9.30788
rho	5.08057	0
control	333.778	332.826
slope	30.9436	28.4057
power	1.22806	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	333	334	66.3	49.5	-0.0608
0.1	10	334	336	30.4	50.2	-0.0857
0.5	9	350	347	59.3	54.6	0.177
5	9	555	557	193	182	-0.0293

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.736349	5	397.472698
A2	-177.114505	8	370.229011
A3	-179.408666	6	370.817331
fitted	-180.005253	5	370.010505
R	-205.572651	2	415.145302

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.9163	6	<0.0001
Test 2	33.2437	3	<0.0001
Test 3	4.58832	2	0.1008
Test 4	1.19317	1	0.2747

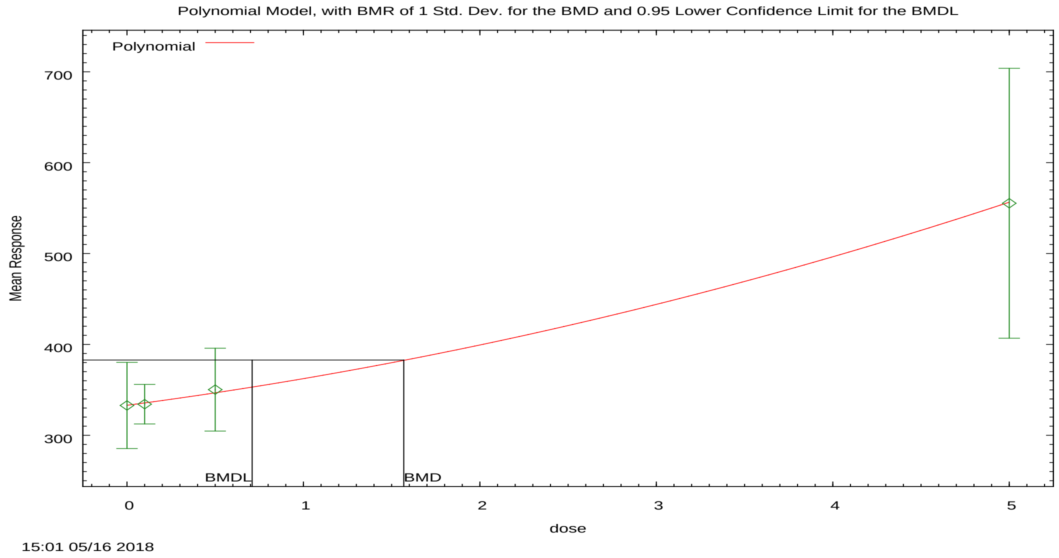

Figure 299. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.56853

BMDL at the 95% confidence level = 0.709326

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-21.6616	9.30788
rho	5.07164	0
beta_0	333.382	332.826
beta_1	25.4879	8.57755

beta_2	3.84048	57.4294
beta_3	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	333	333	66.3	49.4	-0.0356
0.1	10	334	336	30.4	50.4	-0.108
0.5	9	350	347	59.3	54.7	0.172
5	9	555	557	193	182	-0.0248

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.736349	5	397.472698
A2	-177.114505	8	370.229011
A3	-179.408666	6	370.817331
fitted	-180.041834	5	370.083668
R	-205.572651	2	415.145302

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.9163	6	<0.0001
Test 2	33.2437	3	<0.0001
Test 3	4.58832	2	0.1008
Test 4	1.26634	1	0.2605

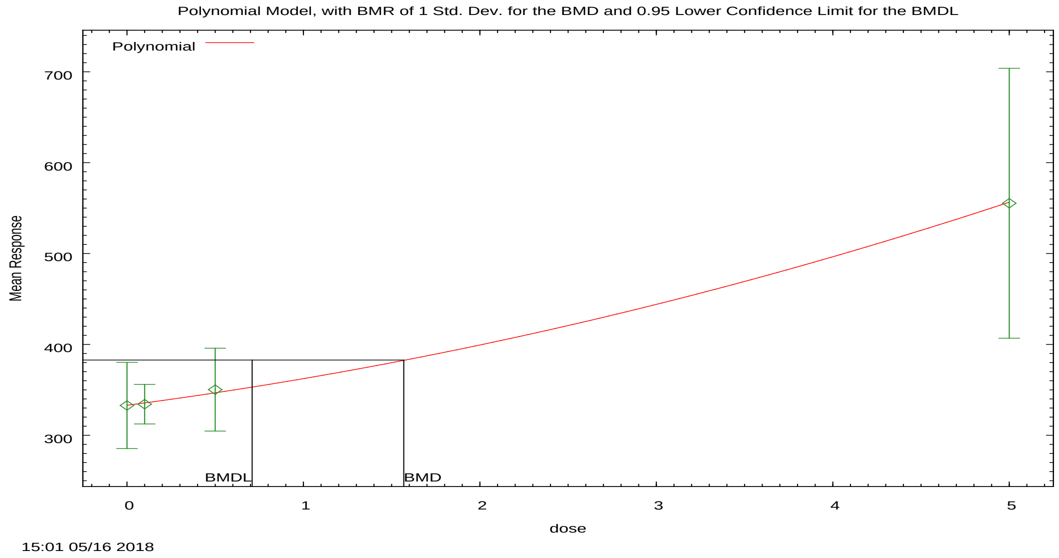

Figure 300. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.56853

BMDL at the 95% confidence level = 0.709326

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-21.6616	9.30788
rho	5.07164	0
beta_0	333.382	331.897
beta_1	25.4879	35.1703

beta_2	3.84048	1.90335

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	333	333	66.3	49.4	-0.0356
0.1	10	334	336	30.4	50.4	-0.108
0.5	9	350	347	59.3	54.7	0.172
5	9	555	557	193	182	-0.0248

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.736349	5	397.472698
A2	-177.114505	8	370.229011
A3	-179.408666	6	370.817331
fitted	-180.041834	5	370.083668
R	-205.572651	2	415.145302

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.9163	6	<0.0001
Test 2	33.2437	3	<0.0001
Test 3	4.58832	2	0.1008
Test 4	1.26634	1	0.2605

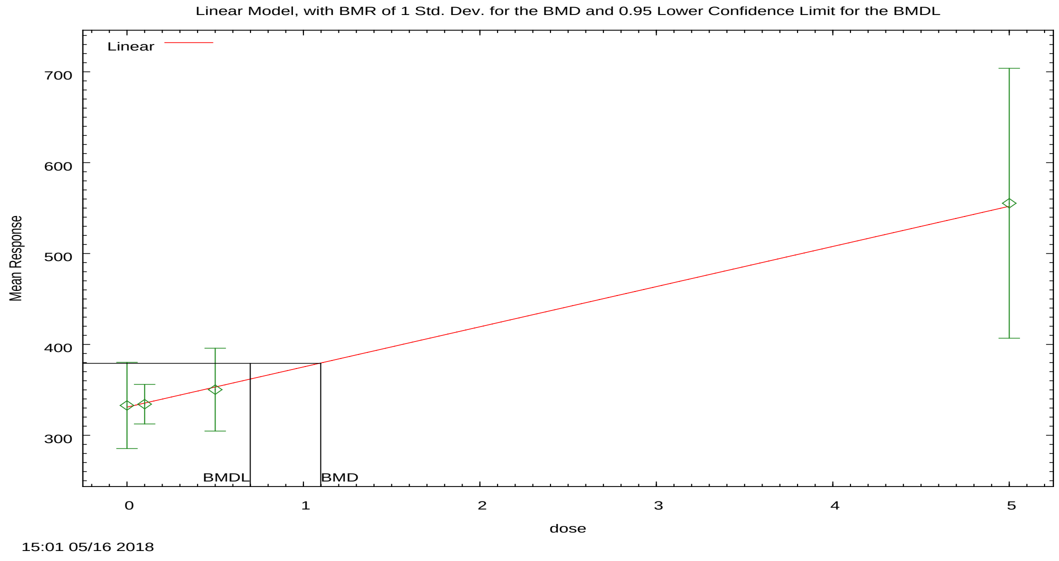

Figure 301. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Liver Weight to Brain Weight in Females (90-Day Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 1.09783

BMDL at the 95% confidence level = 0.698635

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-21.9718	9.30788
rho	5.12574	0
beta_0	330.675	330.186
beta_1	44.1828	44.9779

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	10	333	331	66.3	48.5	0.14
0.1	10	334	335	30.4	50.2	-0.0533
0.5	9	350	353	59.3	57.2	-0.134
5	9	555	552	193	180	0.0623

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-193.736349	5	397.472698
A2	-177.114505	8	370.229011
A3	-179.408666	6	370.817331
fitted	-180.137486	4	368.274971
R	-205.572651	2	415.145302

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	56.9163	6	<0.0001
Test 2	33.2437	3	<0.0001
Test 3	4.58832	2	0.1008
Test 4	1.45764	2	0.4825

BMDS WIZARD OUTPUT REPORT

BMDS Summary of Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice – Liver Weight to Brain Weight (g/100g brain) in Males

1.34. BMDS Summary of Liver weight to brain weight (g/100g brain weight) (Reproductive Mice GenX)

Table 34. Summary of BMD Modeling Results for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD$_{1SD}$ (mg/kg/day)	BMDL$_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2) Exponential (M3)[b]	3.52E-04	941.07	0.774	0.662	1.17	Only one model met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values < 2.0; appropriate variance (continuous data only)). Selected BMDL is from this model.
Exponential (M4) **Exponential (M5)[c]**	**0.570**	**927.48**	**0.232**	**0.165**	**1.40**	
Hill	0.586	927.46	0.229	error[d]	error	
Power[e] Polynomial 3°[f] Polynomial 2°[g] Linear	0.0179	933.21	0.472	0.388	1.22	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.15, 0.27, -0.13, 0.02, respectively.

[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[d] BMD or BMDL computation failed for this model.

[e] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.

[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.

[g] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

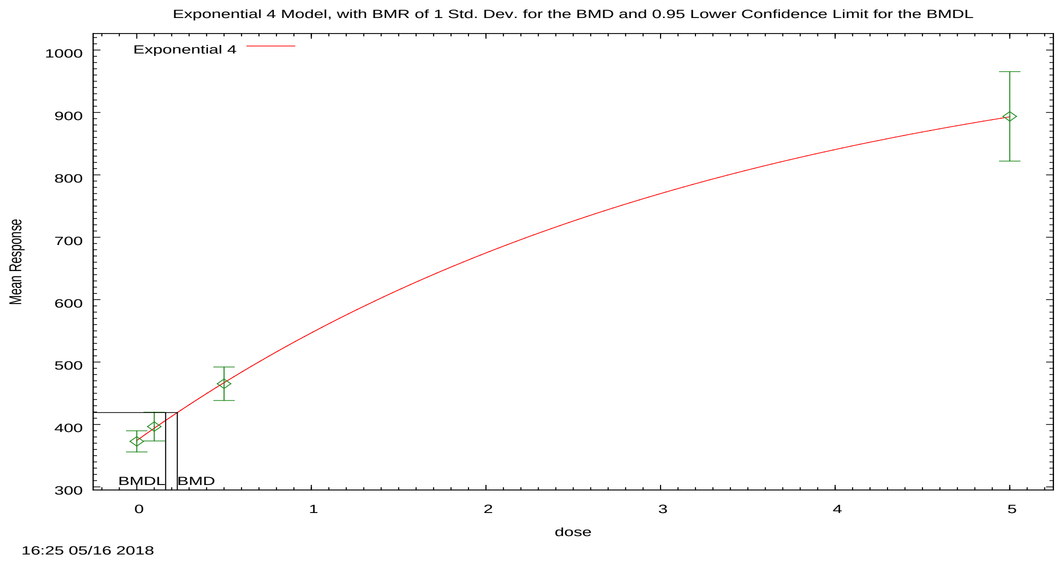

Figure 302. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.23223

BMDL at the 95% confidence level = 0.16532

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-10.3467	-10.4607
rho	3.02939	3.05296
a	374.308	354.287
b	0.297892	0.513265
c	2.78911	2.64868
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	372.9	374.3	41.08	44.76	-0.1535
0.1	24	396.6	394	54.49	48.37	0.2689
0.5	24	465.3	467	63.57	62.58	-0.1333
5	24	893.7	893	169.8	167.1	0.02143

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.6261	5	989.2522
A2	-458.1745	8	932.349
A3	-458.5804	6	929.1608
R	-576.4866	2	1156.973
4	-458.7417	5	927.4834

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.6	6	<0.0001
Test 2	62.9	3	<0.0001
Test 3	0.8118	2	0.6664
Test 6a	0.3226	1	0.5701

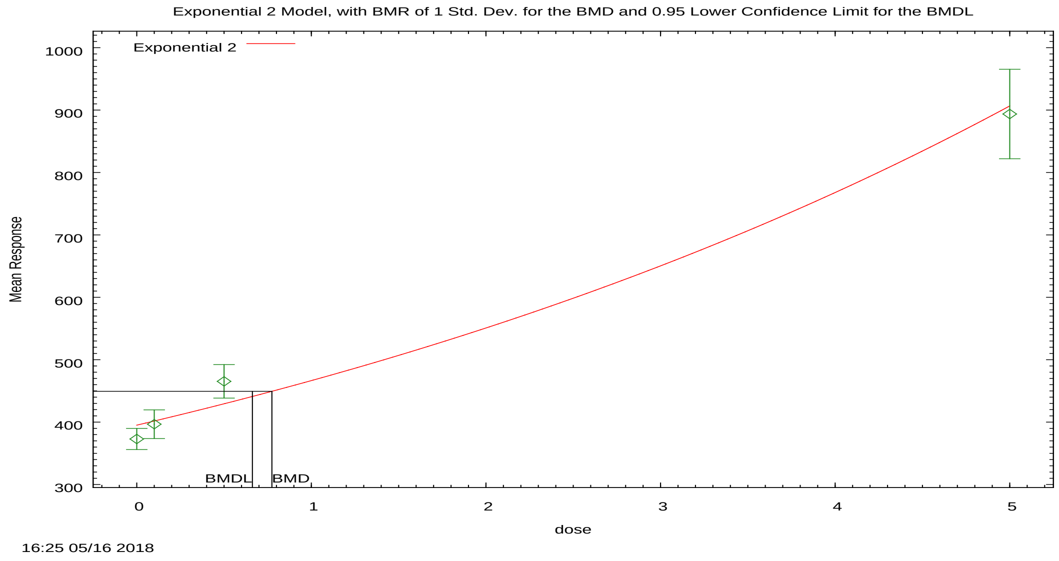

Figure 303. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.77405

BMDL at the 95% confidence level = 0.662372

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-8.47038	-10.4607
rho	2.75225	3.05296
a	395.114	395.162
b	0.166106	0.164785
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	372.9	395.1	41.08	54.21	-2.046
0.1	24	396.6	401.7	54.49	55.47	-0.4516
0.5	24	465.3	429.3	63.57	60.78	2.898
5	24	893.7	906.6	169.8	170	-0.3716

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.6261	5	989.2522
A2	-458.1745	8	932.349
A3	-458.5804	6	929.1608
R	-576.4866	2	1156.973
2	-466.5332	4	941.0663

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.6	6	<0.0001
Test 2	62.9	3	<0.0001
Test 3	0.8118	2	0.6664
Test 4	15.91	2	0.0003517

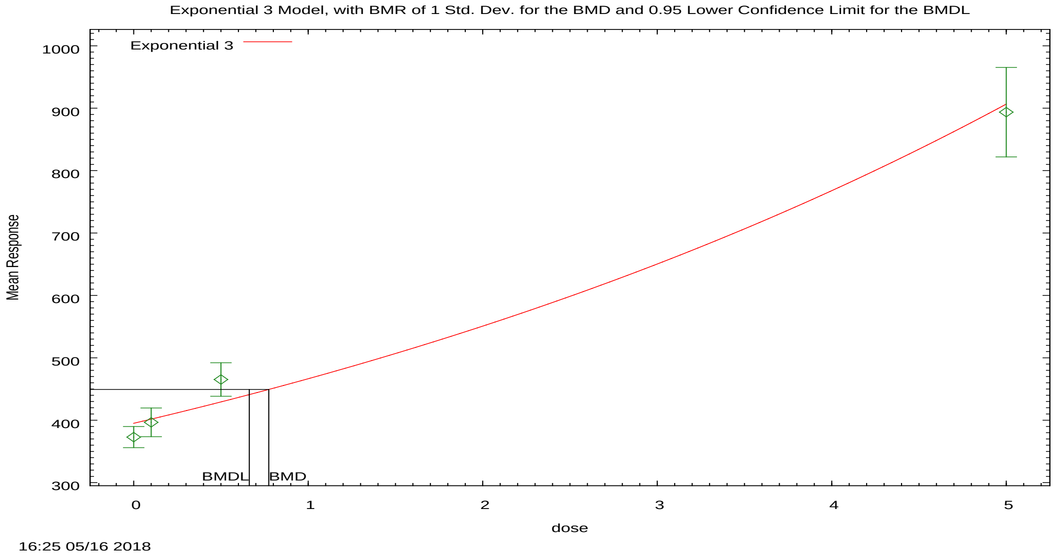

Figure 304. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.77405

BMDL at the 95% confidence level = 0.662372

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-8.47038	-10.4607
rho	2.75225	3.05296
a	395.114	395.162
b	0.166106	0.164785
c	n/a	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	372.9	395.1	41.08	54.21	-2.046
0.1	24	396.6	401.7	54.49	55.47	-0.4516
0.5	24	465.3	429.3	63.57	60.78	2.898
5	24	893.7	906.6	169.8	170	-0.3716

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.6261	5	989.2522
A2	-458.1745	8	932.349
A3	-458.5804	6	929.1608
R	-576.4866	2	1156.973
3	-466.5332	4	941.0663

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.6	6	<0.0001
Test 2	62.9	3	<0.0001
Test 3	0.8118	2	0.6664
Test 5a	15.91	2	0.0003517

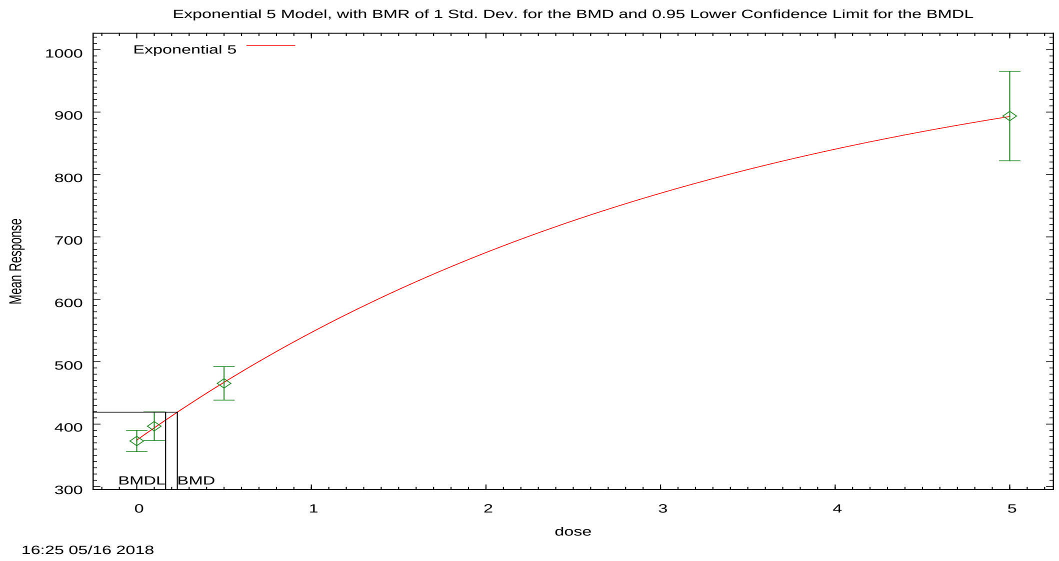

Figure 305. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 0.23223

BMDL at the 95% confidence level = 0.16532

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-10.3467	-10.4607
rho	3.02939	3.05296
a	374.308	354.287
b	0.297893	0.513265

c	2.78911	2.64868
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	372.9	374.3	41.08	44.76	-0.1535
0.1	24	396.6	394	54.49	48.37	0.2689
0.5	24	465.3	467	63.57	62.58	-0.1333
5	24	893.7	893	169.8	167.1	0.02143

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.6261	5	989.2522
A2	-458.1745	8	932.349
A3	-458.5804	6	929.1608
R	-576.4866	2	1156.973
5	-458.7417	5	927.4834

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.6	6	<0.0001
Test 2	62.9	3	<0.0001
Test 3	0.8118	2	0.6664
Test 7a	0.3226	1	0.5701

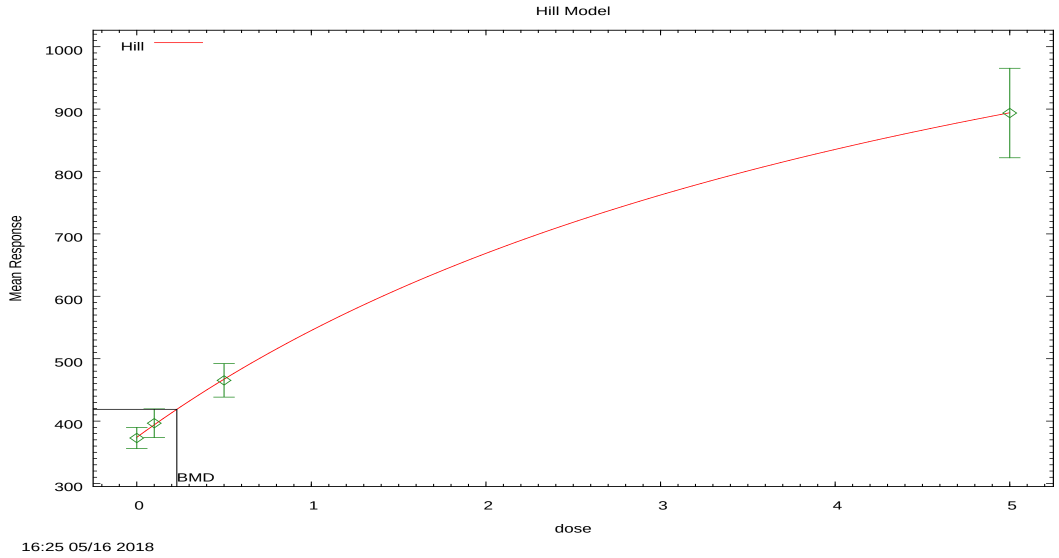

Figure 306. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.229327

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-10.355	9.1375
rho	3.03069	0
intercept	374.154	372.934
v	1057.51	520.775

n	1	0.630167
k	5.1936	7.73496

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	373	374	41.1	44.7	-0.136
0.1	24	397	394	54.5	48.4	0.252
0.5	24	465	467	63.6	62.6	-0.137
5	24	894	893	170	167	0.0247

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.626103	5	989.252206
A2	-458.17449	8	932.34898
A3	-458.580397	6	929.160793
fitted	-458.728897	5	927.457794
R	-576.486609	2	1156.973219

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.624	6	<0.0001
Test 2	62.9032	3	<0.0001
Test 3	0.811814	2	0.6664
Test 4	0.297001	1	0.5858

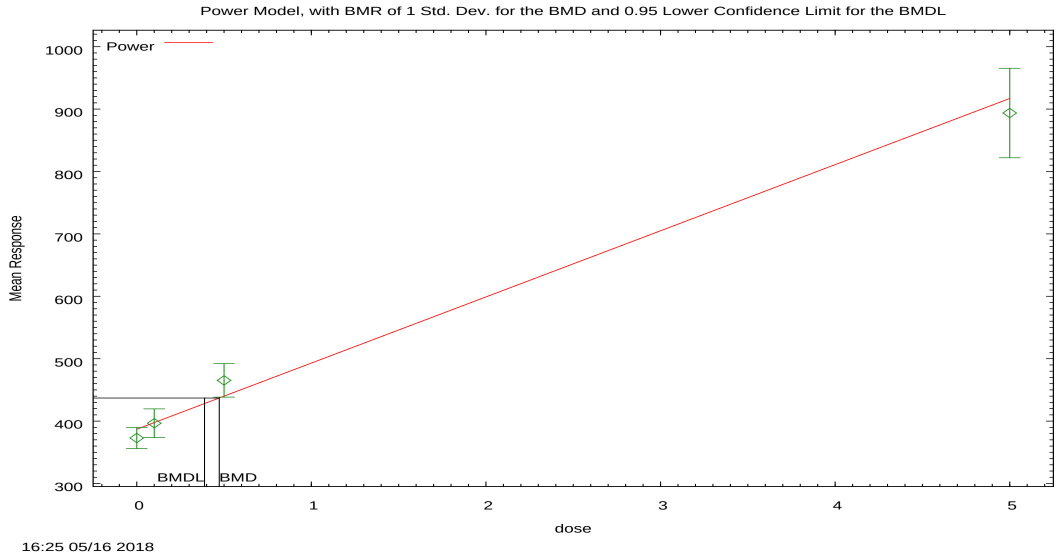

Figure 307. Plot of mean response by dose with fitted curve for Power model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.472329

BMDL at the 95% confidence level = 0.388102

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-9.25889	9.1375
rho	2.86598	0
control	387.098	372.934
slope	105.57	146.664

power	1	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	373	387	41.1	49.9	-1.42
0.1	24	397	398	54.5	51.8	-0.098
0.5	24	465	440	63.6	59.9	2.08
5	24	894	915	170	171	-0.608

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.626103	5	989.252206
A2	-458.17449	8	932.34898
A3	-458.580397	6	929.160793
fitted	-462.606263	4	933.212526
R	-576.486609	2	1156.973219

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.624	6	<0.0001
Test 2	62.9032	3	<0.0001
Test 3	0.811814	2	0.6664
Test 4	8.05173	2	0.01785

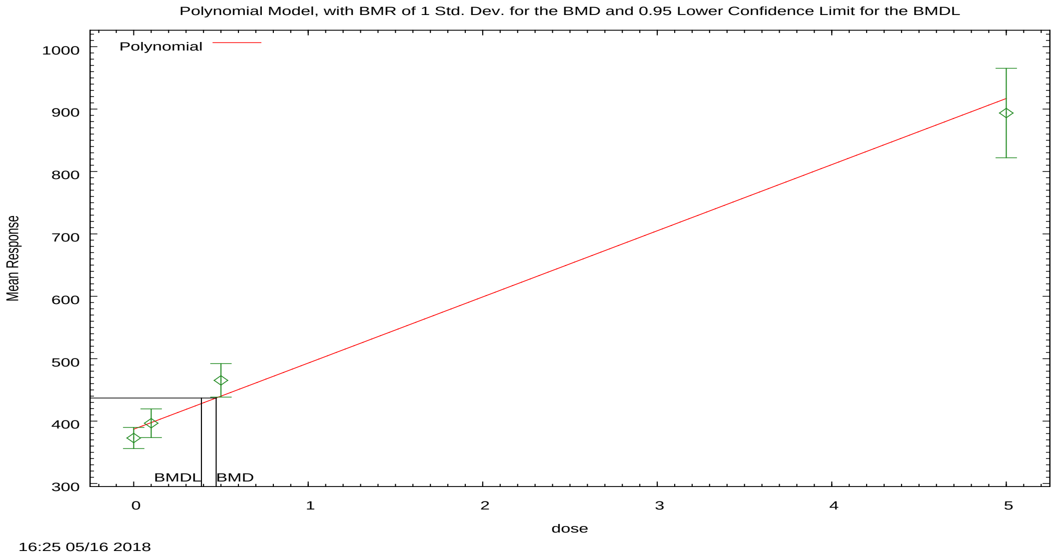

Figure 308. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.472329

BMDL at the 95% confidence level = 0.388102

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-9.25889	9.1375
rho	2.86598	0
beta_0	387.098	372.934
beta_1	105.57	251.026

beta_2	3.92727E-92	0
beta_3	0	22.9559

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	373	387	41.1	49.9	-1.42
0.1	24	397	398	54.5	51.8	-0.098
0.5	24	465	440	63.6	59.9	2.08
5	24	894	915	170	171	-0.608

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.626103	5	989.252206
A2	-458.17449	8	932.34898
A3	-458.580397	6	929.160793
fitted	-462.606263	4	933.212526
R	-576.486609	2	1156.973219

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.624	6	<0.0001
Test 2	62.9032	3	<0.0001
Test 3	0.811814	2	0.6664
Test 4	8.05173	2	0.01785

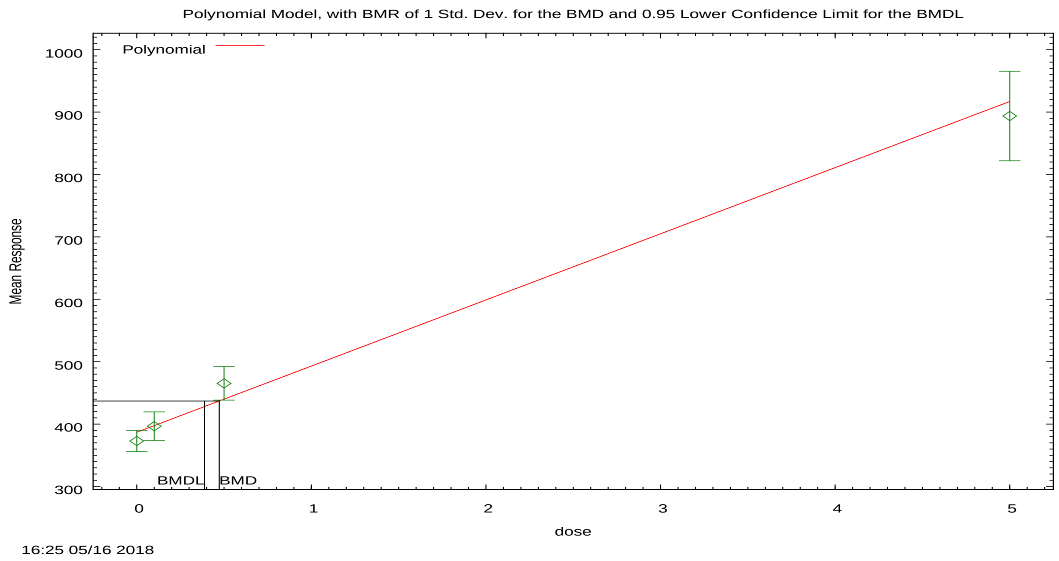

Figure 309. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.472329

BMDL at the 95% confidence level = 0.388102

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-9.2589	9.1375
rho	2.86598	0
beta_0	387.098	375.056
beta_1	105.57	190.277

beta_2	0	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	373	387	41.1	49.9	-1.42
0.1	24	397	398	54.5	51.8	-0.098
0.5	24	465	440	63.6	59.9	2.08
5	24	894	915	170	171	-0.608

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.626103	5	989.252206
A2	-458.17449	8	932.34898
A3	-458.580397	6	929.160793
fitted	-462.606263	4	933.212526
R	-576.486609	2	1156.973219

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.624	6	<0.0001
Test 2	62.9032	3	<0.0001
Test 3	0.811814	2	0.6664
Test 4	8.05173	2	0.01785

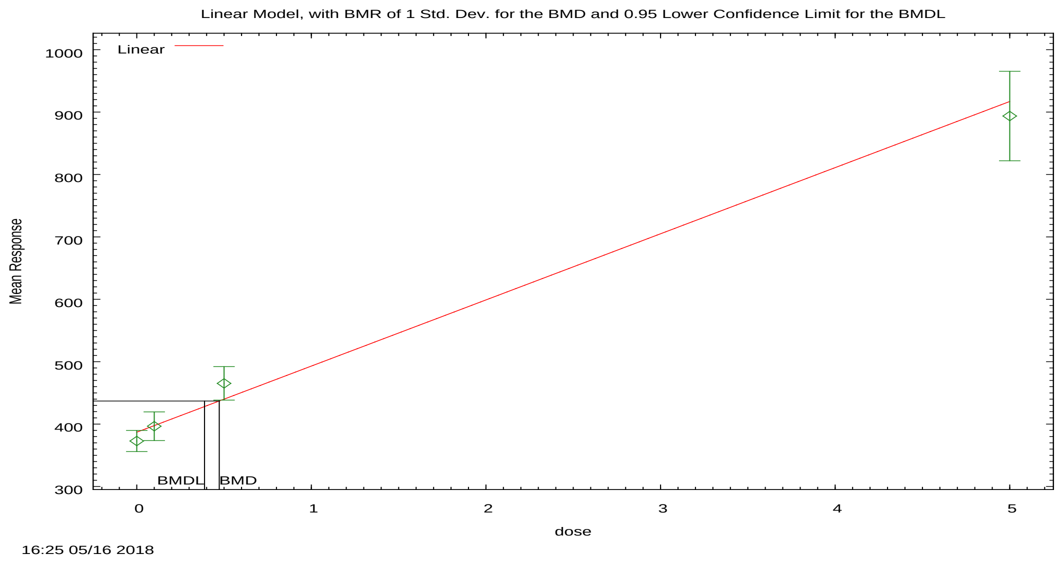

Figure 310. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Liver Weight to Brain Weight in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 0.472329

BMDL at the 95% confidence level = 0.388102

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	-9.2589	9.1375
rho	2.86598	0
beta_0	387.098	390.617
beta_1	105.57	101.084

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	373	387	41.1	49.9	-1.42
0.1	24	397	398	54.5	51.8	-0.098
0.5	24	465	440	63.6	59.9	2.08
5	24	894	915	170	171	-0.608

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-489.626103	5	989.252206
A2	-458.17449	8	932.34898
A3	-458.580397	6	929.160793
fitted	-462.606263	4	933.212526
R	-576.486609	2	1156.973219

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	236.624	6	<0.0001
Test 2	62.9032	3	<0.0001
Test 3	0.811814	2	0.6664
Test 4	8.05173	2	0.01785

BMDS WIZARD OUTPUT REPORT

BMDS Summary of Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats – Percent per Litter with Skeletal Variations

1.35. BMDS Summary of Percent per litter with skeletal variations (%) (Prenatal and Developmental Rats GenX)

Table 35. Summary of BMD Modeling Results for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.563	547.74	716	540	1.33	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.364	549.41	872	548	1.59	
Exponential (M4)	0.206	550.19	614	386	1.59	
Exponential (M5)	N/A[b]	551.41	831	107	7.75	
Hill	N/A[b]	551.41	613	error[c]	error	
Power	0.364	549.41	833	411	2.02	
Polynomial 3°	0.364	549.41	848	636	1.33	
Polynomial 2°	**0.661**	**547.42**	**805**	**635**	**1.27**	
Linear	0.450	548.19	614	386	1.59	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 10, 100, and 1000 mg/kg/day were -0.63, -0.23, 0.89, -0.01, respectively.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

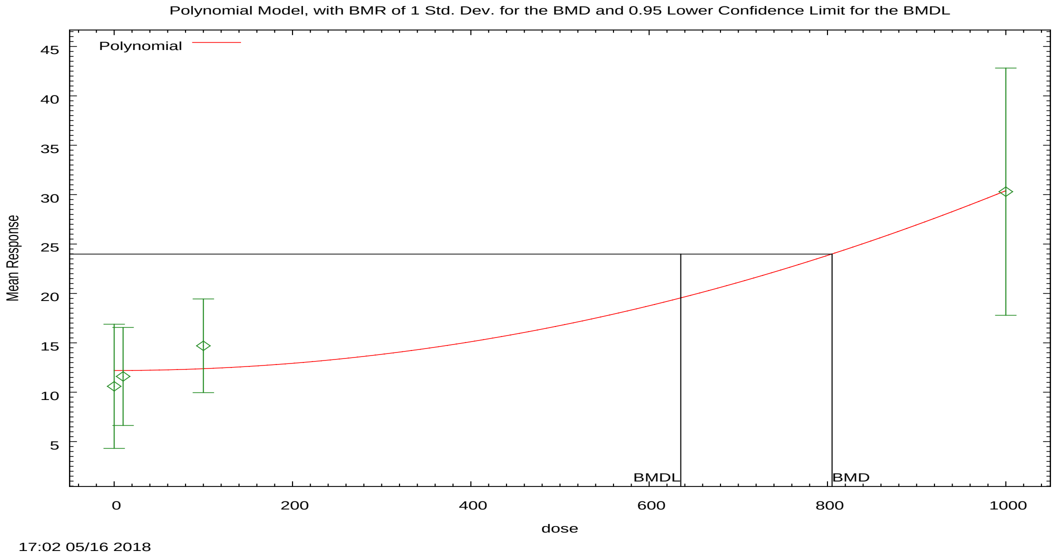

Figure 311. Plot of mean response by dose with fitted curve for Polynomial 2° model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 805.163

BMDL at the 95% confidence level = 635.448

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.438015	5.68628
rho	1.7978	0
beta_0	12.1925	10.8806
beta_1	1.99095E-24	0.0406653
beta_2	0.0000181818	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	12.2	14.2	11.8	-0.634
10	21	11.6	12.2	10.9	11.8	-0.231
100	21	14.7	12.4	10.4	11.9	0.892
1000	21	30.3	30.4	27.5	26.8	-0.0127

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC

A1	-282.118145	5	574.236289
A2	-267.74874	8	551.497479
A3	-269.294095	6	550.58819
fitted	-269.707549	4	547.415099
R	-290.685425	2	585.37085

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.8734	6	<0.0001
Test 2	28.7388	3	<0.0001
Test 3	3.09071	2	0.2132
Test 4	0.826909	2	0.6614

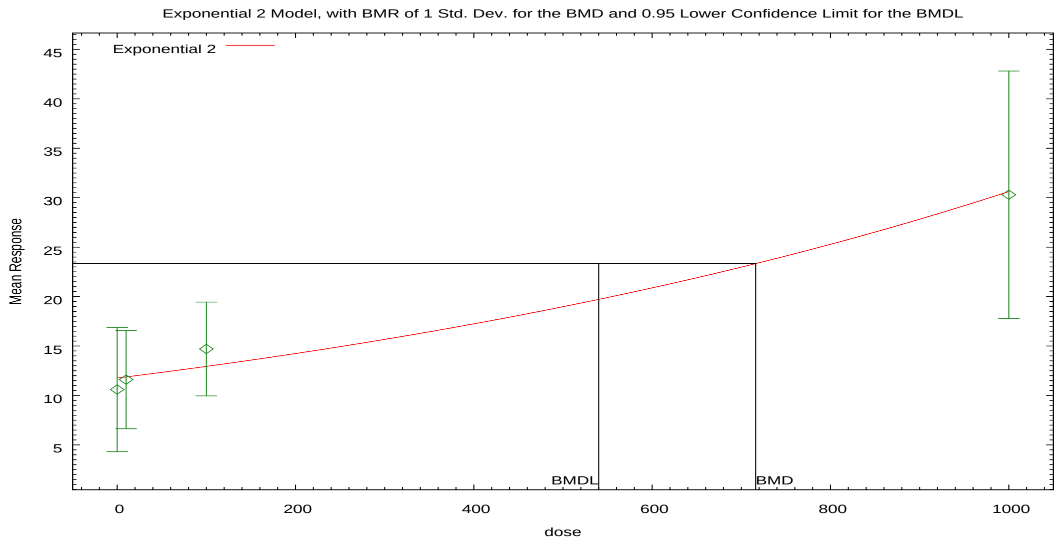

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Figure 312. Plot of mean response by dose with fitted curve for Exponential (M2) model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 716.091

BMDL at the 95% confidence level = 540.031

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.657242	1.03331
rho	1.72078	1.58206
a	11.7578	11.6882
b	0.000957211	0.000965669
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	11.76	14.17	11.58	-0.4691
10	21	11.6	11.87	10.9	11.67	-0.1064
100	21	14.7	12.94	10.42	12.57	0.642
1000	21	30.3	30.62	27.49	26.38	-0.05599

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.1181	5	574.2363
A2	-267.7487	8	551.4975
A3	-269.2941	6	550.5882
R	-290.6854	2	585.3709
2	-269.868	4	547.736

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.87	6	<0.0001
Test 2	28.74	3	<0.0001
Test 3	3.091	2	0.2132
Test 4	1.148	2	0.5633

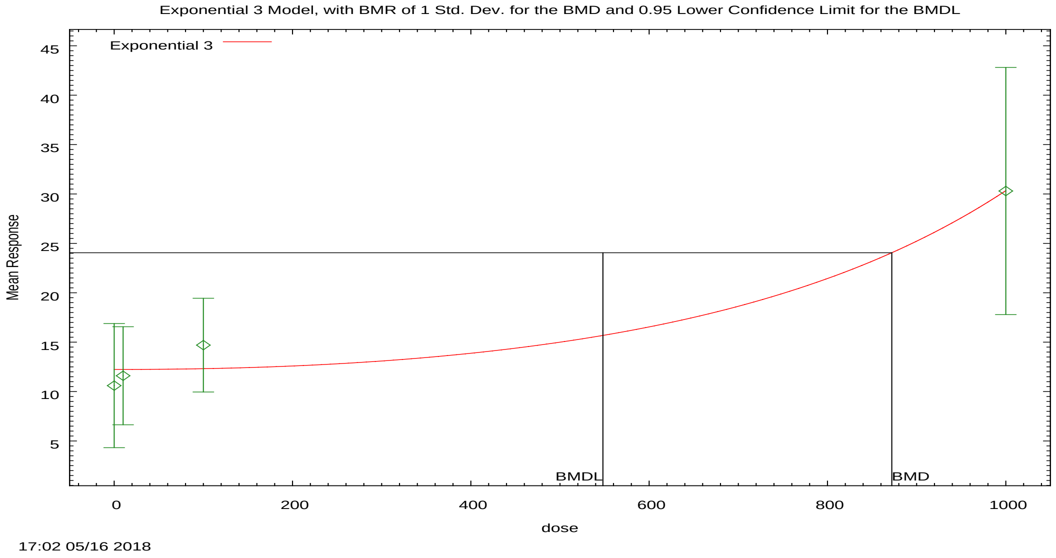

Figure 313. Plot of mean response by dose with fitted curve for Exponential (M3) model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 872.124

BMDL at the 95% confidence level = 548.126

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.41575	1.03331
rho	1.80569	1.58206
a	12.2385	11.6882
b	0.000956119	0.000965669
c	n/a	0
d	2.15848	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	12.24	14.17	11.81	-0.6506
10	21	11.6	12.24	10.9	11.81	-0.2479
100	21	14.7	12.32	10.42	11.88	0.9197
1000	21	30.3	30.33	27.49	26.81	-0.00584

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.1181	5	574.2363
A2	-267.7487	8	551.4975
A3	-269.2941	6	550.5882
R	-290.6854	2	585.3709
3	-269.7063	5	549.4126

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.87	6	<0.0001
Test 2	28.74	3	<0.0001
Test 3	3.091	2	0.2132
Test 5a	0.8244	1	0.3639

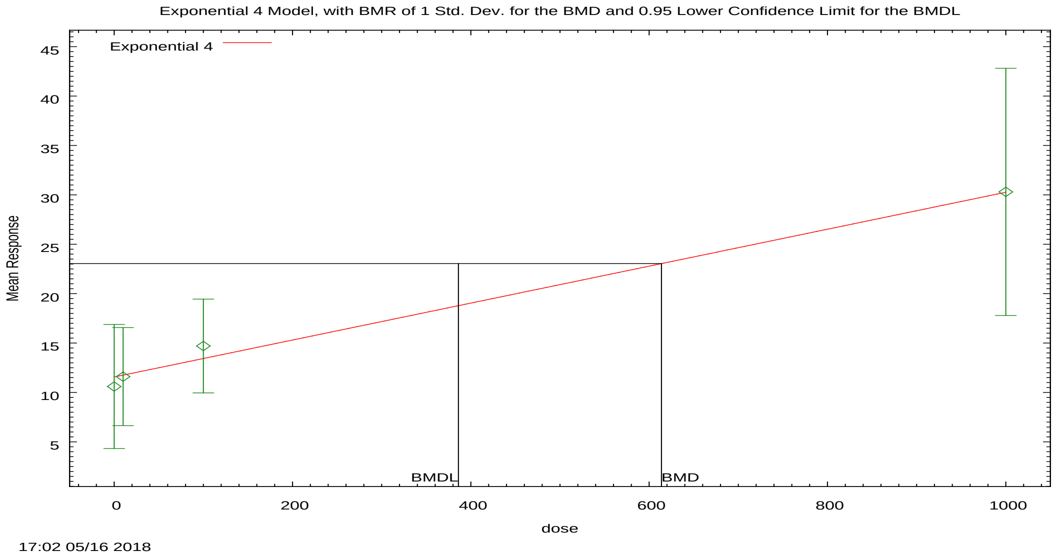

Figure 314. Plot of mean response by dose with fitted curve for Exponential (M4) model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 613.794

BMDL at the 95% confidence level = 386.055

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.713673	1.03331
rho	1.70232	1.58206
a	11.5638	10.07
b	0.0000000754115	0.000156222

c	21444.1	15.0447
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	11.56	14.17	11.48	-0.3939
10	21	11.6	11.75	10.9	11.64	-0.0594
100	21	14.7	13.43	10.42	13.04	0.445
1000	21	30.3	30.26	27.49	26.03	0.00661

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.1181	5	574.2363
A2	-267.7487	8	551.4975
A3	-269.2941	6	550.5882
R	-290.6854	2	585.3709
4	-270.0929	5	550.1858

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.87	6	<0.0001
Test 2	28.74	3	<0.0001
Test 3	3.091	2	0.2132
Test 6a	1.598	1	0.2062

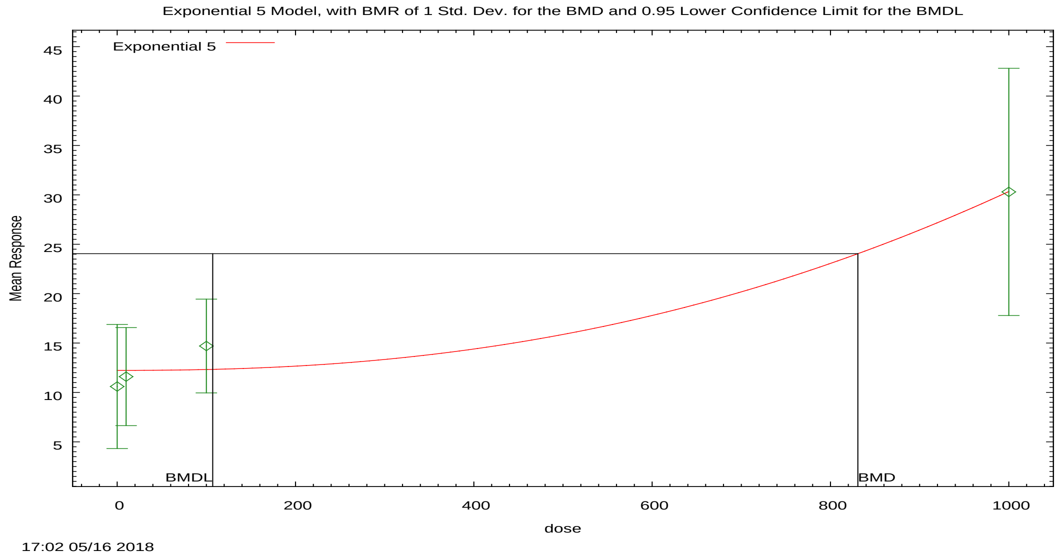

Figure 315. Plot of mean response by dose with fitted curve for Exponential (M5) model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 830.717

BMDL at the 95% confidence level = 107.133

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.417383	1.03331
rho	1.80511	1.58206
a	12.2353	10.07
b	0.00024556	0.000156222

c	41.1806	15.0447
d	2.33795	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	12.24	14.17	11.81	-0.6494
10	21	11.6	12.24	10.9	11.81	-0.2466
100	21	14.7	12.32	10.42	11.88	0.9177
1000	21	30.3	30.34	27.49	26.8	-0.0064

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.1181	5	574.2363
A2	-267.7487	8	551.4975
A3	-269.2941	6	550.5882
R	-290.6854	2	585.3709
5	-269.7062	6	551.4124

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.87	6	<0.0001
Test 2	28.74	3	<0.0001
Test 3	3.091	2	0.2132
Test 7a	0.8243	0	N/A

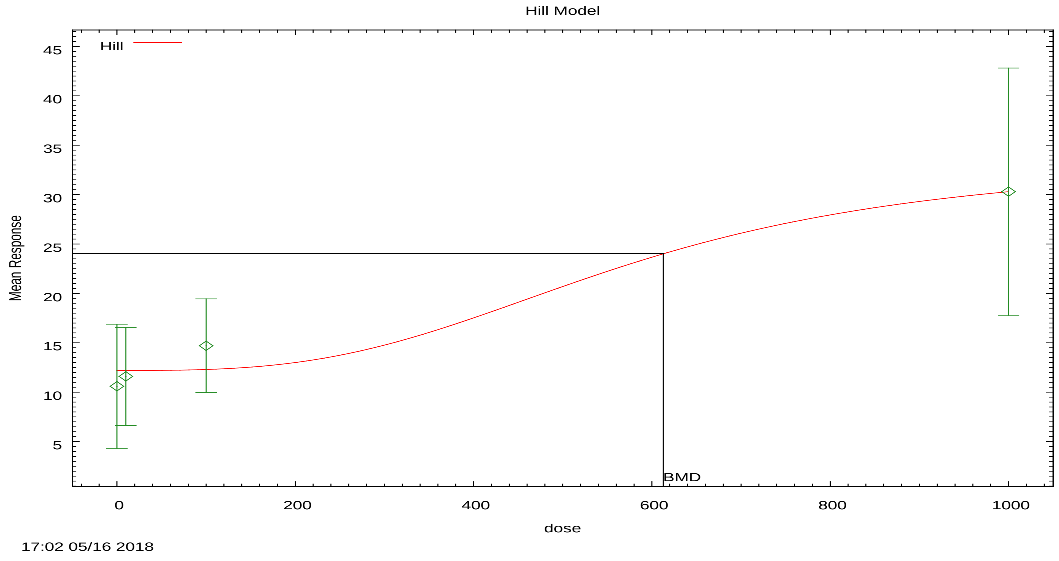

Figure 316. Plot of mean response by dose with fitted curve for Hill model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A modeled variance is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 612.652

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.419997	5.68628
rho	1.80418	0
intercept	12.2301	10.6

v	21.3148	19.7
n	3.09428	0.354929
k	571.214	1568.27

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	12.2	14.2	11.8	-0.648
10	21	11.6	12.2	10.9	11.8	-0.245
100	21	14.7	12.3	10.4	11.9	0.915
1000	21	30.3	30.3	27.5	26.8	-0.0073

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.118145	5	574.236289
A2	-267.74874	8	551.497479
A3	-269.294095	6	550.58819
fitted	-269.70608	6	551.412159
R	-290.685425	2	585.37085

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.8734	6	<0.0001
Test 2	28.7388	3	<0.0001
Test 3	3.09071	2	0.2132
Test 4	0.82397	0	N/A

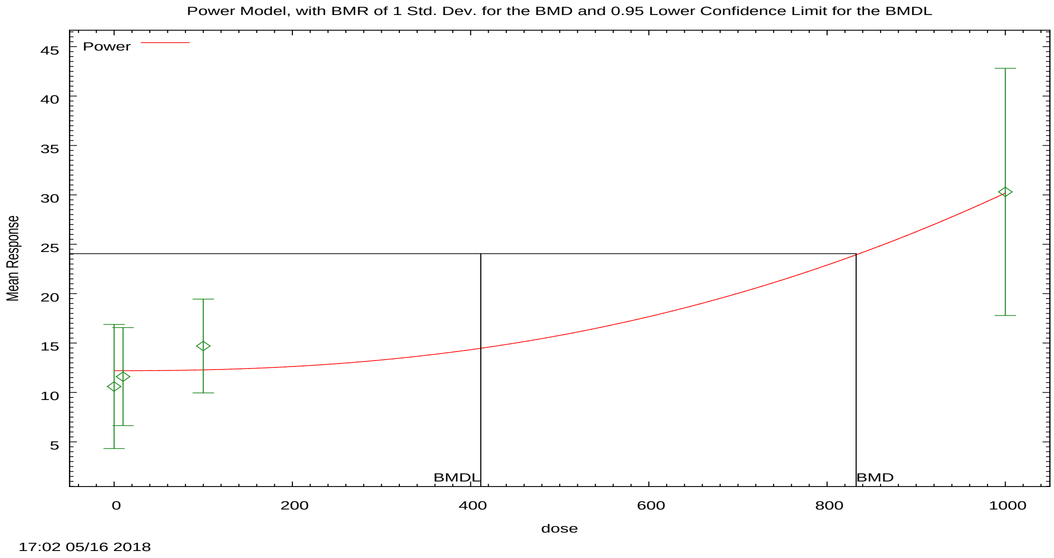

Figure 317. Plot of mean response by dose with fitted curve for Power model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 832.617

BMDL at the 95% confidence level = 411.414

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.417329	5.68628
rho	1.80513	0
control	12.2354	10.6
slope	0.00000183768	0.225303

power	2.33115	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	12.2	14.2	11.8	-0.649
10	21	11.6	12.2	10.9	11.8	-0.247
100	21	14.7	12.3	10.4	11.9	0.918
1000	21	30.3	30.3	27.5	26.8	-0.00637

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.118145	5	574.236289
A2	-267.74874	8	551.497479
A3	-269.294095	6	550.58819
fitted	-269.706226	5	549.412452
R	-290.685425	2	585.37085

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.8734	6	<0.0001
Test 2	28.7388	3	<0.0001
Test 3	3.09071	2	0.2132
Test 4	0.824262	1	0.3639

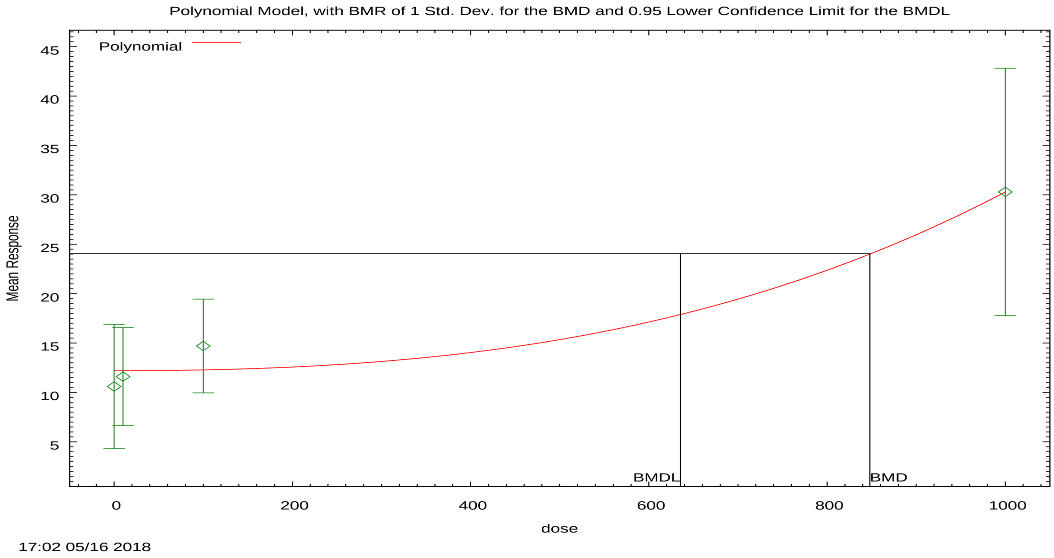

Figure 318. Plot of mean response by dose with fitted curve for Polynomial 3° model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 847.968

BMDL at the 95% confidence level = 635.505

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.416772	5.68628
rho	1.80533	0
beta_0	12.2364	10.6
beta_1	9.13497E-23	0.107194

beta_2	0.00000709061	0
beta_3	0.0000000110091	0.000000638272

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	12.2	14.2	11.8	-0.65
10	21	11.6	12.2	10.9	11.8	-0.247
100	21	14.7	12.3	10.4	11.9	0.919
1000	21	30.3	30.3	27.5	26.8	-0.00618

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.118145	5	574.236289
A2	-267.74874	8	551.497479
A3	-269.294095	6	550.58819
fitted	-269.706361	5	549.412722
R	-290.685425	2	585.37085

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.8734	6	<0.0001
Test 2	28.7388	3	<0.0001
Test 3	3.09071	2	0.2132
Test 4	0.824532	1	0.3639

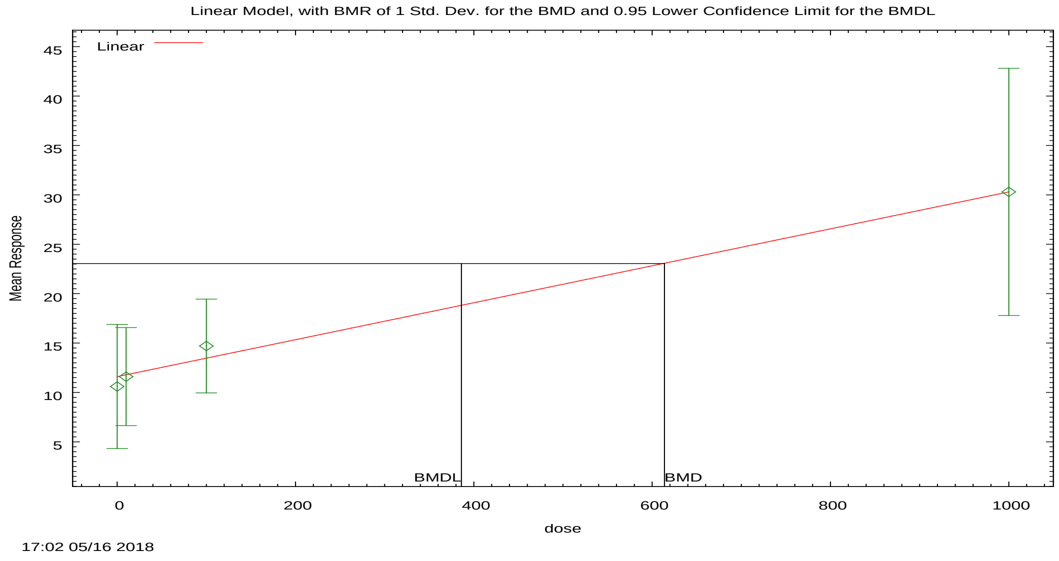

Figure 319. Plot of mean response by dose with fitted curve for Linear model with modeled variance for Percent per Litter with Skeletal Variations (Prenatal and Developmental Rats); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 613.802

BMDL at the 95% confidence level = 386.066

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	0.713678	5.68628
rho	1.70231	0
beta_0	11.5638	11.5676
beta_1	0.0186987	0.0188555

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	10.6	11.6	14.2	11.5	-0.394
10	21	11.6	11.8	10.9	11.6	-0.0594
100	21	14.7	13.4	10.4	13	0.445
1000	21	30.3	30.3	27.5	26	0.0066

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-282.118145	5	574.236289
A2	-267.74874	8	551.497479
A3	-269.294095	6	550.58819
fitted	-270.092862	4	548.185724
R	-290.685425	2	585.37085

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	45.8734	6	<0.0001
Test 2	28.7388	3	<0.0001
Test 3	3.09071	2	0.2132
Test 4	1.59753	2	0.4499

BMDS WIZARD OUTPUT REPORT

BMDS Summary of Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice – Offspring Weight (g) at Postnatal Day 21 in Males

1.36. BMDS Summary of Offspring weight (litter as experimental unit) PND21 Males (Reproductive Mice GenX)

Table 36. Summary of BMD Modeling Results for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.268	152.90	2.12	1.66	1.27	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.416	152.92	4.52	1.86	2.43	
Exponential (M4)	0.268	152.90	2.12	1.25	1.70	
Exponential (M5)	N/A[b]	154.92	3.66	0.540	6.77	
Hill	N/A[b]	154.92	4.21	error[c]	error	
Power	0.416	152.92	4.57	1.99	2.30	
Polynomial 3°	**0.715**	**150.93**	**3.87**	**3.06**	**1.26**	
Polynomial 2°	0.681	151.03	3.40	3.06	1.11	
Linear	0.312	152.59	2.28	1.84	1.24	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.233), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.64, 0.16, 0.48, 0, respectively.
[b] No available degrees of freedom to calculate a goodness of fit value.
[c] BMD or BMDL computation failed for this model.

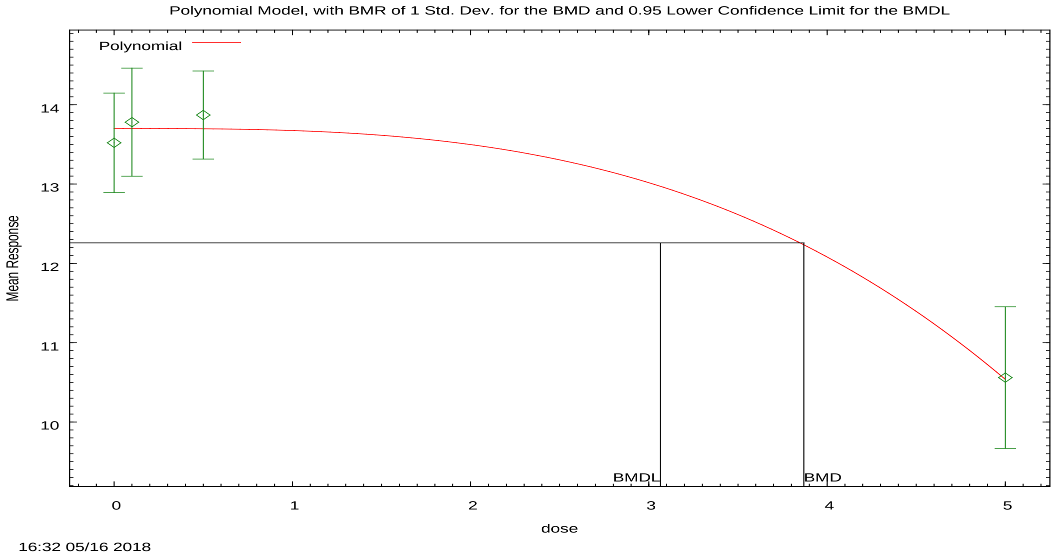

Figure 320. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.86966

BMDL at the 95% confidence level = 3.06466

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.15434	2.24633
rho	n/a	0
beta_0	13.7264	13.52
beta_1	-7.86983E-23	0
beta_2	0	-5.29648
beta_3	-0.0253302	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.5	13.7	1.38	1.47	-0.645
0.1	18	13.8	13.7	1.37	1.47	0.155
0.5	23	13.9	13.7	1.28	1.47	0.479
5	20	10.6	10.6	1.91	1.47	-0.000515

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.130858	5	154.261716
A2	-69.989194	8	155.978389
A3	-72.130858	5	154.261716
fitted	-72.46686	3	150.933721
R	-97.85625	2	199.712499

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.7341	6	<0.0001
Test 2	4.28333	3	0.2325
Test 3	4.28333	3	0.2325
Test 4	0.672005	2	0.7146

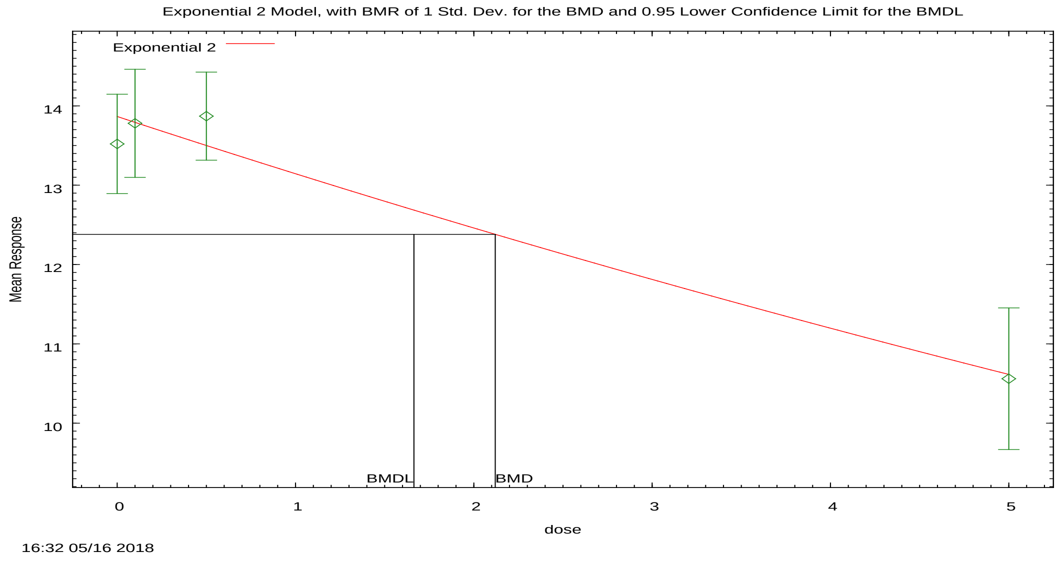

Figure 321. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.12008

BMDL at the 95% confidence level = 1.66414

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.791404	0.759289
rho	n/a	0
a	13.8655	11.9502
b	0.0534487	0.0539212
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.52	13.87	1.38	1.48	-1.066
0.1	18	13.78	13.79	1.37	1.48	-0.03315
0.5	23	13.87	13.5	1.28	1.48	1.195
5	20	10.56	10.61	1.91	1.48	-0.1622

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.13086	5	154.2617
A2	-69.98919	8	155.9784
A3	-72.13086	5	154.2617
R	-97.85625	2	199.7125
2	-73.44756	3	152.8951

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.73	6	<0.0001
Test 2	4.283	3	0.2325
Test 3	4.283	3	0.2325
Test 4	2.633	2	0.268

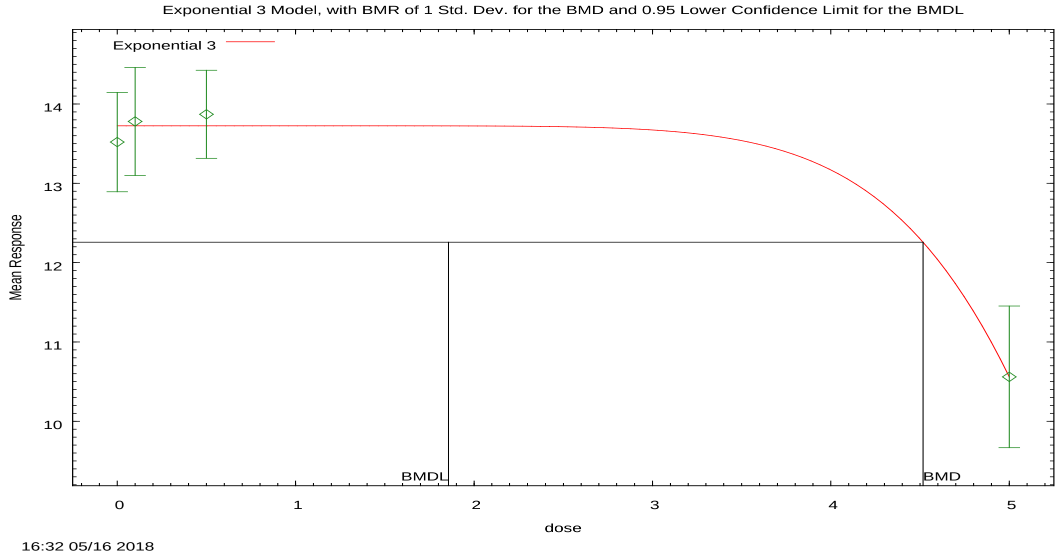

Figure 322. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.51681

BMDL at the 95% confidence level = 1.85773

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.767364	0.759289
rho	n/a	0
a	13.7253	11.9502
b	0.170118	0.0539212
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.52	13.73	1.38	1.47	-0.6411
0.1	18	13.78	13.73	1.37	1.47	0.1581
0.5	23	13.87	13.73	1.28	1.47	0.4728
5	20	10.56	10.56	1.91	1.47	-0.000000008943

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.13086	5	154.2617
A2	-69.98919	8	155.9784
A3	-72.13086	5	154.2617
R	-97.85625	2	199.7125
3	-72.46192	4	152.9238

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.73	6	<0.0001
Test 2	4.283	3	0.2325
Test 3	4.283	3	0.2325
Test 5a	0.6621	1	0.4158

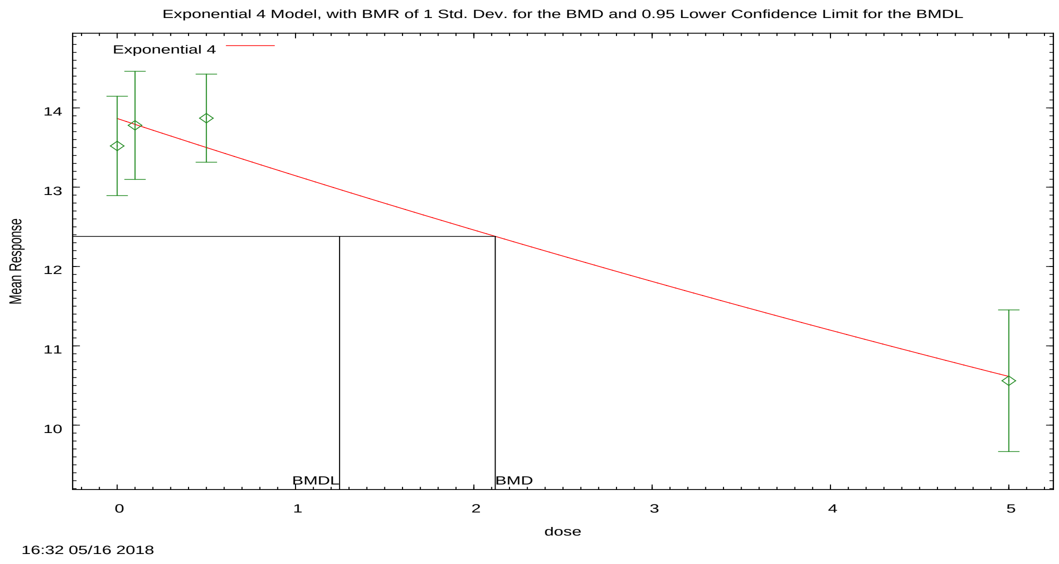

Figure 323. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.12008

BMDL at the 95% confidence level = 1.24698

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.791404	0.759289
rho	n/a	0
a	13.8655	14.5635
b	0.0534487	0.438137

c	0	0.690572
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.52	13.87	1.38	1.48	-1.066
0.1	18	13.78	13.79	1.37	1.48	-0.03315
0.5	23	13.87	13.5	1.28	1.48	1.195
5	20	10.56	10.61	1.91	1.48	-0.1622

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.13086	5	154.2617
A2	-69.98919	8	155.9784
A3	-72.13086	5	154.2617
R	-97.85625	2	199.7125
4	-73.44756	3	152.8951

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.73	6	<0.0001
Test 2	4.283	3	0.2325
Test 3	4.283	3	0.2325
Test 6a	2.633	2	0.268

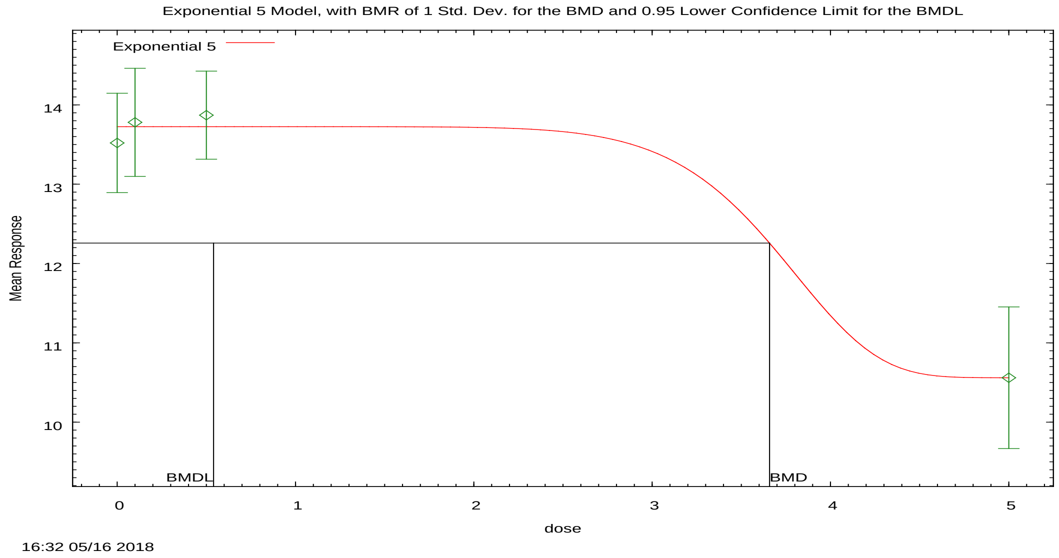

Figure 324. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 3.65823

BMDL at the 95% confidence level = 0.540376

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.767364	0.759289
rho	n/a	0
a	13.7253	14.5635
b	0.25941	0.438137

c	0.769374	0.690572
d	9.03662	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.52	13.73	1.38	1.47	-0.6411
0.1	18	13.78	13.73	1.37	1.47	0.1581
0.5	23	13.87	13.73	1.28	1.47	0.4728
5	20	10.56	10.56	1.91	1.47	-0.0000000894

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.13086	5	154.2617
A2	-69.98919	8	155.9784
A3	-72.13086	5	154.2617
R	-97.85625	2	199.7125
5	-72.46192	5	154.9238

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.73	6	<0.0001
Test 2	4.283	3	0.2325
Test 3	4.283	3	0.2325
Test 7a	0.6621	0	N/A

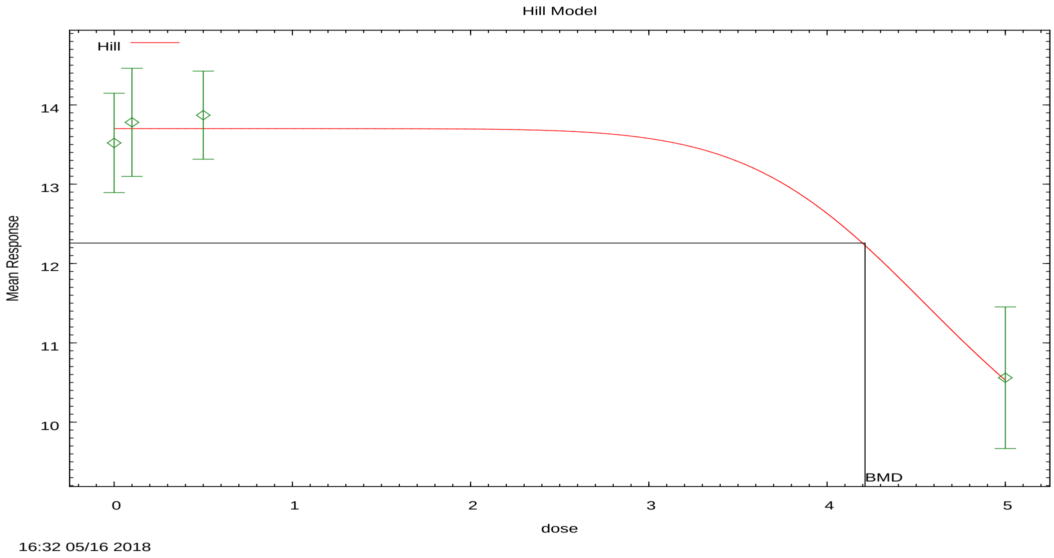

Figure 325. Plot of mean response by dose with fitted curve for Hill model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.21281

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.15408	2.24633
rho	n/a	0
intercept	13.7253	13.52

v	-5.0422	-2.96
n	8.24712	1
k	4.69297	2.98792

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.5	13.7	1.38	1.47	-0.641
0.1	18	13.8	13.7	1.37	1.47	0.158
0.5	23	13.9	13.7	1.28	1.47	0.473
5	20	10.6	10.6	1.91	1.47	0.000000118

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.130858	5	154.261716
A2	-69.989194	8	155.978389
A3	-72.130858	5	154.261716
fitted	-72.461924	5	154.923849
R	-97.85625	2	199.712499

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.7341	6	<0.0001
Test 2	4.28333	3	0.2325
Test 3	4.28333	3	0.2325
Test 4	0.662133	0	N/A

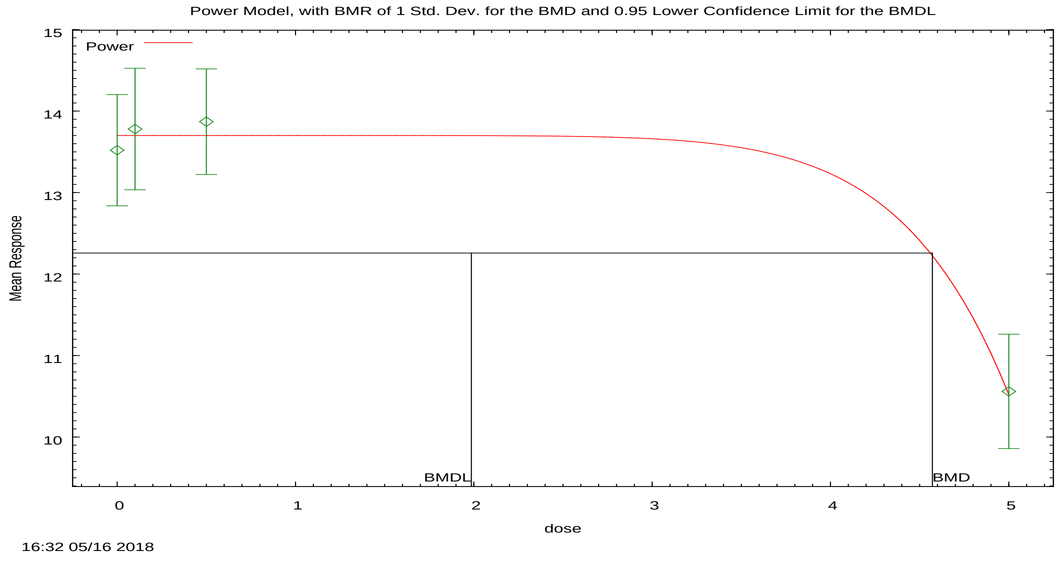

Figure 326. Plot of mean response by dose with fitted curve for Power model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

THE MODEL HAS PROBABLY NOT CONVERGED!!!

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.57146

BMDL at the 95% confidence level = 1.98598

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.15408	2.24633
rho	n/a	0
control	13.7253	10.56

slope	-0.00000319984	3.34953
power	8.57732	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.5	13.7	1.38	1.47	-0.641
0.1	18	13.8	13.7	1.37	1.47	0.158
0.5	23	13.9	13.7	1.28	1.47	0.473
5	20	10.6	10.6	1.91	1.47	0.0000000353

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.130858	5	154.261716
A2	-69.989194	8	155.978389
A3	-72.130858	5	154.261716
fitted	-72.461924	4	152.923849
R	-97.85625	2	199.712499

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.7341	6	<0.0001
Test 2	4.28333	3	0.2325
Test 3	4.28333	3	0.2325
Test 4	0.662132	1	0.4158

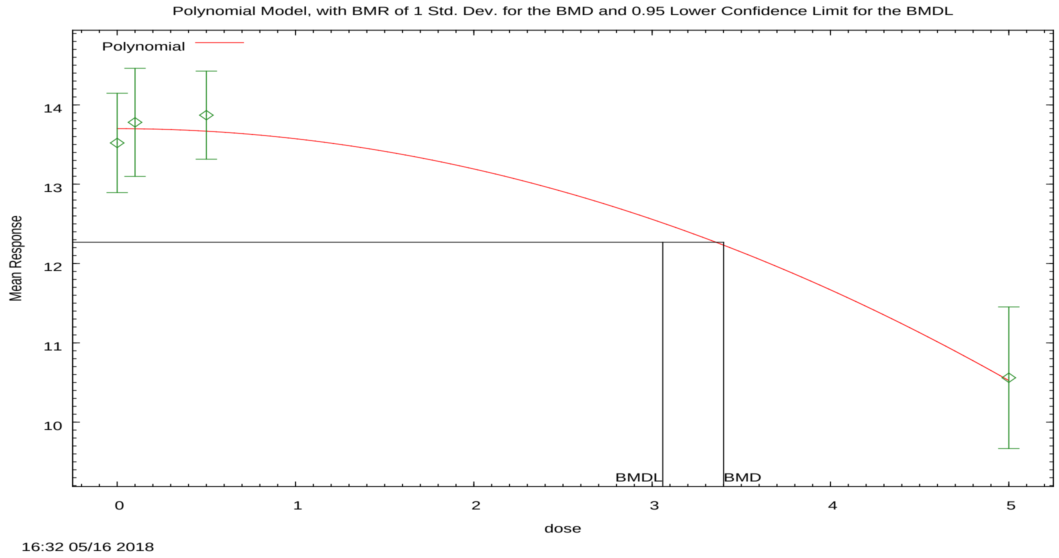

Figure 327. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.40062

BMDL at the 95% confidence level = 3.05942

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.15686	2.24633
rho	n/a	0
beta_0	13.7369	13.6042
beta_1	-2.69168E-23	0

beta_2	-0.126998	-0.263833

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.5	13.7	1.38	1.47	-0.677
0.1	18	13.8	13.7	1.37	1.47	0.128
0.5	23	13.9	13.7	1.28	1.47	0.538
5	20	10.6	10.6	1.91	1.47	-0.00582

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.130858	5	154.261716
A2	-69.989194	8	155.978389
A3	-72.130858	5	154.261716
fitted	-72.514804	3	151.029608
R	-97.85625	2	199.712499

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.7341	6	<0.0001
Test 2	4.28333	3	0.2325
Test 3	4.28333	3	0.2325
Test 4	0.767891	2	0.6812

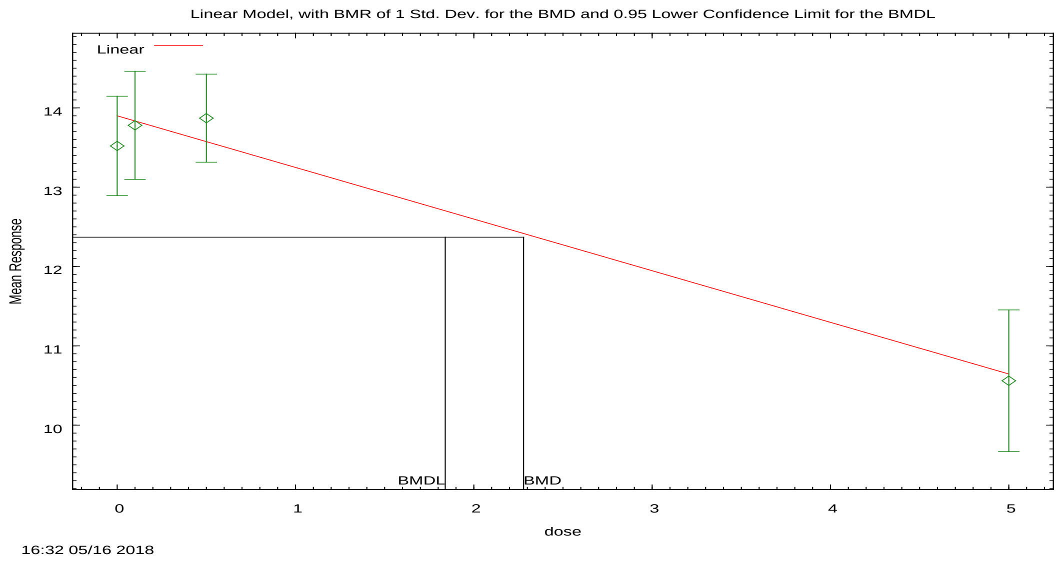

Figure 328. Plot of mean response by dose with fitted curve for Linear model with constant variance for Offspring Weight (litter as experimental unit) at PND21 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.27908

BMDL at the 95% confidence level = 1.83952

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	2.19842	2.24633
rho	n/a	0
beta_0	13.8522	13.8414
beta_1	-0.650574	-0.649196

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.5	13.9	1.38	1.48	-1.03
0.1	18	13.8	13.8	1.37	1.48	-0.0204
0.5	23	13.9	13.5	1.28	1.48	1.11
5	20	10.6	10.6	1.91	1.48	-0.119

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-72.130858	5	154.261716
A2	-69.989194	8	155.978389
A3	-72.130858	5	154.261716
fitted	-73.297359	3	152.594717
R	-97.85625	2	199.712499

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	55.7341	6	<0.0001
Test 2	4.28333	3	0.2325
Test 3	4.28333	3	0.2325
Test 4	2.333	2	0.3115

BMDS WIZARD OUTPUT REPORT

BMDS Summary of Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice – Offspring Weight (g) at Postnatal Day 21 in Females

1.37. BMDS Summary of Offspring weight (litter as experimental unit) PND 21 Females (Reproductive Mice GenX)

Table 37. Summary of BMD Modeling Results for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.169	123.03	2.33	1.80	1.29	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.270	122.69	4.56	2.10	2.17	
Exponential (M4)	0.169	123.03	2.33	1.41	1.65	
Exponential (M5)	N/A[b]	124.69	4.37	0.548	7.98	
Hill	N/A[b]	124.69	4.19	error[c]	error	
Power	0.270	122.69	4.67	2.18	2.14	
Polynomial 3°	**0.541**	**120.71**	**3.95**	**3.66**	**1.08**	
Polynomial 2°	0.503	120.85	3.51	2.15	1.63	
Linear	0.193	122.76	2.45	1.95	1.26	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.486), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.76, -0.09, 0.8, 0, respectively.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

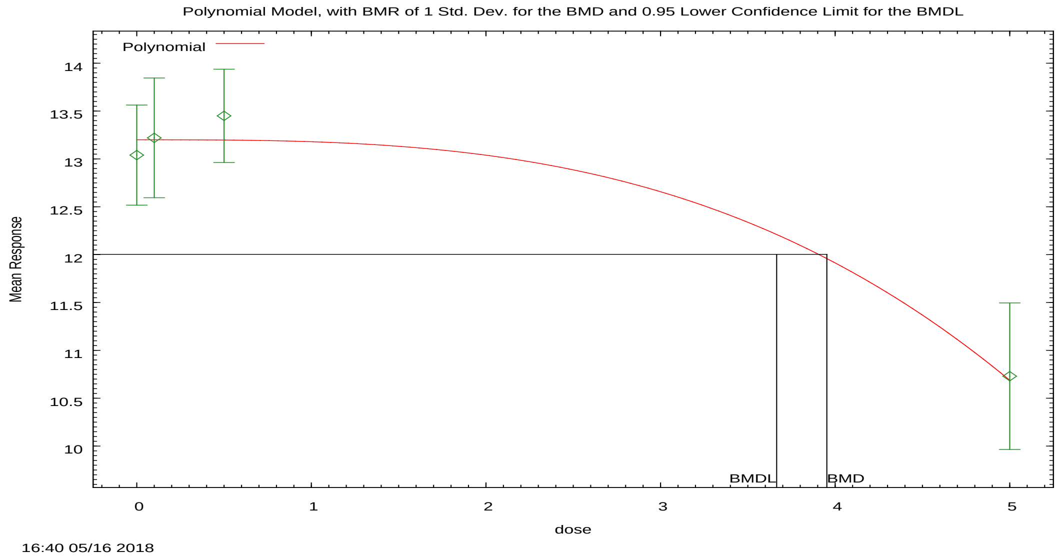

Figure 329. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.9524

BMDL at the 95% confidence level = 3.66495

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	1.54315	1.59957
rho	n/a	0
beta_0	13.2452	13.04
beta_1	-2.55441E-24	0
beta_2	-2.52457E-26	-2.71512
beta_3	-0.0201196	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13	13.2	1.15	1.24	-0.757
0.1	18	13.2	13.2	1.26	1.24	-0.0861
0.5	23	13.4	13.2	1.13	1.24	0.8
5	18	10.7	10.7	1.54	1.24	-0.000904

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.737769	5	123.475538
A2	-55.517751	8	127.035503
A3	-56.737769	5	123.475538
fitted	-57.352978	3	120.705956
R	-78.910547	2	161.821093

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.7856	6	<0.0001
Test 2	2.44004	3	0.4862
Test 3	2.44004	3	0.4862
Test 4	1.23042	2	0.5405

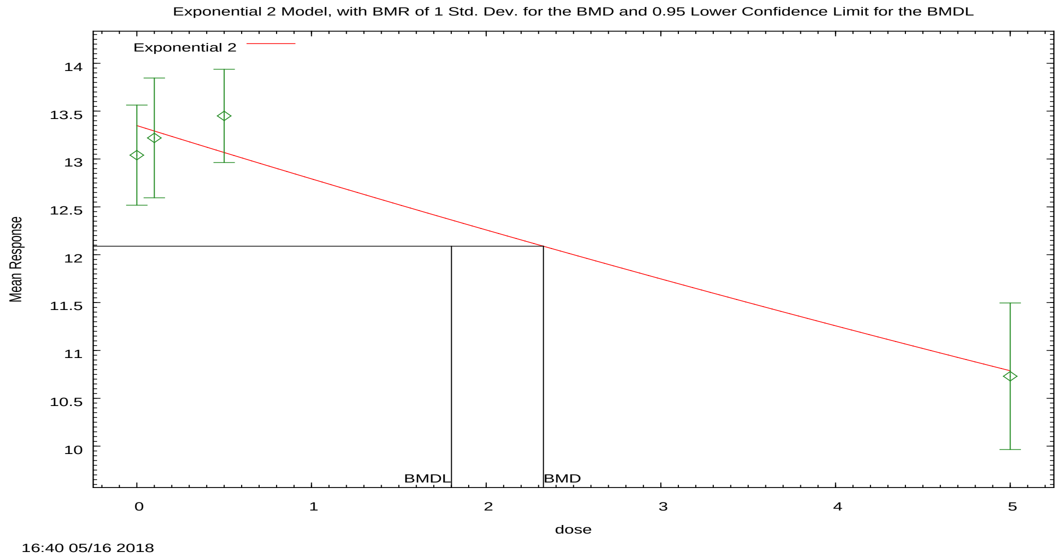

Figure 330. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.32766

BMDL at the 95% confidence level = 1.80118

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.462864	0.418444
rho	n/a	0
a	13.3488	11.9484
b	0.0426095	0.043013
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.04	13.35	1.15	1.26	-1.123
0.1	18	13.22	13.29	1.26	1.26	-0.2426
0.5	23	13.45	13.07	1.13	1.26	1.456
5	18	10.73	10.79	1.54	1.26	-0.1933

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.73777	5	123.4755
A2	-55.51775	8	127.0355
A3	-56.73777	5	123.4755
R	-78.91055	2	161.8211
2	-58.51457	3	123.0291

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.79	6	<0.0001
Test 2	2.44	3	0.4862
Test 3	2.44	3	0.4862
Test 4	3.554	2	0.1692

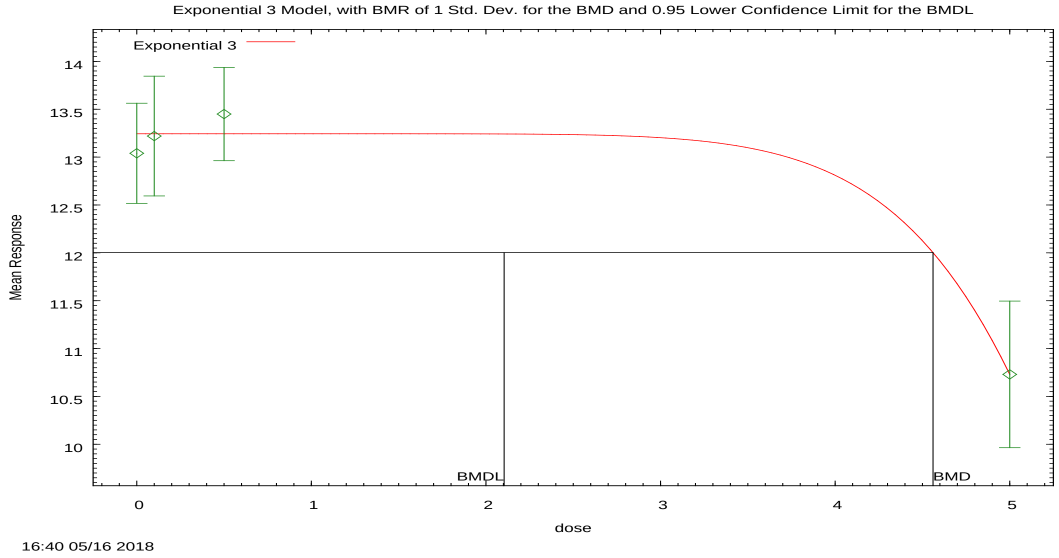

Figure 331. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.56068

BMDL at the 95% confidence level = 2.10402

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.433631	0.418444
rho	n/a	0
a	13.2444	11.9484
b	0.165623	0.043013
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.04	13.24	1.15	1.24	-0.7539
0.1	18	13.22	13.24	1.26	1.24	-0.08319
0.5	23	13.45	13.24	1.13	1.24	0.794
5	18	10.73	10.73	1.54	1.24	0.00001304

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.73777	5	123.4755
A2	-55.51775	8	127.0355
A3	-56.73777	5	123.4755
R	-78.91055	2	161.8211
3	-57.34524	4	122.6905

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.79	6	<0.0001
Test 2	2.44	3	0.4862
Test 3	2.44	3	0.4862
Test 5a	1.215	1	0.2704

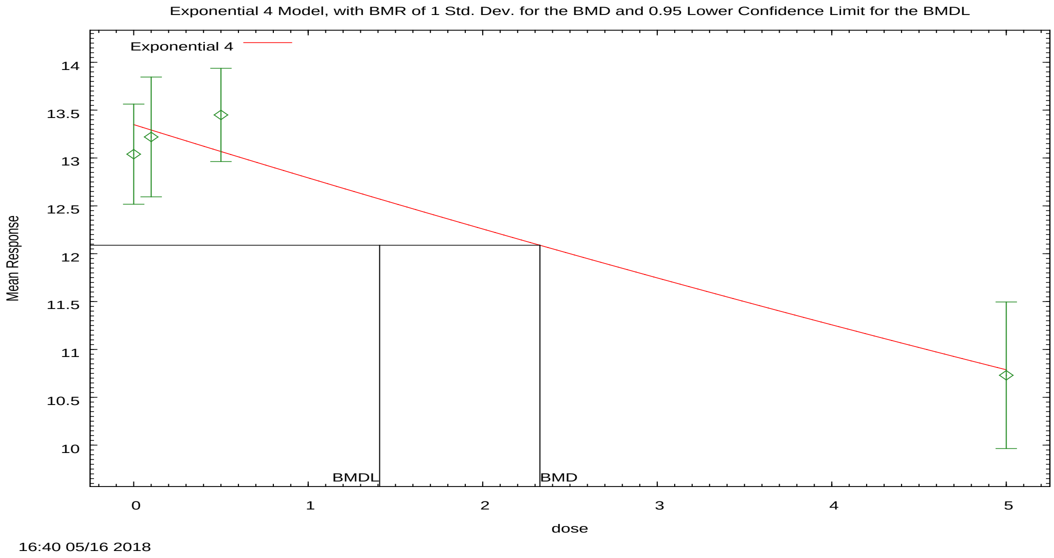

Figure 332. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 2.32766

BMDL at the 95% confidence level = 1.40916

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.462864	0.418444
rho	n/a	0
a	13.3488	14.1225
b	0.0426095	0.407266

c	0	0.7236
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.04	13.35	1.15	1.26	-1.123
0.1	18	13.22	13.29	1.26	1.26	-0.2426
0.5	23	13.45	13.07	1.13	1.26	1.456
5	18	10.73	10.79	1.54	1.26	-0.1933

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.73777	5	123.4755
A2	-55.51775	8	127.0355
A3	-56.73777	5	123.4755
R	-78.91055	2	161.8211
4	-58.51457	3	123.0291

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.79	6	<0.0001
Test 2	2.44	3	0.4862
Test 3	2.44	3	0.4862
Test 6a	3.554	2	0.1692

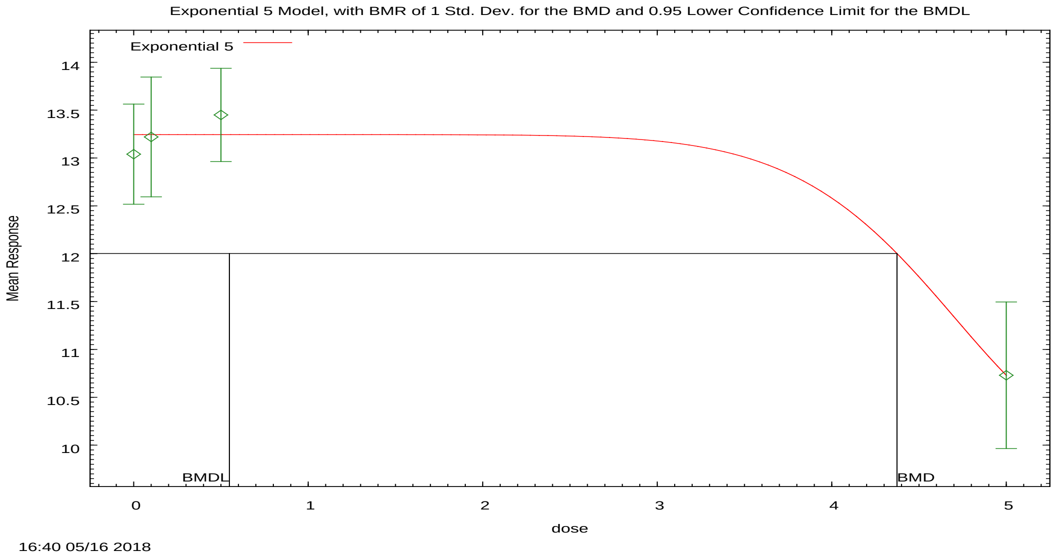

Figure 333. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.3739

BMDL at the 95% confidence level = 0.548167

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	0.433631	0.418444
rho	n/a	0
a	13.2444	14.1225
b	0.209141	0.407266

c	0.752134	0.7236
d	8.34611	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13.04	13.24	1.15	1.24	-0.7539
0.1	18	13.22	13.24	1.26	1.24	-0.08319
0.5	23	13.45	13.24	1.13	1.24	0.794
5	18	10.73	10.73	1.54	1.24	-0.00000003966

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.73777	5	123.4755
A2	-55.51775	8	127.0355
A3	-56.73777	5	123.4755
R	-78.91055	2	161.8211
5	-57.34524	5	124.6905

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.79	6	<0.0001
Test 2	2.44	3	0.4862
Test 3	2.44	3	0.4862
Test 7a	1.215	0	N/A

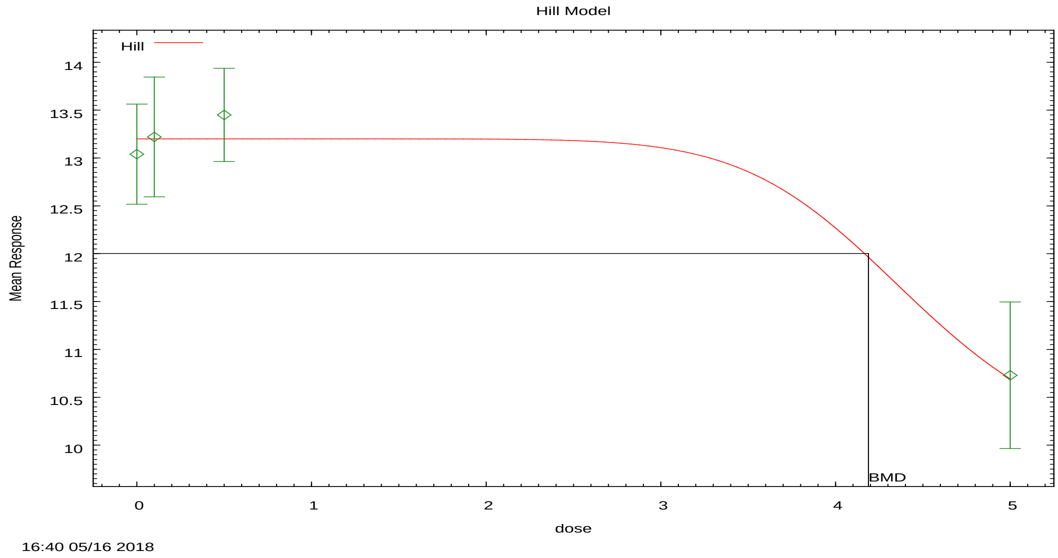

Figure 334. Plot of mean response by dose with fitted curve for Hill model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.18842

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	1.54285	1.59957
rho	n/a	0
intercept	13.2444	13.04
v	-3.38304	-2.31

n	9.0745	1
k	4.4474	3.08915

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13	13.2	1.15	1.24	-0.754
0.1	18	13.2	13.2	1.26	1.24	-0.0832
0.5	23	13.4	13.2	1.13	1.24	0.794
5	18	10.7	10.7	1.54	1.24	-0.0000000356

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.737769	5	123.475538
A2	-55.517751	8	127.035503
A3	-56.737769	5	123.475538
fitted	-57.345245	5	124.690489
R	-78.910547	2	161.821093

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.7856	6	<0.0001
Test 2	2.44004	3	0.4862
Test 3	2.44004	3	0.4862
Test 4	1.21495	0	N/A

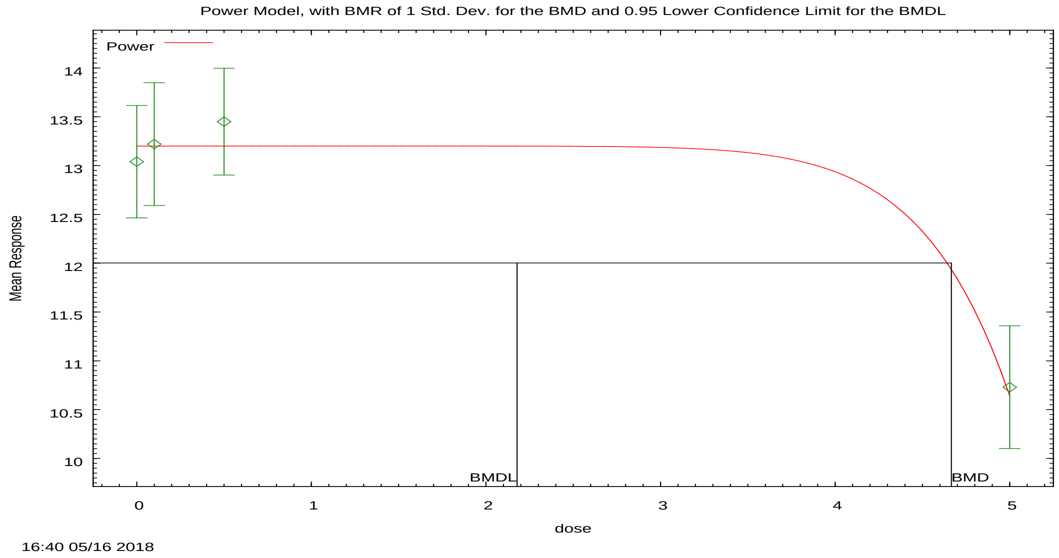

Figure 335. Plot of mean response by dose with fitted curve for Power model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.66568

BMDL at the 95% confidence level = 2.17825

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	1.54285	1.59957
rho	n/a	0
control	13.2444	10.73
slope	-0.000000189638	2.82549

power	10.19	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13	13.2	1.15	1.24	-0.754
0.1	18	13.2	13.2	1.26	1.24	-0.0832
0.5	23	13.4	13.2	1.13	1.24	0.794
5	18	10.7	10.7	1.54	1.24	-0.00000000209

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.737769	5	123.475538
A2	-55.517751	8	127.035503
A3	-56.737769	5	123.475538
fitted	-57.345245	4	122.690489
R	-78.910547	2	161.821093

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.7856	6	<0.0001
Test 2	2.44004	3	0.4862
Test 3	2.44004	3	0.4862
Test 4	1.21495	1	0.2704

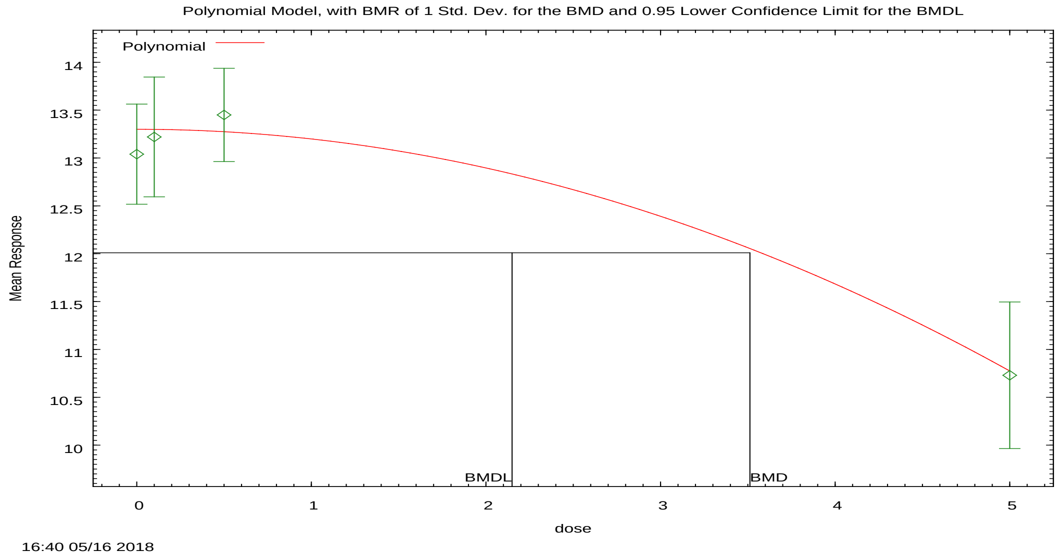

Figure 336. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 3.51186

BMDL at the 95% confidence level = 2.14962

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	1.54593	1.59957
rho	n/a	0
beta_0	13.2532	13.0809
beta_1	0	0

beta_2	-0.100814	-0.273596

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13	13.3	1.15	1.24	-0.786
0.1	18	13.2	13.3	1.26	1.24	-0.11
0.5	23	13.4	13.2	1.13	1.24	0.856
5	18	10.7	10.7	1.54	1.24	-0.00964

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.737769	5	123.475538
A2	-55.517751	8	127.035503
A3	-56.737769	5	123.475538
fitted	-57.425076	3	120.850152
R	-78.910547	2	161.821093

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.7856	6	<0.0001
Test 2	2.44004	3	0.4862
Test 3	2.44004	3	0.4862
Test 4	1.37461	2	0.5029

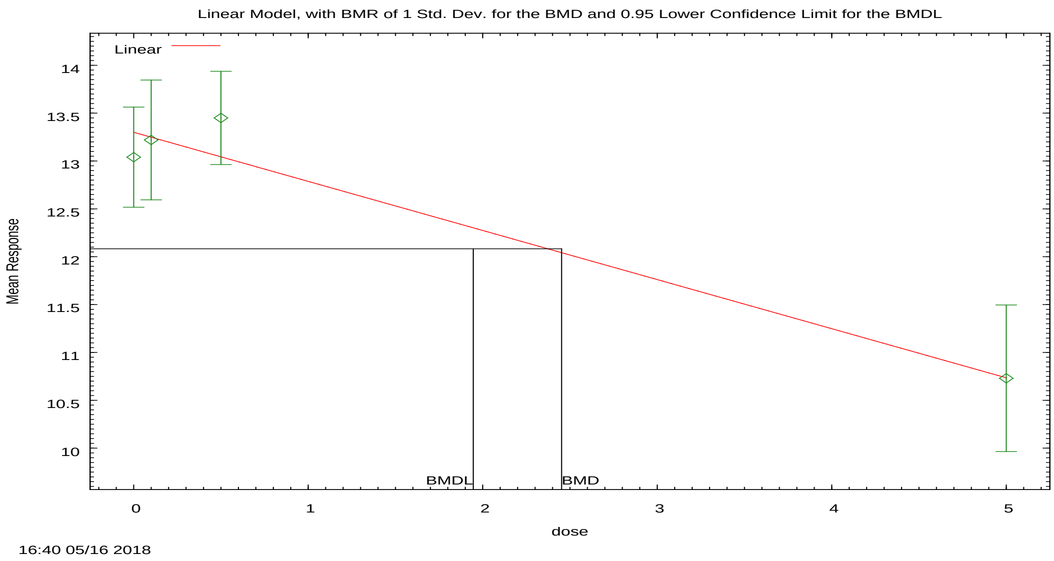

Figure 337. Plot of mean response by dose with fitted curve for Linear model with constant variance for Offspring Weight (litter as experimental unit) at PND 21 in Females (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 2.45188

BMDL at the 95% confidence level = 1.94563

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	1.58335	1.59957
rho	n/a	0
beta_0	13.3413	13.3268
beta_1	-0.513204	-0.511998

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	13	13.3	1.15	1.26	-1.1
0.1	18	13.2	13.3	1.26	1.26	-0.236
0.5	23	13.4	13.1	1.13	1.26	1.39
5	18	10.7	10.8	1.54	1.26	-0.153

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-56.737769	5	123.475538
A2	-55.517751	8	127.035503
A3	-56.737769	5	123.475538
fitted	-58.381829	3	122.763658
R	-78.910547	2	161.821093

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.7856	6	<0.0001
Test 2	2.44004	3	0.4862
Test 3	2.44004	3	0.4862
Test 4	3.28812	2	0.1932

BMDS WIZARD OUTPUT REPORT

BMDS Summary of Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice – Offspring Weight (g) at Postnatal Day 40 in Males

1.38. BMDS Summary of F1 Body weight PND40 (g) Males (Reproductive Mice GenX)

Table 38. Summary of BMD Modeling Results for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)	BMD/BMDL	Basis for model selection
	p-value	AIC				
Exponential (M2)	0.657	235.51	4.68	3.18	1.47	BMDLs from models that met model fit criteria (goodness-of-fit p-value>0.1; scaled residuals with absolute values > 2.0; appropriate variance (continuous data only)) were compared. BMDLs from included models were sufficiently close (< 3-fold difference), so the BMDL from the model with the lowest AIC was selected.
Exponential (M3)	0.595	236.95	4.97	3.30	1.51	
Exponential (M4)	0.657	235.51	4.68	2.01	2.33	
Exponential (M5)	N/A[b]	238.95	4.89	0.549	8.89	
Hill	N/A[b]	238.95	4.94	error[c]	error	
Power	0.595	236.95	4.97	3.36	1.48	
Polynomial 3°	**0.866**	**234.96**	**4.93**	**3.36**	**1.47**	
Polynomial 2°	0.851	234.99	4.88	4.08	1.20	
Linear	0.667	235.48	4.69	3.26	1.44	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.423), selected model in bold; scaled residuals for selected model for doses 0, 0.1, 0.5, and 5 mg/kg/day were -0.38, -0.01, 0.38, 0, respectively.

[b] No available degrees of freedom to calculate a goodness of fit value.

[c] BMD or BMDL computation failed for this model.

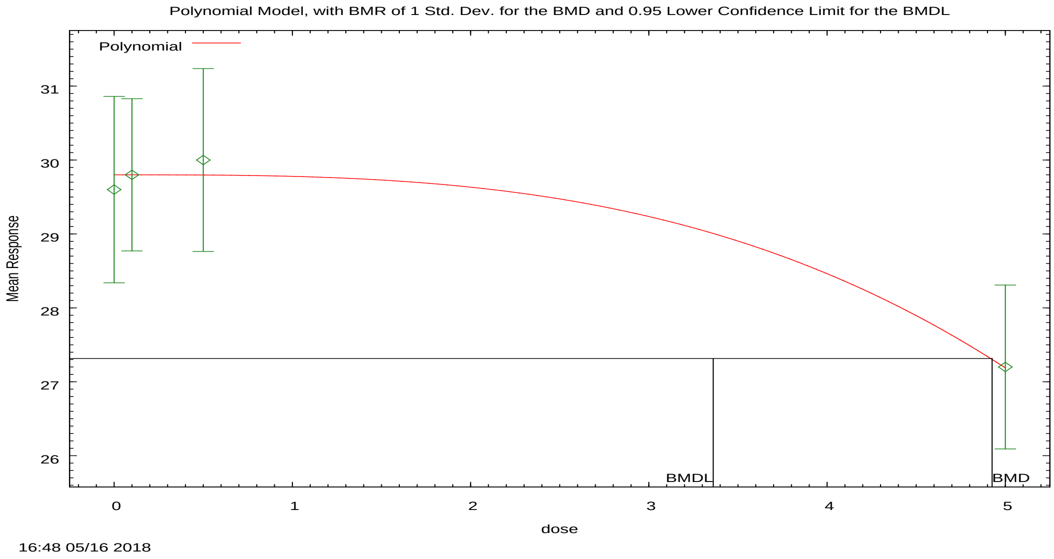

Figure 338. Plot of mean response by dose with fitted curve for Polynomial 3° model with constant variance for Offspring Body weight at PND40 in Males

(Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.92569

BMDL at the 95% confidence level = 3.36106

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.213	6.51263
rho	n/a	0
beta_0	29.8074	29.6
beta_1	0	0
beta_2	0	-3.33252
beta_3	-0.0208569	0

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.8	2.77	2.49	-0.381
0.1	18	29.8	29.8	2.07	2.49	-0.0125
0.5	23	30	29.8	2.86	2.49	0.376
5	19	27.2	27.2	2.3	2.49	-0.000413

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.335534	5	238.671069
A2	-112.934283	8	241.868566

A3	-114.335534	5	238.671069
fitted	-114.479095	3	234.95819
R	-121.737289	2	247.474579

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.606	6	0.007296
Test 2	2.8025	3	0.4231
Test 3	2.8025	3	0.4231
Test 4	0.287121	2	0.8663

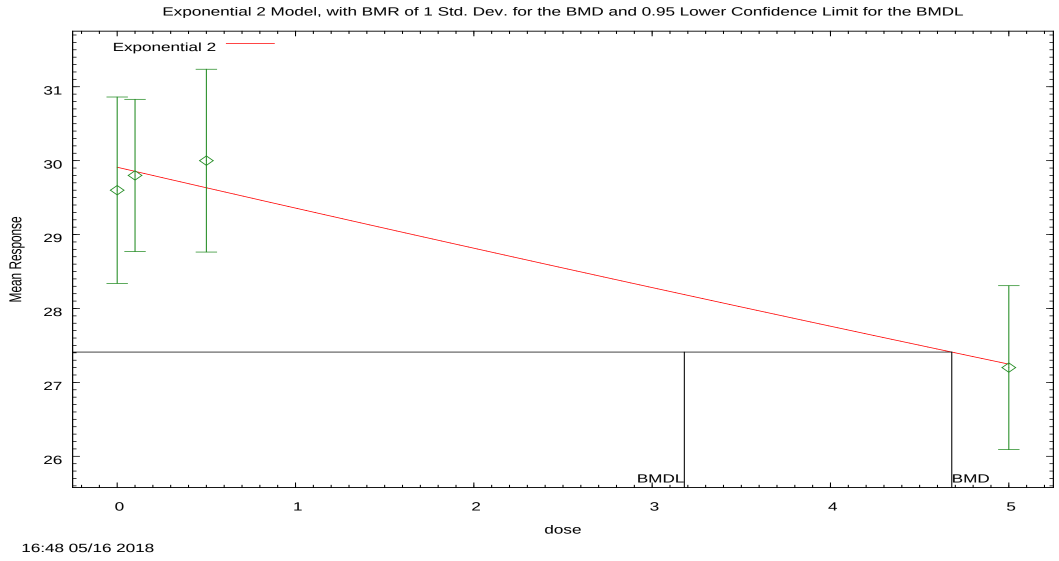

Figure 339. Plot of mean response by dose with fitted curve for Exponential (M2) model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.68011

BMDL at the 95% confidence level = 3.18036

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.83346	1.8231
rho	n/a	0
a	29.9113	28.4519
b	0.0186579	0.0187227
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.91	2.77	2.5	-0.5704
0.1	18	29.8	29.86	2.07	2.5	-0.09421
0.5	23	30	29.63	2.86	2.5	0.7027
5	19	27.2	27.25	2.3	2.5	-0.08207

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.3355	5	238.6711
A2	-112.9343	8	241.8686
A3	-114.3355	5	238.6711
R	-121.7373	2	247.4746
2	-114.755	3	235.5101

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.61	6	0.007296
Test 2	2.803	3	0.4231

Test 3	2.803	3	0.4231
Test 4	0.839	2	0.6574

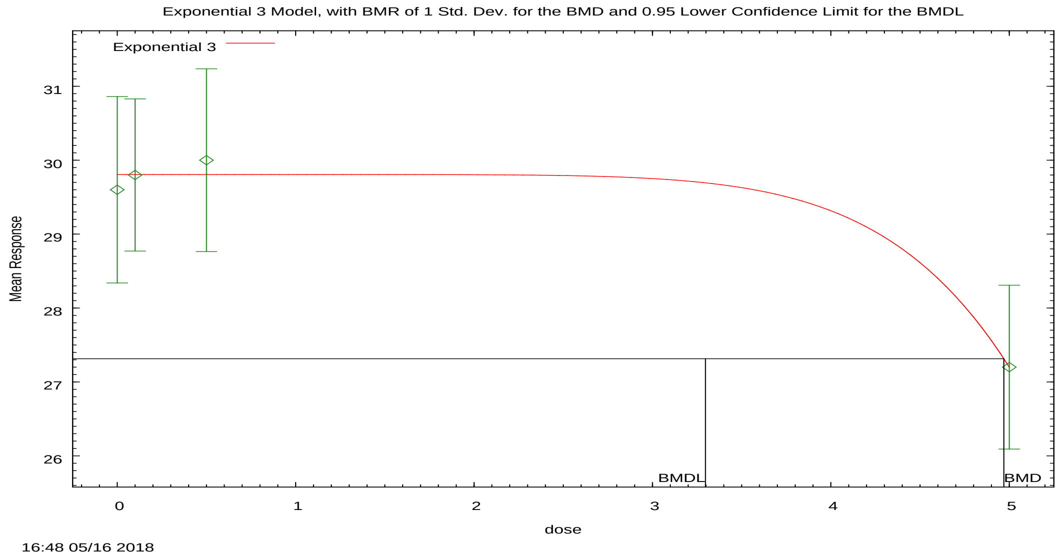

Figure 340. Plot of mean response by dose with fitted curve for Exponential (M3) model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * exp(sign * (b * dose)^d)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.96956

BMDL at the 95% confidence level = 3.29703

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.8266	1.8231

rho	n/a	0
a	29.8065	28.4519
b	0.14635	0.0187227
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.81	2.77	2.49	-0.3796
0.1	18	29.8	29.81	2.07	2.49	-0.01098
0.5	23	30	29.81	2.86	2.49	0.3724
5	19	27.2	27.2	2.3	2.49	0.0000001374

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.3355	5	238.6711
A2	-112.9343	8	241.8686
A3	-114.3355	5	238.6711
R	-121.7373	2	247.4746
3	-114.4772	4	236.9544

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.61	6	0.007296
Test 2	2.803	3	0.4231
Test 3	2.803	3	0.4231
Test 5a	0.2834	1	0.5945

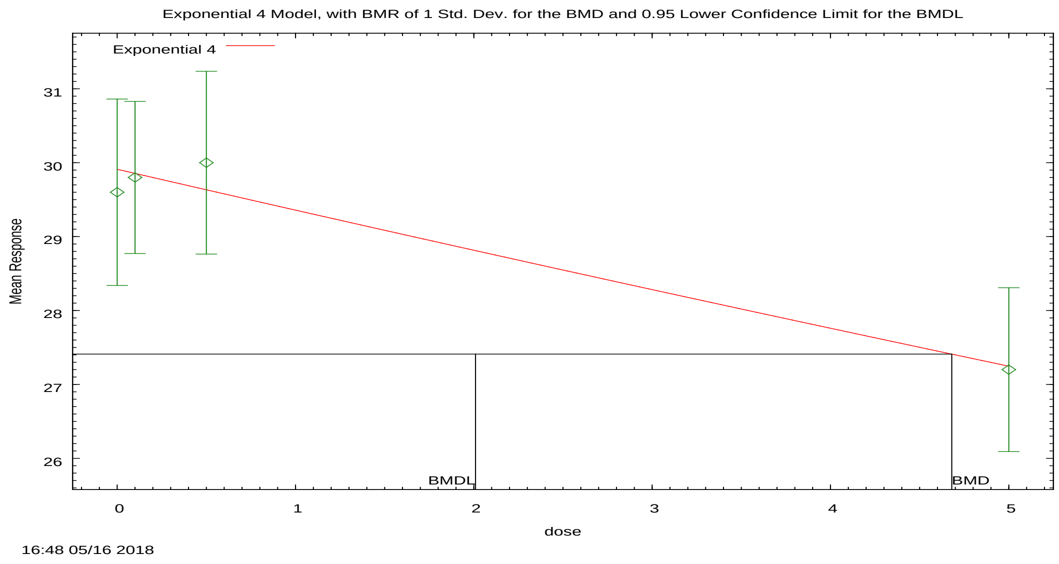

Figure 341. Plot of mean response by dose with fitted curve for Exponential (M4) model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.68011

BMDL at the 95% confidence level = 2.00942

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.83346	1.8231
rho	n/a	0
a	29.9113	31.5
b	0.0186579	0.297243

c	0	0.822373
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.91	2.77	2.5	-0.5704
0.1	18	29.8	29.86	2.07	2.5	-0.09421
0.5	23	30	29.63	2.86	2.5	0.7027
5	19	27.2	27.25	2.3	2.5	-0.08207

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.3355	5	238.6711
A2	-112.9343	8	241.8686
A3	-114.3355	5	238.6711
R	-121.7373	2	247.4746
4	-114.755	3	235.5101

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.61	6	0.007296
Test 2	2.803	3	0.4231
Test 3	2.803	3	0.4231
Test 6a	0.839	2	0.6574

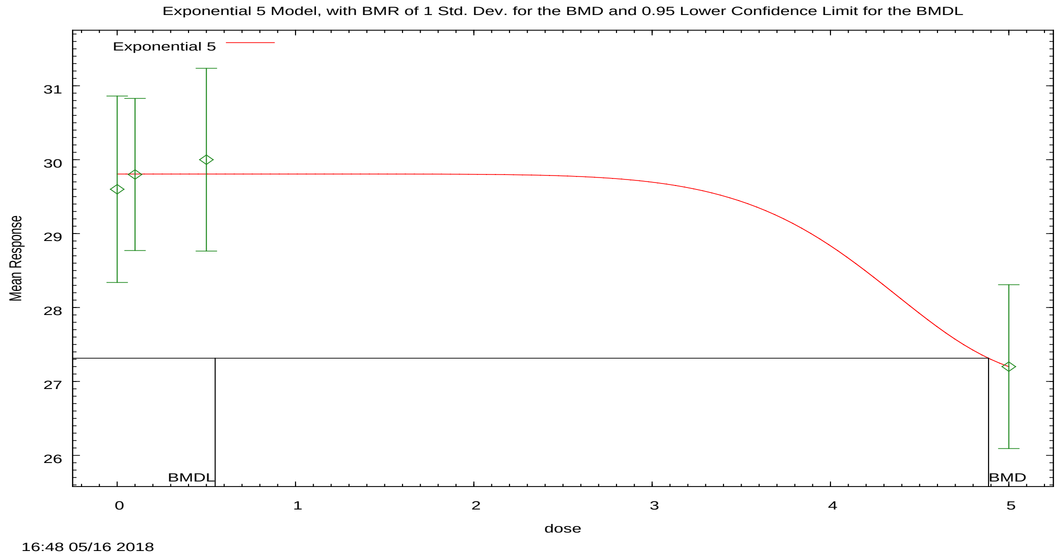

Figure 342. Plot of mean response by dose with fitted curve for Exponential (M5) model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Exponential Model. (Version: 1.11; Date: 03/14/2017)

The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1.0000 Estimated standard deviations from control

BMD = 4.88638

BMDL at the 95% confidence level = 0.549447

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	1.8266	1.8231
rho	n/a	0
a	29.8065	31.5
b	0.225278	0.297243

c	0.905956	0.822373
d	8.21077	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.81	2.77	2.49	-0.3796
0.1	18	29.8	29.81	2.07	2.49	-0.01098
0.5	23	30	29.81	2.86	2.49	0.3724
5	19	27.2	27.2	2.3	2.49	-0.0000001035

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.3355	5	238.6711
A2	-112.9343	8	241.8686
A3	-114.3355	5	238.6711
R	-121.7373	2	247.4746
5	-114.4772	5	238.9544

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.61	6	0.007296
Test 2	2.803	3	0.4231
Test 3	2.803	3	0.4231
Test 7a	0.2834	0	N/A

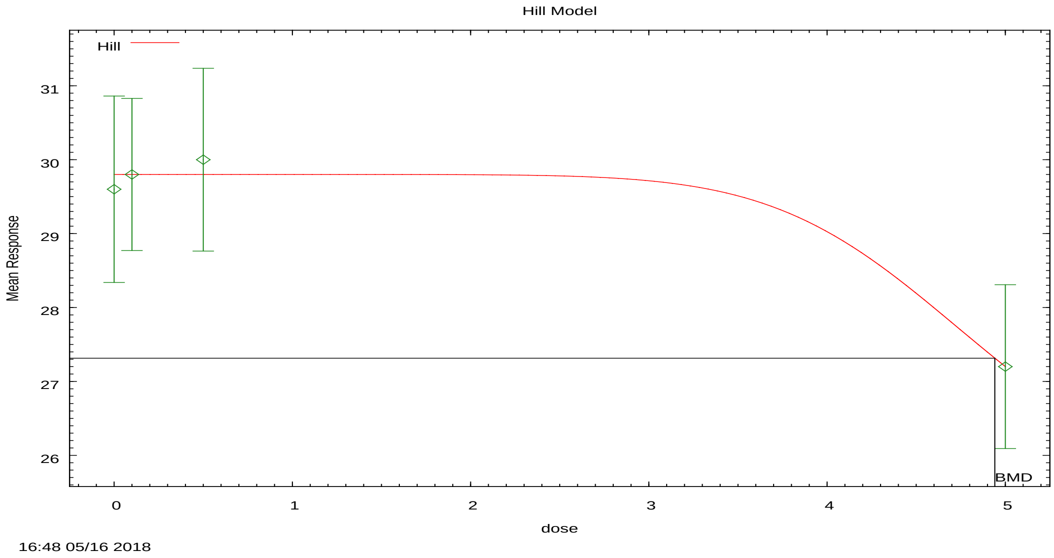

Figure 343. Plot of mean response by dose with fitted curve for Hill model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Hill Model. (Version: 2.18; Date: 03/14/2017)

The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.94093

BMDL at the 95% confidence level = error

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.21272	6.51263
rho	n/a	0
intercept	29.8065	29.6
v	-4.69177	-2.4

n	8.2367	1
k	4.86641	3.07143

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.8	2.77	2.49	-0.38
0.1	18	29.8	29.8	2.07	2.49	-0.011
0.5	23	30	29.8	2.86	2.49	0.372
5	19	27.2	27.2	2.3	2.49	-0.00000031

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.335534	5	238.671069
A2	-112.934283	8	241.868566
A3	-114.335534	5	238.671069
fitted	-114.477219	5	238.954439
R	-121.737289	2	247.474579

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.606	6	0.007296
Test 2	2.8025	3	0.4231
Test 3	2.8025	3	0.4231
Test 4	0.28337	0	N/A

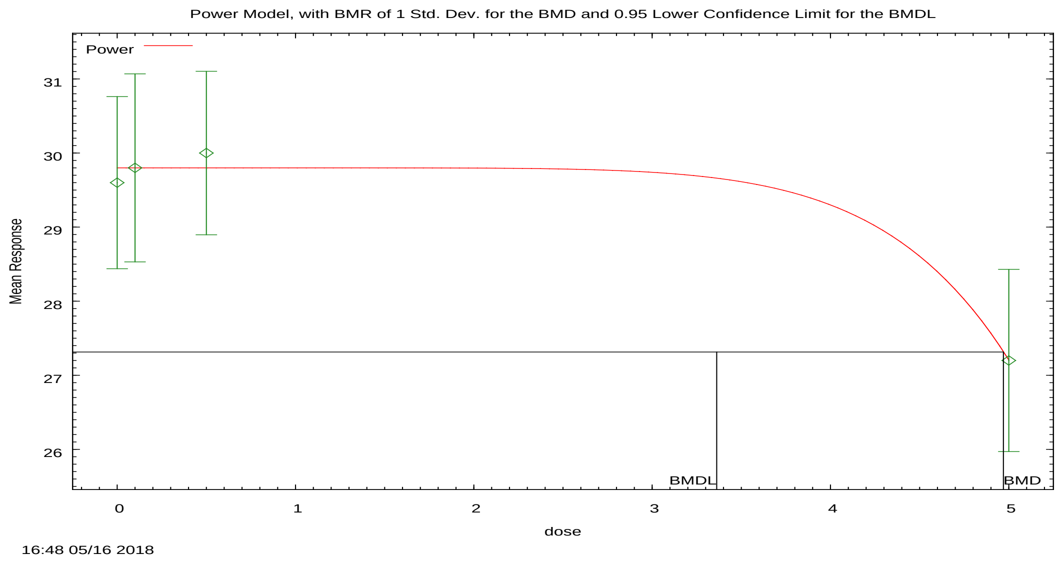

Figure 344. Plot of mean response by dose with fitted curve for Power model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Power Model. (Version: 2.19; Date: 03/14/2017)

The form of the response function is: Y[dose] = control + slope * dose^power

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.96979

BMDL at the 95% confidence level = 3.36188

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.21272	6.51263
rho	n/a	0
control	29.8065	27.2
slope	-0.0000182645	2.89081

power	7.37434	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.8	2.77	2.49	-0.38
0.1	18	29.8	29.8	2.07	2.49	-0.011
0.5	23	30	29.8	2.86	2.49	0.372
5	19	27.2	27.2	2.3	2.49	-0.0000000173

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.335534	5	238.671069
A2	-112.934283	8	241.868566
A3	-114.335534	5	238.671069
fitted	-114.477219	4	236.954439
R	-121.737289	2	247.474579

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.606	6	0.007296
Test 2	2.8025	3	0.4231
Test 3	2.8025	3	0.4231
Test 4	0.28337	1	0.5945

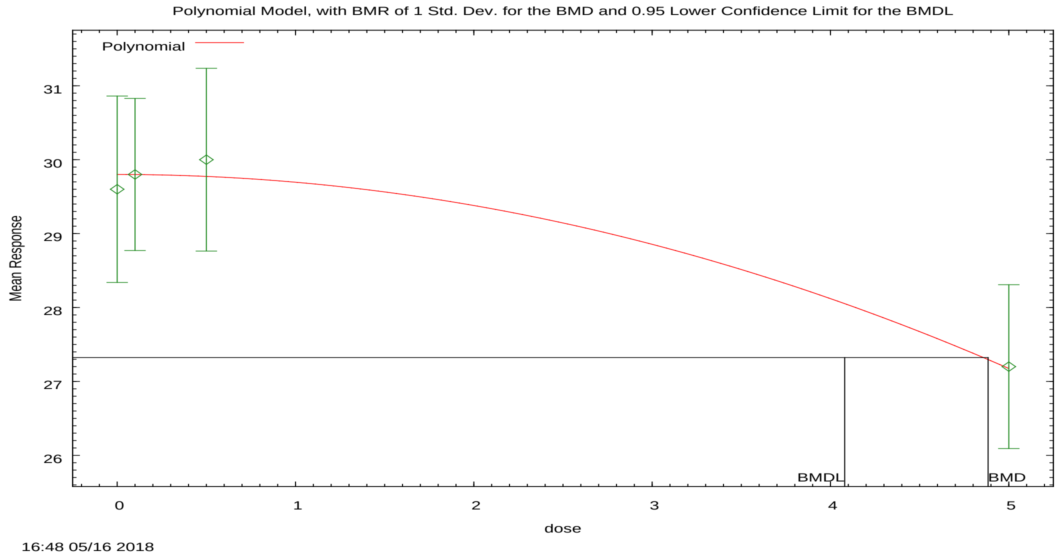

Figure 345. Plot of mean response by dose with fitted curve for Polynomial 2° model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.88385

BMDL at the 95% confidence level = 4.07971

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.2157	6.51263
rho	n/a	0
beta_0	29.8157	29.6512
beta_1	-1.88555E-23	0

beta_2	-0.104525	-0.27028

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.8	2.77	2.49	-0.396
0.1	18	29.8	29.8	2.07	2.49	-0.0249
0.5	23	30	29.8	2.86	2.49	0.405
5	19	27.2	27.2	2.3	2.49	-0.00444

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.335534	5	238.671069
A2	-112.934283	8	241.868566
A3	-114.335534	5	238.671069
fitted	-114.496699	3	234.993397
R	-121.737289	2	247.474579

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.606	6	0.007296
Test 2	2.8025	3	0.4231
Test 3	2.8025	3	0.4231
Test 4	0.322329	2	0.8512

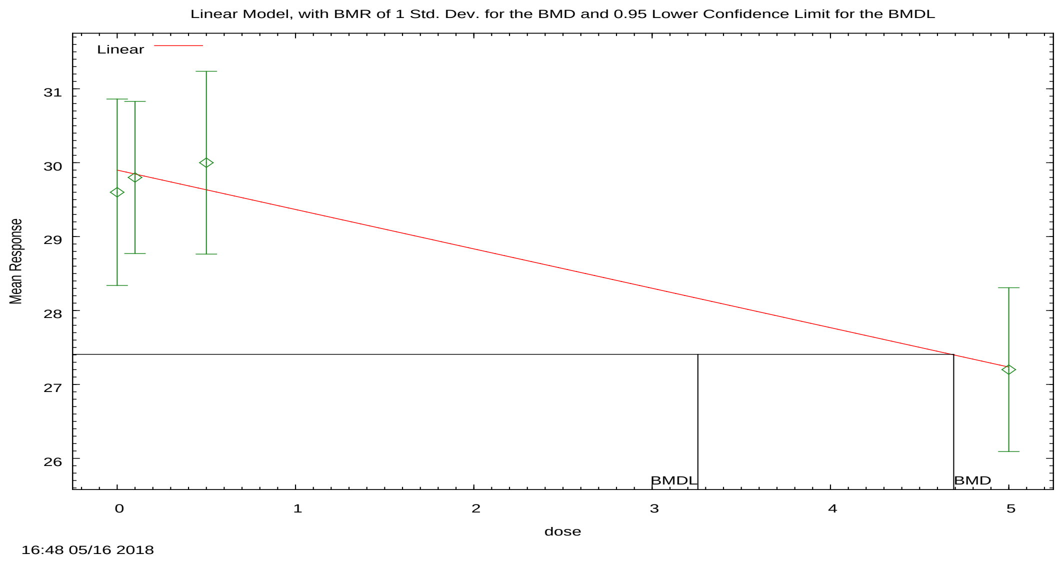

Figure 346. Plot of mean response by dose with fitted curve for Linear model with constant variance for Offspring Body weight at PND40 in Males (Reproductive Mice); BMR = 1 std. dev. change from control mean; dose shown in mg/kg/day.

Polynomial Model. (Version: 2.21; Date: 03/14/2017)

The form of the response function is: Y[dose] = beta_0 + beta_1*dose

A constant variance model is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from the control mean

BMD = 4.69089

BMDL at the 95% confidence level = 3.25646

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	6.2532	6.51263
rho	n/a	0
beta_0	29.9078	29.8942
beta_1	-0.533085	-0.531573

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	21	29.6	29.9	2.77	2.5	-0.564
0.1	18	29.8	29.9	2.07	2.5	-0.0925
0.5	23	30	29.6	2.86	2.5	0.688
5	19	27.2	27.2	2.3	2.5	-0.0739

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.335534	5	238.671069
A2	-112.934283	8	241.868566
A3	-114.335534	5	238.671069
fitted	-114.740315	3	235.480629
R	-121.737289	2	247.474579

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.606	6	0.007296
Test 2	2.8025	3	0.4231
Test 3	2.8025	3	0.4231
Test 4	0.809561	2	0.6671