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Provisional Peer-Reviewed Toxicity Values for

Benzenethiol
(CASRN 108-98-5)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMCL	benchmark concentration lower bound 95% confidence interval
BMD	benchmark dose
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
POD	point of departure
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete-to-complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR BENZENETHIOL (CASRN 108-98-5)

BACKGROUND

HISTORY

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in IRIS (U.S. EPA, 2010a). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by a panel of six EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

DISCLAIMERS

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

Benzenethiol (also called thiophenol or phenylmercaptan) is used as a mosquito larvicide, as a food additive and, as an intermediate in the manufacture of pesticides, pharmaceuticals, and amber dyes. It is a colorless liquid with a disagreeable odor described as penetrating, repulsive, and garlic-like. Benzenethiol is produced commercially by reducing benzenesulfonyl chloride with zinc dust in sulfuric acid or by reacting hydrogen sulfide with chlorobenzene (U.S. EPA, 2007). The molecular formula for benzenethiol is C_6H_5SH (see Figure 1). A table of its chemico-physical properties is provided below (see Table 1).

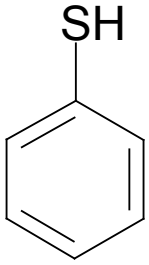

Figure 1. Benzenethiol Structure

Table 1. Physical Properties Table for Benzenethiol[a]	
Property (unit)	**Value**
Boiling point (ºC)	168.3
Melting point (ºC)	−14.9
Density (g/cm^3)	1.07
Vapor pressure at 25ºC (mm Hg)	1.93
pH (unitless)	Feebly acidic
Solubility in water (mg/L at 25ºC)	836
Relative vapor density (air = 1)	3.8
Molecular weight (g/mol)	110.18
Flash point (°C)	50
Octanol/water partition coefficient (unitless)	331.13

[a]Values from http://www.epa.gov/oppt/aegl/pubs/phenyl_mercaptan_interim_nov_2007_v1.pdf and HSDB (searched online 02-17-2010; reviewed 4-16-2009, last revised 6-23-2005).

No reference dose (RfD), reference concentration (RfC), or cancer assessment for benzenethiol is included on the IRIS database (U.S. EPA, 2010a) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2006). CalEPA (2008, 2009a,b,c) has not derived toxicity values for exposure to benzenethiol or prepared a quantitative estimate of carcinogenic potential. Benzenethiol is not included in the *11th Report on Carcinogens* (NTP, 2005). The International Agency for Research on Cancer (IARC, 2009) has not reviewed the carcinogenic potential of benzenethiol. An interim acute exposure guideline level (AEGL) report stated that carcinogenicity studies in humans or animals were not available (U.S. EPA, 2007). Benzenethiol was not included in the CARA list (U.S. EPA, 1994).

The HEAST reported a subchronic RfD of 1.0×10^{-4} mg/kg-day (U.S. EPA, 2010b), derived from a 90-day oral gavage study in rats (American Biogenics Corp., 1989) with a LOAEL of 0.1 mg/kg-day (based on centrilobular eosinophilic changes in the liver) and an uncertainty factor (UF) of 1000. A chronic RfD of 1.0×10^{-5} mg/kg-day was estimated from the subchronic RfD using an additional UF_L of 10 for a total UF_C of 10,000. An electronic search of the online HEAST on February 19, 2010 continued to list this value as the RfD. However, a copy of this study was not available, and the online link to the HEAST Derivation Support Document was not available at the time of the preparation of this PPRTV document.

The American Conference of Governmental Industrial Hygienists (ACGIH, 2009) reported a threshold limit value (TLV) of 0.1 ppm, 0.45 mg/m^3 time-weighted average (TWA), and the National Institute of Occupational Safety and Health (NIOSH, 2005) set a Recommended Exposure Limit (REL) at 0.30 mg/m^3. The Occupational Safety and Health Administration (OSHA, 2009) has not derived a permissible exposure limit (PEL) for benzenethiol. The toxicity of benzenethiol has not been reviewed by ATSDR (2010) to determine oral or inhalation Minimal Risk Levels (MRL).

The World Health Organization (WHO) has not prepared an environmental health criteria (EHC) document on benzenethiol (WHO, 2010). A meeting of the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA) in 1999 evaluated certain food additives and contaminants (FAO/WHO, 1999). Benzenethiol (No. 525) was evaluated using the procedure for safety evaluation of flavoring agents, resulting in new specifications prepared and conclusions of "no safety concern" based on current intake.

Literature searches were conducted on sources published from 1900 through August 2010 for studies relevant to the derivation of provisional toxicity values for benzenethiol, CAS No. 108-98-5. The EPA Health and Environmental Research Online (HERO) evergreen database of scientific literature was used to search the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration; DOE: Information Bridge; DOE: Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics; JSTOR: Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed (MEDLINE and CANCERLIT databases); SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network: ANEUPL; CCRIS; ChemIDplus; CIS; CRISP; DART; EMIC; EPIDEM; ETICBACK; FEDRIP; GENE-TOX; HAPAB; HEEP; HMTC; HSDB; IRIS; ITER; LactMed; Multidatabase Search; NIOSH; NTIS; PESTAB; PPBIB; RISKLINE; TRI; and TSCATS); Virtual Health Library; Web of Science (searches Current Content database among others); WHO; and Worldwide Science. The following databases outside of HERO were searched for risk assessment values: ACGIH; ATSDR; CalEPA; EPA IRIS; EPA HEAST; EPA HEEP; EPA OW; EPA TSCATS/TSCATS2; NIOSH; NTP; OSHA; and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides information for all of the potentially relevant studies. Entries for the principal studies (PS) are bolded. In this document, "statistically significant" denotes a *p*-value of < 0.05.

Table 2. Summary of Potentially Relevant Data for Benzenethiol (CASRN 108-98-5)

Notes[a]	Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b,c]	Reference (Comments)
Human								
1. Oral (mg/kg-day)[b]								
	Subchronic	None						
	Chronic	None						
	Developmental	None						
	Reproductive	None						
	Carcinogenic	None						
2. Inhalation (mg/m^3)[b]								
	Subchronic	None						
	Chronic	None						
	Developmental	None						
	Reproductive	None						
	Carcinogenic	None						
Animal								
1. Oral (mg/kg-day)[b]								
	Subchronic	Albino Rat Daily gavage for 90 days Study is not available for review		Centrilobular eosinophilic changes in the liver	Not available		0.1	American Biogenics Corp. (1989)[d]
	Chronic	None						
PR	**Developmental**	S-D Rat 25 females/dose group Daily gavage in corn oil from Gestation Days (GDs) 6−15. Cesarean section performed on GD 20	0, 20, 35, or 50 mg/kg-day	Maternal: increased relative and absolute liver weights and decreasd gravid uterine weight Developmental: decreased fetal body weights (females)	35 20	Not run	50 35	NTP (1994a)

Table 2. Summary of Potentially Relevant Data for Benzenethiol (CASRN 108-98-5)

Notes[a]	Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b,c]	Reference (Comments)
PR	**Developmental**	New Zealand White Rabbit 26 does in 1-, 10-, and 30-mg/kg-day groups; 15 does in 40-mg/kg-day group Daily gavage in corn oil from GDs 6−19. Cesarean section performed on GD 30	0, 10, 30, or 40 mg/kg-day; 50 mg/kg-day excluded from final assessment because excessive maternal toxicity (mortality and morbidity)	Maternal: decreased body weight gain and food consumption. Body weight loss for overall study, when corrected for gravid uterine weight. No developmental toxicity at 40 mg/kg-day	30 40	Not run	40 Not observed	NTP (1994b)
PS **PR**	**Reproductive**	**S-D Rat** **20 breeding pairs/group** **Daily gavage in corn oil continuously for two generations**	**0, 9, 18, or 35 mg/kg-day**	**Parental: increased liver and kidney weights; hepatocellular hypertrophy; and renal tubule degeneration** **Offspring: decreased F2 pup body weights** **Reproductive: inhibited spermiation in F1 males**	**Not observed** **9** **Not observed**	**2.91**	**9** **18** **9**	**NTP (1996)**
	Carcinogenic	None						
2. Inhalation (mg/m^3)[b]								
	Subchronic	None						
	Chronic	None						
	Developmental	None						
	Reproductive	None						
	Carcinogenic	None						

[a]PS = Principal study; PR = Peer-reviewed.
[b]Dosimetry, NOAEL, BMDL/BMCL and LOAEL values are converted to Human Equivalent Dose (HED in mg/kg-day) or Human Equivalent Concentration (HEC in mg/m^3) units. Noncancer oral data are only adjusted for continuous exposure.
[c]Not reported by the study author but determined from data.
[d]This study, cited in HEAST (U.S. EPA, 2010b), derived a subchronic RfD of 1×10^{-4} mg/kg-day using UF of 1000. Chronic RfD estimated at 1×10^{-5} mg/kg-day from subchronic study (UF = 10,000).

HUMAN STUDIES

Oral and Inhalation Exposure

No studies investigating the effects of subchronic or chronic oral exposure to benzenethiol in humans have been identified. No quantitative data were located regarding the toxicity of benzenethiol to humans following chronic or subchronic inhalation exposure. Data concerning human exposure to benzenethiol are limited to odor threshold data. An online search of Haz-map (2010) reported that benzenethiol causes tearing of the eyes and is a skin and respiratory irritant. Volunteers tolerated 8 ppm for 10 seconds (eye irritation), and a single breath of 35 ppm (nasal irritation).

ANIMAL STUDIES

Oral Exposure

Subchronic Studies

In a subchronic oral study conducted by American Biogenics Corp. (1989), albino rats were exposed to benzenethiol by daily gavage for 90 days. This study was cited in the HEAST (U.S. EPA, 2010b) and reported a LOAEL of 0.1 mg/kg-day based on centrilobular eosinophilic changes in the liver. An electronic search revealed the online HEAST on February 19, 2010 continued to list this value as the RfD. However, a copy of this study was not available, and the online link to the HEAST Derivation Support Document was not available at the time of the preparation of this PPRTV document. Additionally, eosinophilic changes in the hepatocytes, without corroborating evidence of liver toxicity that may or may not be available in the original manuscript (e.g., increased alanine aminotransferase, liver weights, or incidences of other microscopic findings in the liver), could be considered an adaptive response to the test material.

No other studies could be located regarding the effects of subchronic oral exposure of animals to benzenethiol.

Chronic Studies

No studies could be located regarding the effects of chronic oral exposure of animals to benzenethiol.

Developmental and Reproduction Studies

The effects of oral exposure of benzenethiol to animals have been evaluated in a developmental toxicity study in rats (NTP, 1994a), a range-finding toxicity study in rabbits (NTP, 1992), a subsequent full developmental toxicity study in rabbits (NTP, 1994b), and a reproductive toxicity study in rats (NTP, 1996).

Developmental Toxicity Study in Rats

In the developmental toxicity study in rats (NTP, 1994a), benzenethiol (>99% pure) was administered via gavage in corn oil to time-mated Sprague-Dawley (S-D) rats (Crl:CD®BR) (25/dose group) at dose levels of 0, 20, 35, or 50 mg/kg-day from Gestation Days (GDs) 6−15. Animals were observed daily for clinical signs of toxicity. Body weights were recorded on GDs 0, 3, 6 through 15, 18, and 20. Food and water consumption were recorded for the animals in each group on GDs 1, 3, 6, 9, 12, 15, 18, and 20. The dams were euthanized on GD 20 and subjected to a gross necropsy. The liver, right kidney, and gravid uterus were weighed. The numbers of corpora lutea in each ovary were counted. The number of implantation sites in the uterus was counted, and any uterus with no visible implantation sites was stained with 10%

ammonium sulfide to detect early resorptions. Live fetuses were euthanized, weighed, examined for external abnormalities, and dissected for visceral examination. Half of the fetuses in each litter were decapitated prior to dissection; the heads were fixed in Bouin's solution and then examined by a free-hand sectioning technique. All fetal carcasses were stained with Alcian Blue/Alizarin Red S and examined for skeletal malformations.

In the NTP (1994a) study, four rats in the high-dose group died or were sacrificed in extremis. Among the animals surviving to scheduled necropsy on GD 20, pregnancy rates were 100, 100, 96, and 100% in the 0-, 20-, 35-, and 50-mg/kg-day groups, respectively. Clinical signs consisted primarily of rooting behavior after dose administration. The incidence of rooting behavior increased with both dose and time, with this behavior first noted on GDs 11, 8, and 6 in the 20-, 35-, and 50-mg/kg-day groups, respectively, reaching a maximum incidence of 0% (control), 28% (low dose), 92% (mid-dose) and 100% (high dose) by GD 15. This behavior was not observed after the treatment period was concluded. The study authors concluded that the rooting behavior was indicative of an aversion to the dosing formulation. Absolute and relative (to body weight) maternal food consumption (g/kg-day) was statistically decreased by 9−28% ($p < 0.05$) in all treated groups for the first 3 days of dosing (GDs 6−9). Only the high dose, 50 mg/kg-day, maintained a statistical ($p < 0.05$) reduction in relative food consumption for GDs 9−12. For the last 3 days of dosing, GDs 12−15, the relative food consumption for all treatment groups was statistically the same as the control group. Overall, absolute and relative maternal food consumption was decreased for the high-dose (50 mg/kg-day) group by 14−18% ($p < 0.05$) for the entire dosing period (GDs 6−15). Conversely, relative maternal food consumption was increased by 11% ($p < 0.05$) in the 50-mg/kg-day dams during the posttreatment period (GDs 15−20), and absolute and relative maternal water consumption at 50 mg/kg-day was 20−33% higher than the control group throughout the treatment and posttreatment intervals. Maternal body-weight change was statistically dose-dependently decreased by 31−102% ($p < 0.05$) in all treatment groups for GDs 6−9 (see Table B.1). Maternal body weight was significantly decreased by 6−8% at 50 mg/kg-day compared to controls from GD 9 to termination on GD 20. Additionally in the 50-mg/kg-day group, body-weight gain was decreased by 25% ($p < 0.05$) for GDs 9−12, by 33% ($p < 0.05$) for the overall treatment period (GDs 6−15), by 20% ($p < 0.05$) for the overall gestation period (GDs 0−20), and by 17% ($p < 0.05$) when corrected for gravid uterine weight. The effects on maternal food and water consumption likely resulted in the changes in maternal body-weight gain throughout the dosing period. Relative (percent body weight) and adjusted (for maternal body weight) liver weights were increased by 10−18% ($p < 0.05$) over controls in the 50-mg/kg-day group. Gravid uterine weight was decreased by 22% ($p < 0.05$) at the high dose. The maternal LOAEL is 50 mg/kg-day based on increases in relative and adjusted maternal liver weights and decreases in gravid uterine weight. The maternal NOAEL is 35 mg/kg-day.

Table B.2 presents cesarean section and fetal examination data from the NTP (1994a) study. Postimplantation loss was increased at 50 mg/kg-day, as evidenced by increases in the percent of resorptions/litter (15.5% vs. 1.5% controls) and the number of litters with resorptions (52 vs. 24 controls). The number of live fetuses per litter was decreased by 20% at 50 mg/kg-day compared to controls. Male and female fetal body weights were 10% lower than controls at this dose. At 35 mg/kg-day, female fetal body weights were significantly decreased by 5% ($p < 0.05$) compared to controls. The incidence of external malformations (including anophthalmia, an open eye, cleft lip and/or palate, anasarca, gastroschisis, micromelia, and

syndactyly of the hind and forepaw) was increased in the high-dose group (1.9% fetuses; 19.0% litters) compared to concurrent controls (0.3%; 4.0% litters). This incidence also exceeded the provided historical control incidence of 0.2% fetuses in 1.2% litters. The historical control data comprised 1222 fetuses from 82 litters from studies conducted in 1988 by NIEHS/NTP Contract No. N01-ES-55080 (RTI Project No. 311U-2717) and NIEHS/NTP Contract No. N01-ES-95255 (RTI Project No. 311U-4349). Combined, these data result in a NOAEL for developmental toxicity of 20 mg/kg-day and a LOAEL of 35 mg/kg-day based on reduced female fetal body weight. This developmental toxicity study in rats is considered acceptable because a maternal LOAEL was observed, and comprehensive fetal examinations were conducted to determine external, visceral, and skeletal malformations and variations.

Developmental Toxicity Study in Rabbits

The dose levels for the definitive developmental toxicity study were based on data from preliminary rabbit range-finding studies (NTP, 1992; summaries reported in NTP [1994b]). In those studies, pregnant New Zealand White rabbits were dosed with corn oil (vehicle) or benzenethiol (>99% pure) at 0.5, 1, 2, 5, or 10 mg/kg-day on GDs 6−19, and nonpregnant female New Zealand White rabbits were dosed with 20, 40, or 50 mg/kg-day corn oil for 14 consecutive days. Animals were weighed and observed for clinical signs of toxicity. No clinical signs were observed in the adult animals at doses up to 40 mg/kg-day. At 50 mg/kg-day, one or two nonpregnant females were described as slightly sedated postdosing on 2 days during the dosing period. One of these animals died on Day 10. The study authors noted no effects on body weight in either the pregnant or nonpregnant animals. No significant dose-related developmental toxicity was noted. Therefore, the highest doses for the definitive developmental toxicity study were selected to be 40 and 50 mg/kg-day in an effort to induce some maternal toxicity without significant maternal lethality. The low exposure of 10 mg/kg-day was expected to produce no maternal or developmental toxicity, based on the reported lack of treatment-related effects in this preliminary study.

In the definitive developmental toxicity study in rabbits (NTP, 1994b), benzenethiol (>99% pure) was administered via gavage in corn oil to artificially inseminated New Zealand White rabbits at dose levels of 0, 10, 30, 40, or 50 mg/kg-day from GDs 6−19. Twenty-four to 26 animals were assigned to each dose group, with the exception of the 40-mg/kg-day group, to which 15 does were assigned. The authors stated that a slightly higher dose of 50 mg/kg-day was excluded from the final assessment due to excessive maternal toxicity, with 6/13 does dying during the first week of treatment; the remaining animals in the 50-mg/kg-day group were then euthanized by GD 14. Maternal body weights were determined on GDs 0, 3, 6 through 19, 25, and 30. Animals were observed for clinical signs of toxicity at least once daily before, during, and after the treatment period. Maternal food consumption was recorded every 3 days from GDs 0 through 18, and also on GDs 19, 22, 25, 28, and 30. All surviving does were euthanized on GD 30. The does were subjected to postmortem examination, cesarean section, organ-weight analyses, and gross necropsy. The liver, right kidney, and gravid uterus were weighed. The numbers of corpora lutea in each ovary were counted. The number of implantation sites in the uterus was counted, and any uterus with no visible implantation sites was stained with 10% ammonium sulfide to detect early resorptions. Live fetuses were euthanized, weighed, examined for external abnormalities, and dissected for visceral examination. Half of the fetuses in each litter were decapitated prior to dissection; the heads were fixed in Bouin's solution and

then examined by a free-hand sectioning technique. All fetal carcasses were stained with Alcian Blue/Alizarin Red S and examined for skeletal malformations.

NTP (1994b) reported two deaths during the study; one doe in the 10-mg/kg-day group died following dosing on GD 13, and one doe in the 30-mg/kg-day group died after dosing on GD 6. Maternal relative (to body weight) food consumption was marginally affected by treatment. In the treated animals, relative food consumption was comparable to controls before the initiation of dosing; however, during the dosing period, relative food consumption showed a statistically significant decreased linear trend, with decreases of 15 and 19% compared to controls at 30 and 40 mg/kg-day, respectively (see Table B.3). Despite the decreased linear trend, no individual exposure group demonstrated statistically significant decreases in food consumption compared to the control group during treatment. After the dosing period, the trend toward decreased food consumption was no longer evident.

Statistically significant pair-wise reductions in maternal body weight gain from the NTP (1994b) study were observed in the 30- and 40-mg/kg-day groups only for GDs 12−15 (decreased 77−92%), the same period in which the largest reductions in food consumption were seen in those two groups. A statistically significant ($p < 0.05$) decreased trend in maternal weight gain was observed for the overall dosing period (GDs 6−19), with decreases of 14, 30, and 61% compared to controls in the 10-, 30-, and 40-mg/kg-day groups, respectively. When corrected for gravid uterine weight, the maternal animals at 40 mg/kg-day experienced a body weight loss of −51.0 g compared to a body-weight gain of 61.9 g in the controls. Necropsy of maternal animals on GD 30 revealed no effects on maternal absolute or relative liver or right kidney weight. Gravid uterine weight was also unaffected by treatment. There were no effects of treatment on the numbers of resorptions (early, late, or complete litter), or fetal body weights or sex ratio. There were no treatment-related external, visceral, or skeletal variations or malformations in the fetuses. The investigators reported: a maternal NOAEL of 30 mg/kg-day; minor and transient decreases in body weight gains and food consumption at 30- and 40 mg/kg-day; and excessive toxicity at 50 mg/kg-day based on maternal mortality and morbidity in this study and in the dose-finding studies (as cited in NTP, 1994b). However, the data support a maternal LOAEL of 40 mg/kg-day, based on the decreased body weight gain and food consumption, along with the body weight loss when corrected for gravid uterine weight. Although body weight gain and food consumption were also decreased at 30 mg/kg-day, this dose level is considered the NOAEL because the decreases were of a smaller magnitude and did not affect the corrected body weight gain. No effects of benzenethiol treatment on fetal development or pregnancy were observed, indicating a developmental NOAEL of 40 mg/kg-day. Assessment of potential developmental toxicity at 50 mg/kg-day was precluded by excessive maternal toxicity. This developmental toxicity study in rabbits is considered acceptable because a maternal LOAEL was observed, and comprehensive fetal examinations were conducted to determine external, visceral, and skeletal malformations and variations.

Reproduction Study

The study by NTP (1996) is selected as the principal study for deriving the subchronic and chronic p-RfD values. In a multigeneration reproduction toxicity study (NTP, 1996), male and female F0 generation S-D (Crl:CD®BR) rats (Charles River Laboratories, Portage, MI) were administered benzenethiol (101% pure by HPLC) by daily gavage in corn oil at doses of 9, 18, or 35 mg/kg-day (20/sex/dose) and allowed to cohabitate for 16 weeks. Except when paired

together during mating, the animals were housed individually. During cohabitation, any litters born to the F0 animals were euthanized on Postnatal Day (PND) 1. Litters born after 17 weeks (F1) were raised until PND 21, when selected weanlings were administered benzenethiol at the same doses as their parents. On PND 81, the F1 animals were allowed to cohabitate for 1 week and were euthanized following delivery of their litters (F2).

During the continuous breeding phase of the NTP (1996) study, all litters were evaluated on PND 1 and then euthanized. The total number of pups born, number of live and dead pups, number of male and female pups, and total pup weight of each sex were obtained. Parental male and female weights were obtained following delivery, and the dam was also weighed on PNDs 4, 7, 14 and 21. Feed consumption measurements for lactating dams were obtained on PNDs 1, 4, 7, 11, 14, 18 and 21. All animals were observed twice daily for mortality and signs of toxicity. Upon sacrifice of animals, the following organs were weighed: liver, kidneys, right cauda epididymis, right epididymis, prostate, seminal vesicles with coagulating glands, right testis, and ovaries. Liver and kidneys were microscopically examined. However, clinical chemistry parameters were not evalutated. Spermatid head count was determined from the right testis. Sperm density, morphology, and motion analyses (computer-assisted) were evaluated from the right cauda epididymis. Sperm parameters included: motility; velocity (μm/sec); linearity; ALH max (μm); ALH mean (μm); beat/cross frequency (Hz/sec); average radius (μm); circular cells; circular over motile cells (%); circular over all cells (%); epididymal sperm density (1000 sperm/mg caudal tissue) and morphology (% abnormal); spermatids/mg testis; and total spermatids/testis.

Table B.4 shows selected male body-weight results from the NTP (1996) study. Throughout the study, the body weights of the 35-mg/kg-day F0 males were 7−15% lower than controls. F0 female body weights were not affected by treatment. Body weights of the 35-mg/kg-day F1 parental males were 11−13% less than controls on Weeks 2 and 4, respectively, at delivery of the F1 dams' litters, and at necropsy.

In the F0 generation (NTP, 1996), relative (to body weight) liver weights were increased by 20, 35, and 50% (males) and by 11, 18, and 36% (females) in the 9-, 18-, and 35-mg/kg-day groups, respectively (see Table B.5). Absolute liver weights were increased by 24, 34, and 29% (males) and by 5, 13, and 25% (females). In the F1 generation, at 9, 18, and 35 mg/kg-day, absolute liver weights were increased over controls by 24, 30, and 34% in the males, and by 9, 15, and 34% in the females. Relative liver weights were increased by 18, 37, and 62% in the F1 males, and by 13, 17, and 42% in the F1 females. Centrilobular hepatocellular hypertrophy was observed in the parents as follows (see Table B.6): in the F0 males (90−100% vs. 0% controls) at 18 and 35 mg/kg-day; in the F0 females (90−100% vs. 0% controls) at 9, 18, and 35 mg/kg-day; in the F1 males (100% vs. 0% controls) at 9, 18, and 35 mg/kg-day; and in the F1 females at 9 (30%), 18 (100%), and 35 (100%) mg/kg-day. The hepatocellular hypertrophy showed a dose-dependent increase in severity in both sexes from both generations. Aside from the hepatocellular hypertrophy, there were no other gross or microscopic changes in the liver indicative of liver toxicity.

In the NTP (1996) study, F0 relative kidney weights of the 9-, 18-, and 35-mg/kg-day animals were increased by 30, 53, and 104% (males) and by 8, 5, and 20% (females), respectively (see Table B.7). Absolute kidney weights were increased by 35, 53, and 76% in the

9-, 18-, and 35-mg/kg-day males; whereas in the females, absolute kidney weights were only increased at 35 mg/kg-day (12% over controls). In the F1 generation, absolute kidney weights were increased by 62, 61, and 118% over controls in the 9, 18, and 35 mg/kg-day males, respectively, and by 17% in the 35-mg/kg-day females. Relative kidney weights were increased by 52, 67, and 163% in the F1 males, and by 12, 6, and 26% in the F1 females. Table B.8 depicts the incidences of gross findings in the kidneys at necropsy. In the F0 males, at 35 mg/kg-day, there was a treatment-related increase in the incidence of enlarged kidneys (2/10 vs. 0/10 controls) and pitted kidneys (4/10 vs. 1/10 controls). In the F1 males, at necropsy, there was a treatment-related increase in the incidence of enlarged kidneys at 9, 18, and 35 mg/kg-day (20, 10, and 40%, respectively, vs. 0% controls), pale kidneys at 9, 18, and 35 mg/kg-day (90, 100, and 90% respectively, vs. 0% controls), and soft kidneys at 35 mg/kg-day (20% vs. 0% controls). Increased incidences of renal tubule degeneration (see Table B.9) were observed in the F0 males (100% vs. 50% controls) and F1 males (100% vs. 0% controls) at 9, 18, and 35 mg/kg-day, in the F0 females at 9, 18, and 35 mg/kg-day (20−40% vs. 10% controls), and in the F1 females at 35 mg/kg-day (40% treated vs. 0% controls). Renal tubule degeneration also showed a dose-dependent increase in severity in both sexes from both generations.

The investigators reported a LOAEL for parental toxicity at 9 mg/kg-day in the NTP (1996) study, based on liver and kidney toxicity (increases in both absolute and relative liver and kidney weights, as well as centrilobular hepatocellular hypertrophy and renal tubule degeneration) in both F0 and F1 generations. A parental NOAEL was not established.

Reproductive evaluations were performed on sperm and reproductive organs of both the F0 and F1 generations in the NTP (1996) study. Sperm motility was decreased by 6% compared to controls at 18 mg/kg-day and by 5% at 35 mg/kg-day compared to controls (see Table B.10). Inhibited spermiation of Stage VIII−X tubules was observed in the F1 males at 9 mg/kg-day (60%), 18 mg/kg-day (60%), and 35 mg/kg-day (90%) compared to controls (0%). The mean percent of tubules affected was 10, 9.5, and 7.7% of the "vulnerable" tubules in the 9, 18, and 35 mg/kg-day groups, respectively. Spermatid and spermatocyte cellular morphology appeared normal in all animals. Neither epithelial disorganization nor cell sloughing was observed in any testes examined. No microscopic lesions were observed in the epididymis or ovaries of the F1 animals. All of the other above-mentioned parameters regarding sperm count and computer-assisted motion analyses in the treated groups were comparable to controls. Other reproductive endpoints at necropsy were comparable among dose groups. The LOAEL for reproductive toxicity is 9 mg/kg-day based on inhibited spermiation in the F1 males. A reproductive NOAEL was not established.

The offspring (F1 and F2) of exposed parents in the NTP (1996) study were examined for number of live pups, the number of male and female pups, and body-weight changes, and the total pup weight of each sex was recorded on PNDs 1, 4, 7, 14, and 21. Selected pup body-weight data are included in Table B.11. Five F1 litters were born during the 16 weeks of cohabitation of the F0 generation. The F1 live pup weight (adjusted for litter size) was decreased by 4 and 6% in the 9- and 35-mg/kg-day dose groups, respectively. In the offspring from the final F1 litter, the pup weights at 35-mg/kg-day were significantly decreased by 14−16% in the males on PNDs 4 and 7 and in the females on PND 7; however, no differences were observed on PNDs 1, 14, or 21. There was no treatment-related increase in preweaning mortality of the

F1 animals. In the F1 mating trial, live F2 pup weight for the combined sexes was decreased by 9 and 12% in the 18-and 35-mg/kg-day dose groups, respectively, when compared to controls. Other endpoints were unchanged. The investigators reported a LOAEL for offspring toxicity of 35 mg/kg-day based on decreased pup body weights. However, the data indicate a LOAEL of 18 mg/kg-day based on decreased body weights in the F2 pups. Although the decrease at this dose is relatively minor, it is dose-dependent, statistically significant, and (for pups) often biologically adverse. The NOAEL is 9 mg/kg-day.

Using the 35-mg/kg-day dose, a crossover mating trial in the NTP (1996) study revealed the females as the affected sex. When naive males were mated with control or 35-mg/kg-day females, the mean live pup weight and adjusted live pup weight were reduced in the 35-mg/kg-day group by 8−9%. No other treatment-related effects were seen (total number of pups born, number of live and dead pups, number of males and female pups, and total pup weight by sex were obtained). When naive females were mated with control or 35-mg/kg-day males, reproductive parameters were comparable between dose groups. No differences were observed in the pregnancy index, cumulative days to litter, mean average litters per pair, proportion of pups born alive, or sex ratio of pups. This study meets the criteria for an acceptable reproductive toxicity study, in that it was conducted for two generations under continuous exposure and examined a comprehensive suite of parameters to determine effects on parents, offspring, and reproduction.

Inhalation Exposure

The only inhalation studies found were short-term (acute and subacute) lethality studies in rats and mice. Summaries of these studies are included below in the following section on "Other Data (Short-Term Tests, Other Examination)".

Subchronic Studies

No studies could be located regarding the effects of subchronic inhalation exposure of animals to benzenethiol.

Chronic Studies

No studies could be located regarding the effects of chronic inhalation exposure of animals to benzenethiol.

Developmental and Reproduction Studies

No studies could be located regarding the effects of inhaled benzenethiol on reproduction or fetal development.

Other Data (Short-Term Tests, Other Examination)

Acute and Subacute Inhalation Studies

Fairchild and Stokinger (1958) exposed groups of 5−10 Swiss-derived male mice (body weight 25−28 g) to 20-, 31-, 41-, 52-, or 79-ppm benzenethiol and 5−10 Wistar-derived male rats (body weight 180−220 g) to 20-, 31-, 41-, 52-, 79-, or 132-ppm benzenethiol for 4 hours, followed by a 15-day observation period. Clinical signs included increased respiration and restlessness (hyperactivity), uncoordinated movement, staggering gait, muscular weakness, partial skeletal muscle paralysis beginning in the hind limbs, light to severe cyanosis, tolerance of a prone position, and mild-to-heavy sedation. Animals exposed to "maximal lethal

concentrations" typically died from respiratory arrest during exposure or shortly after removal from the chamber. Animals exposed to "minimal lethal concentrations" typically died while in a semiconscious condition of "long duration." Surviving animals often remained in a semi-conscious state of sedation and lethargy 4 to 6 hours post exposure before showing signs of recovery. For mice, an LC_{50} value of 28 ppm was calculated by the study authors. A BMC_{01} of 26.5 ppm and $BMCL_{05}$ of 18.5 ppm were also calculated by the study authors. LC_{05} and LC_{01} values could not be calculated by the method of Litchfield and Wilcoxon because there were not at least two concentrations showing between 0 and 100% mortality. In rats, an LC_{50} value of 33 ppm was calculated by the study authors. A BMC_{01} of 17.7 ppm and $BMCL_{05}$ of 13.4 ppm were also calculated by the study authors. An LC_{05} value of 15.5 ppm and LC_{01} value of 10.3 ppm were calculated by the method of Litchfield and Wilcoxon.

In an acute inhalation toxicity study conducted by Stauffer Chemical Company (1969), groups of five albino rats/sex/dose were exposed to 244-, 346-, or 595-ppm benzenethiol for 1 hour, followed by a 14-day observation period. Clinical signs included ocular edema and erythema, and slight nasal discharge in all test groups. "Acute depression" was reported in the 244-ppm group, and dyspnea, gagging, fasiculation, and cyanosis were reported in the 346- and 595-ppm groups while the animals were in the exposure chamber. There were no treatment-related deaths in the 244-ppm group, and all animals in this dose group appeared grossly normal at necropsy after terminal sacrifice. Treatment-related mortality was noted in 3/10 animals at 346 ppm and 10/10 animals at 595 ppm. Decedents exhibited areas of hemorrhage in the lungs, while survivors in the 346-ppm group appeared grossly normal. The authors calculated an LC_{50} of 422 ppm. No further experimental details were available.

In a subacute inhalation toxicity study conducted by Hazleton Laboratories (1951), 7 adult male albino rats and 12 adult male albino mice were exposed to an "atmosphere saturated with benzenethiol" for 6 hours on the first exposure day and for 8 hours on each of the 3 succeeding days. The mice exhibited excitement, preening, and slight salivation during the first 6-hour exposure period. The following morning, 7 mice were found dead, but the surviving 5 mice appeared normal (Group A). A second group of 13 adult albino male mice was added to the experiment (Group B). All mice were then exposed 8 hours/day, for 3 consecutive days. Of the five remaining mice from Group A, two died on Day 2 of exposure, two died on Day 4, and the one died 3 days after the final exposure. Hemorrhagic lungs, irritation of the intestines, and spotted livers and kidneys were noted at necropsy. Group B mice also exhibited preening, lacrimation, and salivation immediately upon exposure and, subsequently, were lethargic and appeared unkempt. Mortality was observed in 11/13 mice from Group B; deaths occurred from Day 1 through 3 days after the final exposure. Hemorrhagic lungs, irritated intestines, and spotty livers and kidneys were noted in both decedents and animals terminated 3 days after the final exposure. Rats showed preening, lacrimation, and marked salivation during exposure, followed by unkempt appearance and lethargy. One rat died overnight after the final exposure, and another died 3 days after the final exposure. Hemorrhagic lungs, intestinal irritation, and mottled livers and kidneys were noted in the decedents. Surviving rats terminated 3 days after the final exposure showed gas-filled and irritated stomachs and intestines, pale brown kidneys, small spleens, mottled livers, and irritated eyes.

Metabolism, Mode-of-Action and Structure-Activity Relationship Studies

A discussion of the metabolism, mechanism of toxicity, and structure-activity relationships with related chemicals and their relative toxicity can be found in a report deriving the interim Acute Exposure Guideline Levels (AEGLs) for benzenethiol (U.S. EPA, 2007).

Table 3 summarizes the studies on short-term inhalation, mechanism of toxicity, structure-activity relationships, genotoxicity, and metabolism.

Table 3. Other Studies

Tests	Materials and Methods	Results	Conclusions	References
Acute inhalation mouse	20-, 31-, 41-, 52-, or 79-ppm vapor for 4 hours, followed by a 15-day observation period.	Clinical signs indicative of central nervous system depression and respiratory distress, including increased respiration, restlessness (hyperactivity), uncoordinated movement, staggering gait, muscular weakness, skeletal muscle paralysis, light to severe cyanosis, and coma.	The only inhalation studies found were short-term lethality studies in rats and mice. Therefore, these acute studies are included. LC_{50} = 28 ppm BMC_{01} = 26.5 ppm $BMCL_{05}$ = 18.5 ppm	Fairchild and Stokinger (1958)
Acute inhalation rat	20-, 31-, 41-, 52-, 79-, or 132-ppm vapor for 4 hours, followed by a 15-day observation period.	Clinical signs indicative of central nervous system depression and respiratory distress, including increased respiration, restlessness (hyperactivity), uncoordinated movement, staggering gait, muscular weakness, skeletal muscle paralysis, light to severe cyanosis, and coma.	LC_{50} = 33 ppm LC_{05} = 15.5 ppm LC_{01} = 10.3 ppm BMC_{01} = 17.7 ppm $BMCL_{05}$ = 13.4 ppm	Fairchild and Stokinger (1958)
Acute inhalation rat	20-, 31-, 41-, 52-, 79-, or 132-ppm vapor for 4 hours, followed by a 15-day observation period for benzenethiol and ethyl mercaptan.	LC_{50}s (4-hours): Benzenethiol: 33 ppm Ethyl mercaptan: 4740 ppm Methyl mercaptan: 675 ppm Hydrogen sulfide: 444 ppm	Relative toxicity compared to similar chemicals (Quantitative structure-activity relationship [QSAR]) indicates that the toxicity of benzenethiol is greater than ethyl mercaptan (approximately 140-fold) and methyl mercaptan (approximately 20-fold).	Fairchild and Stokinger (1958)
Acute inhalation rat	5/sex/dose group exposed to 244-, 346-, or 595-ppm vapor for 1 hour followed by a 14-day observation period.	Clinical signs included: ocular edema and erythema and slight nasal discharge in all groups; “acute depression” at 244 ppm; and dyspnea, gagging, fasciculation, and cyanosis at ≥346 ppm. Lung hemorrhage observed in decedents.	LC_{50} = 422 ppm	Stauffer Chemical Company (1969)

Table 3. Other Studies

Tests	Materials and Methods	Results	Conclusions	References
Subacute inhalation rat and mouse	"Saturated" atmosphere for 6 hours on the first day followed by 8 hours on each of 3 succeeding days.	Similar clinical signs as acute studies listed above. At necropsy, hemorrhagic lungs, intestinal irritation, and mottled liver and kidneys noted.	No NOAEL, LOAEL, or LC_{50} reported because animals were only exposed to one concentration, which was not measured (i.e., only referred to as "saturated").	Hazleton Laboratories (1951)
Mechanistic human RBC in vitro	Adult human blood samples were suspended with or without 5-mM glucose and various concentrations of benzenethiol, 4-aminothiophenol, or corresponding disulfides. The percentage of oxyhemoglobin, methemoglobin, and nonintact hemoglobin was determined. Intracellular levels of NADH, NADPH, and reduced glutathione were measured. Flux through the hexose monophosphate shunt was measured by following $^{14}CO_2$ formation from the labeled glucose. Flux through glycolysis was determined by measurements of pyruvate and lactate in the medium and red blood cell compartment.	Auto-oxidation of benzenethiol resulted in production of a reactive oxygen species, causing the conversion of oxyhemoglobin to methemoglobin. Reduction of the disulfide by intracellular glutathione caused cyclic reduction/oxidation reactions, resulting in oxidative flux. Glycolysis and the hexose monophosphate shunt were inhibited at the intermediate (0.5-mM benzenethiol) and high levels of oxidative stress.	Benzenethiol at 0.25-mM concentration indicated a level of oxidative stress to which the cell is capable of an adaptive response.	Amrolia et al. (1989)
Mechanistic	Benzenethiol and other mercaptans induce toxicity by interrupting electron transport via inhibition of cytochrome oxidase. As a result of the electron transfer blockage, oxidative phosphorylation and aerobic metabolism may be affected, peripheral tissue P_{O2} increases, and the uploading gradient for oxyhemoglobin decreases. High oxygen concentrations are found in the venous return, resulting in a flushed appearance of the skin and mucous membranes. An increased demand is placed on glycolysis, resulting in lactic acidemia. Repeated-dose studies indicate that kidney effects may be due to the phenol moiety.			EPA (2007); NIOSH (1978)
Genotoxicity	Tested for reverse mutation in *Salmonella typhimurium* (Ames assay) with and without metabolic activation.	Negative in strain TA100 and TA98 with or without S9 activation.	These results indicate that benzenethiol is not mutagenic in the Ames assay.	Lavoie et al. (1979)

Table 3. Other Studies

Tests	Materials and Methods	Results	Conclusions	References
Metabolism rat	Oral administration of ^{35}*S*-methylphenyl sulfone. One hour after administration, excreted urine was extracted with benzene, and the aqueous layer was acidified with sulfuric acid and extracted with ether. The benzene-soluble and water-soluble products were analyzed using thin layer chromatography and gas-liquid chromatography.	^{35}*S*-methylphenyl sulfone was the only benzene-soluble metabolite identified. Trace amounts of methylphenyl sulfoxide were also identified.	Benzenethiol readily undergoes *S*-methylation, followed by oxidation of phenylsulfide to methylphenyl sulfone.	McBain and Menn (1969)

DERIVATION OF PROVISIONAL VALUES

Table 4 below presents a summary of noncancer oral reference values. No cancer values could be derived (see Table 5). Because there were no subchronic or chronic inhalation studies, the toxicity values were not converted to HEC units. For the oral noncancer studies by gavage, the only conversion was to provide an adjusted daily dose.

DERIVATION OF ORAL REFERENCE DOSE

Derivation of Subchronic p-RfD

The multigenerational study by NTP (1996) is selected as the principal study for derivation of a subchronic p-RfD. The critical endpoints are increased absolute and relative kidney weights and incidences of renal tubule degeneration in the male rats.

Table 4. Summary of Reference Values for Benzenethiol (CASRN 108-98-5)

Toxicity Type (units)	Species/Sex	Critical Effect	*p*-Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic p-RfD (mg/kg-day)	S-D Rat/M	Increased kidney weights[a]	1×10^{-2}	BMDS	2.91	300	NTP (1996)
Chronic p-RfD (mg/kg-day)	S-D Rat/M	Increased kidney weights[a]	1×10^{-3}	BMDS	2.91	3000	NTP (1996)
Subchronic p-RfC (mg/m^3)	None	None	None	None	None	None	None
Chronic p-RfC (mg/m^3)	None	None	None	None	None	None	None

[a] Renal tubule degeneration was observed in 100% of the treated F0 males compared to 50% controls and was dose-dependently increased in severity.

Table 5. Summary of Cancer Values for Benzenethiol (CASRN 108-98-5)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	None	None	None	None
p-IUR	None	None	None	None

Table 6 summarizes the studies available for use in deriving provisional oral toxicity values for benzenethiol; these studies include a developmental gavage study in rats (NTP, 1994a), a developmental gavage study in rabbits (NTP, 1994b), and a two-generation reproductive study in rats (NTP, 1996). The developmental toxicity studies in rats and rabbits (NTP, 1994a,b) reported developmental effects in rats only at high dose (50 mg/kg-day; external malformations) and no developmental effects in rabbits. The body weight changes reported in these studies were associated with decreased food intake at the lowest dose (20 mg/kg-day). In contrast, the renal and hepatic effects (increased renal and hepatice weight, renal tubular degeneration, and hepatocellular hypertrophy) in the reproductive study (NTP, 1996) provide a LOAEL (9 mg/kg-day) and is therefore selected for derivation of the subchronic p-RfD. The selection of this study is justified because the F0 parents were dosed for 16 weeks, during which time, the dams had five litters. The pups of the first four litters were terminated on PND 1, and parents for the F1 generation were selected from the final litter. These parental animals were allowed to cohabitate on PND 81 for 1 week, and were euthanized following delivery of their litters (F2). Therefore, overall post-natal dosing of these F1 parental rats was comparable to F0 generation. Renal tubular degeneration was observed in male rats from both the F0 and F1 generation at 9 mg/kg-day. Hepatocellular hypertrophy was also observed in male rats at 9 mg/kg-day in the F1 generation and 18 mg/kg-day in the F0 generation. Increased relative kidney and liver weights were also observed at all doses in both F0 and F1 generation rats, with the male rats demonstrating more sensitivity. Since the systemic effects were observed at a lower dose (9 mg/kg-day) in contrast to the developmental effects observed at a higher dose (50 mg/kg-day), it appears the parental animals are more sensitive to benezenethiol; the selection of POD of 9.0 mg/kg-day may be protective of both parental and developmental effects.

Table 6. Summary of Oral Systemic Toxicity Studies for Benzenethiol

References	#/Sex (M/F)	Exposure (mg/kg-day)	Frequency/ Duration	$NOAEL_{ADJ}$[a] (mg/kg-day)	$LOAEL_{ADJ}$[b] (mg/kg-day)	Critical Endpoint
NTP (1994a)	25 F rats	0, 20, 35, 50	7 d/wk for GDs 6−15 gavage	[c]	20	Decreased body-weight gain and food consumption
NTP (1994b)	15−26 F rabbits	0, 10, 30, 40, 50	7 d/wk for GDs 6−19 gavage	10	30	Decreased body-weight gain and food consumption
NTP (1996)	20/20 rats	0, 9, 18, 35	7 d/wk for 16 wks (males)/19 wks (females)	[c]	9	Increased kidney weights, renal tubule degeneration
NTP (1996)	20/20 rats	0, 9, 18, 35	7 d/wk for 16 wks (males)/19 wks (females)	[c]	9	Increased liver weights, hepatocellular hypertrophy

[a]$NOAEL_{ADJ}$ = NOAEL × (gavage schedule).
[b]$LOAEL_{ADJ}$ = LOAEL × (gavage schedule).
[c]No NOAEL was identified. A NOAEL is considered equal to a LOAEL/10 for screening purposes.

Data from the F0 male and female rats from the reproduction study (NTP, 1996) study indicating treatment-related findings in the liver and kidney are considered in order to select a point of departure (POD) for the derivation of the subchronic p-RfD. The treatment-related effects in the liver included increased liver weight and hepatocellular hypertrophy. Evidence of toxic effects on the kidney was characterized by increased kidney weights and increased incidence and severity of renal tubule degeneration. Given the similarity in responses between both generations, the endpoints from which the subchronic oral RfD is derived are restricted to the F0 generation which are more amenable to benchmark dose modeling.

Data depicting treatment-related effects on the liver in the F0 rats are considered for BMD modeling. The histological data from the F0 males are not suitable for BMD modeling, as the incidence of hepatocellular hypertrophy was 0, 0, 100, and 90% in the F0 males at 0, 9, 18, and 35 mg/kg-day, respectively. An attempt at BMD modeling of dichotomous data for hepatocellular hypertrophy in the F0 males results in all seven dichotomous models failing the goodness-of-fit test (p-value < 0.1). In the F0 females, the incidence of hepatocellular hypertrophy was 0, 90, 100, and 100% of the rats in the 0, 9, 18, and 35 mg/kg-day groups, respectively. The gamma, log logistic, and log probit models all result in a BMD/BMDL ratio > 20. The remaining dichotomous models yield BMDL values ranging from 0.2-1.3 mg/kg-day. The low BMDL values are due to the steep dose-response curve; however, it is for this very reason that their precision is questionable. In order to adequately describe the lower part of the dose-response curve, an intermediate dose level between the control group (with 0% incidence) and the 9 mg/kg-day group (with 90% incidence) is necessary. Furthermore, although 90% of the F0 females exhibited hepatocellular hypertrophy at the low dose, the severity at this dose was only minimal to mild.

Absolute and relative liver weight data, presented in Tables 7 through 10, were considered for BMD modeling. The data on increased absolute and relative liver weights in F0 male rats exposed to benzenethiol via gavage (NTP, 1996) were modeled using the continuous-variable models in the EPA Benchmark Dose Software (BMDS), version 2.1 (U.S. EPA, 1999). Per EPA policy, in the absence of a biologically relevant benchmark response level (BMR), a default BMR of 1 standard deviation (SD) above the control mean is used for modeling.

Table 7. Absolute Liver Weights (g) in the F0 Male Rats Following 16-Week Exposure to Benzenethiol to be Used for BMD Analysis[a]

DOSE (mg/kg-day)	$DOSE_{ADJ}$ (mg/kg-day)	Number of Subjects	Response[b]
0	0	20	27.5 ± 4.20
9	9	10	34.2 ± 5.69*
18	18	10	36.9 ± 6.01*
35	35	10	35.4 ± 5.38*

[a]NTP (1996).
[b]Means ± SD. Standard deviation was calculated from standard error × √n
*Statistically significantly different from control ($p \leq 0.05$) by pair-wise comparison.

Table 8. Relative Liver Weights (mg/g Body Weight) in the F0 Male Rats Following 16-Week Exposure to Benzenethiol to be Used for BMD Analysis[a]

DOSE (mg/kg-day)	$DOSE_{ADJ}$ (mg/kg-day)	Number of Subjects	Response[b]
0	0	20	35.3 ± 4.07
9	9	10	42.2 ± 3.16*
18	18	10	47.7 ± 6.96*
35	35	10	53.0 ± 5.69*

[a]NTP (1996).
[b]Means ± SD. Standard deviation was calculated from standard error × √n
*Statistically significantly different from control ($p \leq 0.05$) by pair-wise comparison.

Table 9. Absolute Liver Weights (g) in the F0 Female Rats Following 19-Week Exposure to Benzenethiol to be Used for BMD Analysis[a]

DOSE (mg/kg-day)	$DOSE_{ADJ}$ (mg/kg-day)	Number of Subjects	Response[b]
0	0	20	16.3 ± 1.70
9	9	10	17.1 ± 1.14
18	18	10	18.5 ± 1.77*
35	35	10	20.3 ± 1.96*

[a]NTP (1996).
[b]Means ± SD. Standard deviation was calculated from standard error × √n
*Statistically significantly different from control ($p \leq 0.05$) by pair-wise comparison.

Table 10. Relative Liver Weights (mg/g Body Weight) in the F0 Female Rats Following 19-Week Exposure to Benzenethiol to be Used for BMD Analysis[a]

DOSE (mg/kg-day)	$DOSE_{ADJ}$ (mg/kg-day)	Number of Subjects	Response[b]
0	0	20	35.0 ± 2.41
9	9	10	38.9 ± 2.88*
18	18	10	41.3 ± 4.11*
35	35	10	47.6 ± 5.06*

[a]NTP (1996).
[b]Means ± SD. Standard deviation was calculated from standard error × √n
*Statistically significantly different from control ($p \leq 0.05$) by pair-wise comparison.

When data for absolute liver weights in the F0 males are modeled using constant variance, the linear, polynomial, and power models fail the goodness-of-fit test (*p*-value test 4 < 0.1). Although the Hill model with constant variance provides the lowest AIC and lowest BMDL, the BMD/BMDL ratio is >20, indicating unacceptable uncertainty at the lower end of the dose-response curve. When these data are modeled using nonconstant variance, all four continuous variable models result in the wrong variance model (*p*-value test 2 < 0.1).

When relative liver weight data for the F0 males are modeled using constant variance, all four continuous variable models indicate a poor variance model (*p*-value test 3 is < 0.1) and wrong variance models. Results from subsequent modeling of the relative liver weight data using nonconstant variance are included in Table 11. The Hill and polynomial models fail the goodness-of-fit test. The linear and power models produce identical results, indicating that the simpler linear model is more appropriate, with a BMDL of 5.20 mg/kg-day.

Table 11. Model Predictions for Increases in Relative Liver Weights in the Male F0 Rats Exposed Orally to Benzenethiol for 16 weeks[a]

Model Name	Homogeneity Variance *p*-Value	Goodness of Fit *p*-Value[b]	AIC for Fitted Model	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
Hill	0.060	<0.1	214.71	5.96	3.56
Linear	**0.060**	**0.122**	**214.91**	**7.17**	**5.20**
Polynomial[c]	0.060	<0.0001	10.00	-999.00	-999.00
Power	0.060	0.122	214.91	7.17	5.20

[a]NTP (1996).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Invalid BMD and BMDL
AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose.

Results from modeling liver weight data from the F0 females (Table 12) indicate that constant variance models are appropriate for absolute liver weight data and nonconstant variance models are appropriate for relative liver weight data. For absolute liver weights, the linear model with constant variance results in the lowest AIC and lowest BMDL (10.70 mg/kg-day). For relative liver weights, the linear nonconstant variance model is the simplest model that fits the data, yielding a BMDL of 4.91 mg/kg-day.

Table 12. Model Predictions for Increases in Absolute and Relative Liver Weights in the Female F0 Rats Exposed Orally to Benzenethiol for 19 weeks[a]

Model Name	Homogeneity Variance *p*-Value	Goodness of Fit *p*-Value[b]	AIC for Fitted Model	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
Absolute Liver Weights (constant variance)					
Hill	0.389	<0.1	107.53	14.15	8.15
Linear	**0.389**	**0.877**	**103.79**	**13.89**	**10.70**
Polynomial	0.389	0.608	105.79	13.95	10.70
Power	0.389	0.615	105.78	14.29	10.71
Model Name	**Variance Model *p*-Value**	**Goodness of Fit *p*-Value[b]**	**AIC for Fitted Model**	**BMD_{1SD} (mg/kg-day)**	**$BMDL_{1SD}$ (mg/kg-day)**
Relative Liver Weights (nonconstant variance)					
Hill	0.036	0.663	173.54	5.96	-999.00
Linear	**0.036**	**0.850**	**171.68**	**6.56**	**4.91**
Polynomial	0.036	0.850	171.68	6.56	4.91
Power	0.036	0.850	171.68	6.56	4.91

[a]NTP (1996).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose.

In summary, treatment-related effects of benzenethiol on the liver are limited to increased liver weights and hepatocellular hypertrophy. There are no other histopathology findings in the liver. Overall, the lowest BMDL value is for relative kidney weight in the F0 males: therefore, the effects on kidneys are considered to be the most appropriate critical effect for the POD for benzenethiol.

The BMDL modeling results for absolute and relative kidney weights of F0 male rats are shown in Tables 13 and 14, respectively. The data on increased absolute and relative kidney weights in male rats exposed to benzenethiol via gavage (NTP, 1996) are modeled using the continuous-variable models in the EPA BMDS (version 2.1). Per EPA policy, in the absence of a biologically relevant benchmark response level (BMR), a default BMR of 1 SD above the control mean is used.

Table 13. Absolute Kidney Weights (mg) in the F0 Male Rats Following 16-Week Oral Exposure to Benzenethiol to be Used for BMD Analysis[a]

DOSE (mg/kg-day)	$DOSE_{ADJ}$ (mg/kg-day)	Number of Subjects	Response[b]
0	0	20	4390.1 ± 581
9	9	10	5920.2 ± 683*
18	18	10	6719.7 ± 816*
35	35	9	7717.6 ± 1758*

[a]NTP (1996).
[b]Means ± SD. Standard deviation was calculated from standard error × √n
*Statistically significantly different from control ($p \leq 0.05$) by pair-wise comparison

Table 14. Relative Kidney Weights (mg/g Body Weight) in the F0 Male Rats Following 16-Week Oral Exposure to Benzenethiol to be Used for BMD Analysis[a]

DOSE (mg/kg-day)	$DOSE_{ADJ}$ (mg/kg-day)	Number of Subjects	Response[b]
0	0	20	5.7 ± 0.63
9	9	10	7.4 ± 1.26*
18	18	10	8.7 ± 1.17*
35	35	9	11.6 ± 2.22*

[a]NTP (1996).
[b]Means ± SD. Standard deviation was calculated from standard error × √n
*Statistically significantly different from control ($p \leq 0.05$) by pair-wise comparison

When data for both absolute and relative kidney weights in the F0 males are modeled using constant variance, all four continuous variable models indicate poor variance and wrong variance models. The results from modeling of absolute and relative kidney weight data for the F0 males using nonconstant variance are presented in Table 15.

Table 15. Model Predictions for Increases in Absolute and Relative Kidney Weights in the Male F0 Rats Exposed Orally to Benzenethiol for 16 weeks[a]

Model Name	Homogeneity Variance *p*-Value	Goodness-of-Fit *p*-Value[b]	AIC for Fitted Model	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
Absolute Kidney Weights					
Hill[c]	<0.0001	0.660	712.48	3.00	-999.00
Linear	**<0.0001**	**0.136**	**714.28**	**4.83**	**3.52**
Polynomial[d]	<0.0001	<0.0001	906.57	-999.00	15.68
Power	<0.0001	0.136	714.28	4.83	3.52
Model Name	**Variance Model *p*-Value[b]**	**Goodness-of-Fit *p*-Value[b]**	**AIC for Fitted Model**	**BMD_{1SD} (mg/kg-day)**	**$BMDL_{1SD}$ (mg/kg-day)**
Relative Kidney Weights					
Hill[e]	<0.0001	0.408	60.19	3.46	2.22
Linear	**<0.0001**	**0.634**	**58.41**	**3.84**	**2.91**
Polynomial	<0.0001	0.634	58.41	3.84	2.91
Power	<0.0001	0.634	58.41	3.84	2.91

[a]NTP (1996).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Invalid BMDL; hit bound (n = 1)
[d]Invalid BMD; p-value 4 < 0.1 (i.e., fails p-value criteria for goodness of fit)
[e]Lowest BMDL; hit bound (n = 1)
AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose.

For absolute kidney weight data in the F0 males, the Hill model with nonconstant variance results in an invalid BMDL, and the polynomial model fails the *p*-value criteria for goodness of fit. The linear and power models both adequately fit the data with identical results, indicating that the BMDL of 3.52 mg/kg-day associated with the simpler linear model best describes the data. In fact, the modeling output and graph indicate that the power model reverts to a linear function.

For relative kidney weight data in the F0 males, nonconstant variance models for the linear, polynomial, and power models all result in the same values, again with the linear model best describing the data with BMDL of 2.91 mg/kg-day. Visual inspection of each graph reveals linear outputs for the linear, polynomial, and power models. The scaled residuals for all of the nonconstant variance models for relative kidney in the F0 males are < 2.0. Although the Hill model results in the lowest BMDL at 2.22 mg/kg-day, the model parameter (n = 1) hits a bound implied by some inequality constraint and thus has no standard error. Furthermore, because the range of the BMDL values is < 3-fold, the estimated BMDL is considered sufficiently close, and the BMDL with the lowest AIC value is selected for the POD. Therefore, the BMDL

(2.91 mg/kg-day) from the linear nonconstant variance model of relative kidney weight data in the F0 males is used as the POD in deriving a subchronic p-RfD.

The subchronic p-RfD for benzenethiol, based on the $BMDL_{1SD}$ of 2.91 mg/kg-day for increased relative kidney weight in the F0 male rat (NTP, 1996), is derived as follows:

Subchronic p-RfD = $BMDL_{1SD} \div UF$
= 2.91 mg/kg-day ÷ 300
= **0.0097 mg/kg-day or 1×10^{-2} mg/kg-day**

Tables 16 and 17, respectively, summarize the UFs and the confidence descriptor for the subchronic p-RfD for benzenethiol.

Table 16. Uncertainty Factors for Subchronic p-RfD of Benzenethiol[a]

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans. There are no data to determine whether humans are more or less sensitive than rats to nephrotoxicity of benzenethiol.
UF_D	3	A UF_D of 3 is selected because, although the database includes by this route one acceptable two-generation reproduction study in rats (NTP, 1996), one acceptable developmental study in rats (NTP, 1994a), and one acceptable developmental study in rabbits (NTP, 1994b), it is lacking a comprehensive general toxicity study.
UF_H	10	A UF_H of 10 for is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
UF_L	1	A UF_L of 1 is applied because the POD was developed using a BMDL.
UF_S	1	A UF_S of 1 is applied because the principal study (NTP, 1996) is a reproduction study in which the F0 parents were dosed for 16 weeks (comparable to a typical 13-week subchronic study). Furthermore, the endpoints utilized for the p-RfD are based on findings in the F0 generation.
$UF_C \leq 3000$	300	

[a]Source: NTP (1996).

Table 17. Confidence Descriptor for Subchronic p-RfD for Benzenethiol		
Confidence Categories	**Designation[a]**	**Discussion**
Confidence in study	M	Confidence in the key study is medium. NTP (1996) assessed comprehensive endpoints in an appropriate number of animals for a two-generation reproduction study, and the duration of exposure for the parental generation was appropriate for assessing subchronic toxicity. However, a full complement of organs was not examined microscopically, and clinical chemistry and hematology measurements were not conducted. The study included multiple effect levels, but a NOAEL is not identified. The key study is supported by high quality developmental toxicity studies in rats and rabbits conducted by NTP (1994a,b). The critical effect and subchronic p-RfD is supported by the presence of a dose-response relationship.
Confidence in database	M	The database includes acceptable developmental toxicity studies in two species (rabbits and rats) and an acceptable two-generation reproduction study in rats.
Confidence in subchronic p-RfD[b]	M	The overall confidence in the subchronic p-RfD is medium.

[a]L = Low, M = Medium, H = High.
[b]The overall confidence cannot be greater than lowest entry in table.

Derivation of Chronic p-RfD

No chronic studies are available for the derivation of a chronic p-RfD. The available oral studies are a developmental toxicity study in rats (NTP, 1994a), a developmental toxicity study in rabbits (NTP, 1994b), and a two-generation reproduction study in rats (NTP, 1996). The same study that was used for the derivation for the subchronic p-RfD (NTP, 1996) is used to derive the chronic p-RfD.

Therefore, the chronic p-RfD for benzenethiol, based on the $BMDL_{1SD}$ of 2.91 mg/kg-day for increased kidney weights in the F0 male rat (NTP, 1996), is derived as follows:

$$\textbf{Chronic p-RfD} = BMDL_{1SD} \div UF$$
$$= 2.91 \text{ mg/kg-day} \div 3000$$
$$= \textbf{0.00097 mg/kg-day or } \mathbf{1 \times 10^{-3}} \textbf{ mg/kg-day}$$

Tables 18 and 19, respectively, summarize the UFs and the confidence descriptor for the chronic p-RfD for benzenethiol.

Table 18. Uncertainty Factors for Chronic p-RfD of Benzenethiol[a]

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans. There are no data to determine whether humans are more or less sensitive than rats to nephrotoxicity of benzenethiol.
UF_D	3	A UF_D of 3 is applied because although the database includes one two-generation reproduction study in rats (NTP, 1996), one developmental study in rats (NTP, 1994a), and one developmental study in rabbits (NTP, 1994b), it is lacking a comprehensive general toxicity study.
UF_H	10	A UF_H of 10 for is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
UF_L	1	A UF_L of 1 is applied because the POD was developed using a BMDL.
UF_S	10	A UF_S of 10 is applied for extrapolation of subchronic data to chronic data. The principal study (NTP, 1996) is a reproduction study in which the F0 parents were dosed for 16 weeks (comparable to a typical 13-week subchronic study). It is the only longer duration study available, and the study did not evaluate all of the typical toxicity endpoints.
$UF_C \leq 3000$	3000	

[a]Source: NTP (1996).

Table 19. Confidence Descriptor for Chronic p-RfD for Benzenethiol		
Confidence Categories	**Designation[a]**	**Discussion**
Confidence in study	M	Confidence in the key study is medium. NTP (1996) assessed comprehensive endpoints in an appropriate number of animals for a two-generation reproduction study, and the duration of exposure for the parental generation was appropriate for assessing subchronic toxicity. However, a full complement of organs was not examined microscopically, and clinical chemistry and hematology measurements were not conducted. The study included multiple effect levels, but a NOAEL is not identified. The key study is supported by high quality developmental toxicity studies in rats and rabbits conducted by NTP (1994a,b). The critical effect and the chronic p-RfD is supported further by the presence of a dose-response relationship.
Confidence in database	M	The database includes developmental toxicity studies in two species (rabbits and rats) and a two-generation reproduction study. The database does lack a true chronic study.
Confidence in chronic p-RfD[b]	M	The overall confidence in the chronic p-RfD is medium.

[a]L = Low, M = Medium, H = High.
[b]The overall confidence cannot be greater than lowest entry in table.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic and Chronic p-RfC

No studies are available for the derivation of a subchronic or chronic p-RfC for benzenethiol. The only inhalation studies found are short-term lethality studies in rats and mice. Route-to-route extrapolation from oral to inhalation was not considered because suitable physiologically-based pharmacokinetic models are not available.

DERIVATION OF PROVISIONAL CANCER VALUES

Cancer Weight-of-Evidence Descriptor

Table 20 provides a cancer weight-of-evidence descriptor of "inadequate information to assess carcinogenic potential" for benzenethiol due to the lack of chronic toxicity or carcinogenicity data.

Table 20. Cancer WOE Descriptor for Benzenethiol			
Possible WOE Descriptor	**Designation[a]**	**Route of Entry (Oral, Inhalation, or Both)**	**Comments**
"Carcinogenic to Humans"	N/A	N/A	No human cancer studies are available.
"Likely to be Carcinogenic to Humans"	N/A	N/A	There is no adequate evidence of plausible association between human exposure and cancer. Positive tumors were observed in rats and mice, indicating suggestive evidence.
"Suggestive of Evidence of Carcinogenic Potential"	N/A	N/A	There is no evidence from human and animal studies that is suggestive of carcinogenicity.
"Inadequate Information to Assess Carcinogenic Potential"	**X**	**Both**	**Under the 2005 *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 2005), the available evidence from exposure to benzenethiol is inadequate to assess carcinogenic potential.**
"Not Likely to be Carcinogenic to Humans"	N/A	N/A	No strong evidence of noncarcinogenicity in humans is available.

[a]The designation N/A means not available, and X indicates the assigned cancer WOE descriptor.

Derivation of p-OSF

No human or animal studies examining the carcinogenicity of benzenethiol following oral exposure have been located. Therefore, derivation of a p-OSF is precluded.

Derivation of p-IUR

No human or animal studies examining the carcinogenicity of benzenethiol following inhalation exposure have been located. Therefore, derivation of a p-IUR is precluded.

APPENDIX A. PROVISIONAL SCREENING VALUES

No screening values are presented.

APPENDIX B. DATA TABLES

Table B.1. Maternal Body-Weight Changes, Food Consumption, Water Consumption, and Liver Weights of Rats Exposed to Benzenethiol via Gavage from GDs 6−15[a]

Parameter/Interval	Exposure Group (mg/kg-day)			
	0	20	35	50
Body-weight change (g)				
Treatment GDs 6−9	14.4 ± 1.0[b]	9.9 ± 0.9* (↓31)	7.1 ± 1.1* (↓88)	−0.3 ± 1.8* (↓102)
GDs 9−12	16.3 ± 1.3	19.1 ± 0.9	16.4 ± 1.3	12.3 ± 1.7* (↓25)
GDs 12−15	21.1 ± 1.1	23.7 ± 1.2	22.2 ± 1.7	22.8 ± 1.5 (↑8)
Overall treatment (GDs 6−15)	52.0 ± 2.1	52.7 ± 1.9	45.7 ± 1.9	34.8 ± 3.2* (↓33)
Gestation (GDs 0−20)	153.7 ± 4.3	153.1 ± 3.9	148.5 ± 3.6	122.6 ± 5.9* (↓20)
Gravid uterine weight (g)	92.7 ± 2.1	86.9 ± 3.4	89.4 ± 2.1	72.0 ± 5.5* (↓22)
Corrected weight gain[c]	61.0 ± 3.6	66.3 ± 2.2	59.1 ± 2.5	50.7 ± 4.3* (↓17)
Food consumption				
Treatment (GDs 6−15)				
Absolute (g/day)	22.2 ± 0.5	21.3 ± 0.4	21.1 ± 0.4	18.2 ± 0.7* (↓18)
Relative (g/kg-day)	71.6 ± 0.9	69.3 ± 0.8	68.9 ± 1.1	61.9 ± 2.0* (↓14)
Posttreatment (GDs 15−20)				
Absolute (g/day)	27.4 ± 0.6	27.3 ± 0.6	28.2 ± 0.6	28.5 ± 0.6
Relative (g/kg-day)	73.3 ± 1.3	73.1 ± 1.1	75.9 ± 1.3	81.5 ± 1.1* (↑11)
Water consumption				
Treatment (GDs 6−15)				
Absolute (g/day)	37.6 ± 1.2	37.9 ± 1.1	39.9 ± 1.2	45.1 ± 3.0* (↑20)
Relative (g/kg-day)	122.2 ± 3.4	122.7 ± 3.2	129.9 ± 3.9	152.1 ± 9.1* (↑24)
Posttreatment (GDs 15−20)				
Absolute (g/day)	47.5 ± 1.5	47.3 ± 1.0	50.2 ± 1.4	59.0 ± 3.0* (↑24)
Relative (g/kg-day)	127.0 ± 3.9	126.2 ± 2.4	135.4 ± 4.0	168.6 ± 8.2* (↑33)
Liver weights				
Absolute (g)	17.3 ± 0.3	18.3 ± 0.3	18.5 ± 0.3	19.2 ± 0.4
Relative (% body weight)	4.4 ± 0.1	4.6 ± 0.1	4.6 ± 0.1	5.2 ± 0.1* (↑18)
(% adjusted weight)	5.8 ± 0.1	5.8 ± 0.1	6.0 ± 0.1	6.4 ± 0.1* (↑10)

[a]NTP (1994a). Data were obtained from Table 3 on page 20 and Table A1-3 on page 37 of the study report.
[b]Means ± SE, () = percent change compared to control.
[c]Weight change during gestation minus gravid uterine weight.
*Significantly different from control ($p \leq 0.05$), Williams', and/or Dunnett's test.

Table B.2. Cesarean Section and Fetal Examination Data from Time-mated Female Rats Exposed to Benzenethiol via Gavage from GDs 6−15[a]

Parameter/Interval	Exposure Group (mg/kg-day)			
	0	20	35	50
All litters				
Resorptions/litter (%)	1.5 ± 0.6 [b]	1.0 ± 0.6	2.3 ± 0.9	15.5 ± 5.5*
Litters with resorptions (%)	24	12	29	52*
Live litters				
Number of live fetuses	15.8 ± 0.4	15.1 ± 0.6	15.7 ± 0.4	12.6 ± 1.0* (↓20)
Fetal body weights				
Males	3.84 ± 0.06	3.84 ± 0.10	3.73 ± 0.06	3.45 ± 0.11* (↓10)
Females	3.70 ± 0.05	3.57 ± 0.06	3.51 ± 0.05* (↓5)	3.34 ± 0.09* (↓10)
Fetal external malformations				
No. fetuses (litters) examined	394	378	376	265
No. fetuses (litters) with external malformations	1 (1)	0 (0)	0 (0)	5 (4)
Percent externally malformed fetuses (litters)	0.3 (4.0)	0.0 (0.0)	0.0 (0.0)	1.9 (19.0)
Number fetuses (litters) with				
Anophthalmia, right	---	---	---	1 (1)
Open eye, left	---	---	---	1 (1)
Anasarca	---	---	---	4 (3)
Gastroschisis	---	---	---	1 (1)
Micromelia	---	---	---	2 (2)
Syndactyly, hindpaw	---	---	---	1 (1)
Syndactyly, forepaw	---	---	---	1 (1)

[a]NTP (1994a). Data were obtained from Tables 4 and 5 on pages 21 and 22 of the study report.
[b]Means ± SE, () = percent change compared to control.
*Significantly different from control ($p \leq 0.05$), Williams', and/or Dunnett's test.

Table B.3. Maternal Food Consumption and Body-Weight Changes in New Zealand White Rabbits Exposed to Benzenethiol via Gavage from GDs 6−19[a]

Parameter/Interval	Exposure Group (mg/kg-day)			
	0	10	30	40
Food consumption[b]				
Pretreatment (GDs 0−5)				
Absolute (g/day)	185 ± 6.7	193 ± 7.0	197 ± 6.5	197 ± 10.0
Relative (g/kg-day)	52.5 ± 1.7	54.0 ± 2.2	55.1 ± 2.0	51.2 ± 2.0
Treatment (GDs 6−19)				
Absolute (g/day)	163 ± 7.5	157 ± 7.5	139 ± 9.4	139 ± 8.7
Relative (g/kg-day)	43.1 ± 1.7	41.3 ± 2.0	36.6 ± 2.3 (↓15)	34.8 ± 2.1 (↓19)[c]
Posttreatment (GDs 20−30)				
Absolute (g/day)	143 ± 8.8	154 ± 9.3	140 ± 9.7	156 ± 12.8
Relative (g/kg-day)	36.7 ± 2.1	38.6 ± 2.2	35.1 ± 2.2	37.6 ± 2.3
Body-weight change (g)				
Pretreatment (GDs 0−6)	189 ± 27	210 ± 33	220 ± 22	183 ± 37
Treatment (GDs 6−19)	216 ± 32	185 ± 31 (↓14)	152 ± 37 (↓30)	84 ± 58 (↓61)[c]
Treatment (GDs 12−15)	96 ± 14	47 ± 21	22 ± 22* (↓77)	8 ± 24* (↓92)[c]
Posttreatment (GDs 19−30)	136 ± 28	208 ± 27	114 ± 35	223 ± 26
Overall (GDs 0−30)	541 ± 49	603 ± 61	486 ± 56	491 ± 56
Gravid uterine weight (g)	476.84 ± 29.25	465.05 ± 49.86	469.58 ± 43.00	542.14 ± 25.78
Corrected weight change	61.9 ± 60.6	137.7 ± 87.7	15.9 ± 66.8	−51.0 ± 78.7

[a]NTP (1994b). Data were obtained from Table 4 on page 21 and Table A1−3 on page 38 of the study report.
[b]Means ± SE, () = percent change compared to control.
[c]Significant linear trend.
*Significantly different from control ($p \leq 0.05$), Williams', and/or Dunnett's test.

Table B.4. Parental Male Body Weights in S-D Rats Exposed to Benzenethiol via Gavage[a]

Time Point/Interval	Exposure Group (mg/kg-day)			
	0	9	18	35
F0 Generation body weights at delivery of each litter (g)				
Litter 1	512.83 ± 9.61[b]	494.96 ± 7.30	486.75 ± 9.38* (↓5)	476.01 ± 10.79* (↓7)[c]
Litter 2	584.48 ± 12.36	570.38 ± 10.50	559.32 ± 9.99	532.97 ± 9.77* (↓9)[c]
Litter 3	644.46 ± 14.29	618.33 ± 12.49	612.23 ± 13.02	571.48 ± 13.50* (↓11)[c]
Litter 4	696.85 ± 18.36	659.40 ± 18.72	647.99 ± 15.20	589.78 ± 13.67* (↓15)[c]
Litter 5	695.42 ± 25.80	660.65 ± 17.39	681.23 ± 17.67	613.90 ± 15.94* (↓12)[c]
F0 Body weights (g)				
Week 1	398.7 ± 3.5	382.6 ± 7.4	381.4 ± 6.3*(↓4)	368.7 ± 6.8* (↓8)[c]
Week 6	528.8 ± 9.0	512.0 ± 6.5	501.0 ± 9.1*(↓5)	487.9 ± 8.3* (↓8)[c]
Week 12	627.4 ± 12.9	619.2 ± 10.0	613.2 ± 10.8	563.1 ± 10.3* (↓10)[c]
Week 18	690.9 ± 15.1	686.3 ± 14.5	666.1 ± 13.4	603.2 ± 11.7* (↓13)[c]
F1 Generation body weights at delivery of litter (g)				
Litter 1	595.0 ± 18.7	593.8 ± 13.8	570.1 ± 12.5	511.8 ± 16.2* (↓14)[c]
F1 Body weights (g)				
Week 2	523.0 ± 13.0	523.7 ± 11.7	511.1 ± 7.9	462.9 ± 9.6* (↓11)[c]
Week 4	570.3 ± 13.4	572.4 ± 12.5	548.5 ± 7.8	498.5 ± 8.9* (↓13)[c]

[a]NTP (1996). Data were obtained from Tables 2-4, 2-5, 4-2, and 4-3 on pages 50, 51, 71, and 72 of the study report.
[b]Means ± SE, () = percent change compared to control.
[c]Significant linear trend.
*Significantly different from control ($p \leq 0.05$) by pair-wise comparison.

Table B.5. Parental Liver Weights in S-D Rats Exposed to Benzenethiol via Gavage[a]

Parameter	Exposure Group (mg/kg-day)			
	0	9	18	35
F0 Males				
Terminal body weights (g)	777.3 ± 16.7[b]	808.4 ± 32.7	777.3 ± 33.9	666.0 ± 16.8* (↓14)[c]
Liver				
Absolute (g)	27.5 ± 0.94	34.2 ± 1.8* (↑24)	36.9 ± 1.9* (↑34)	35.4 ± 1.7* (↑29)[c]
Relative (mg/g bw)	35.3 ± 0.91	42.2 ± 1.0* (↑20)	47.7 ± 2.2* (↑35)	53.0 ± 1.8* (↑50)[c]
F0 Females				
Terminal body weights (g)	464.8 ± 11.2	441.8 ± 12.0	451.8 ± 16.1	428.8 ± 12.4
Liver				
Absolute (g)	16.3 ± 0.38	17.1 ± 0.36 (↑5)	18.5 ± 0.56* (↑13)	20.3 ± 0.62* (↑25)[c]
Relative (mg/g bw)	35.0 ± 0.54	38.9 ± 0.91* (↑11)	41.3 ± 1.3* (↑18)	47.6 ± 1.6* (↑36)[c]
F1 Males				
Terminal body weights (g)	639.0 ± 17.1	670.4 ± 14.9	608.6 ± 7.7	528.8 ± 13.2* (↓17)[c]
Liver				
Absolute (g)	23.8 ± 0.84	29.4 ± 1.2* (↑24)	31.0 ± 0.78* (↑30)	31.8 ± 1.0* (↑34)[c]
Relative (mg/g bw)	37.2 ± 0.86	43.9 ± 1.5* (↑18)	50.9 ± 0.88* (↑37)	60.2 ± 1.5* (↑62)[c]
F1 Females				
Terminal body weights (g)	371.2 ± 8.2	358.0 ± 16.7	363.1 ± 8.7	350.9 ± 15.9
Liver				
Absolute (g)	14.3 ± 0.41	15.6 ± 0.83 (↑9)	16.4 ± 0.78* (↑15)	19.1 ± 0.66* (↑34)[c]
Relative (mg/g bw)	38.6 ± 0.79	43.7 ± 1.5* (↑13)	45.1 ± 2.1* (↑17)	54.9 ± 1.4* (↑42)[c]

[a]NTP (1996). Data were obtained from Tables 3-3, 3-5, 4-5, and 4-7 on pages 59, 61, 75, and 77 and text table on page 34 of the study report.
[b]Means ± SE, () = percent change compared to control.
[c]Significant linear trend.
*Significantly different from control ($p \leq 0.05$) by pair-wise comparison.

Table B.6. Incidences of Hepatocellular Hypertrophy in Sprague-Dawley Rats Exposed to Benzenethiol via Oral Gavage for 2 Generations[a]

Generation/Sex	Exposure Group (mg/kg-day)			
	0	**9**	**18**	**35**
F0 Males Total	**0**	**0**	**10**	**9**
Minimal	---	---	4	---
Mild	---	---	5	5
Moderate	---	---	1	4
F0 Females Total	**0**	**9**	**10**	**10**
Minimal	---	6	2	---
Mild	---	3	5	3
Moderate	---	---	3	4
Marked	---	---	---	3
F1 Males Total	**0**	**10**	**10**	**10**
Minimal	---	4	2	---
Mild	---	5	3	---
Moderate	---	1	5	10
F1 Females Total	**0**	**3**	**10**	**10**
Minimal	---	3	6	---
Mild	---	---	4	3
Moderate	---	---	---	6
Marked	---	---	---	1

[a]NTP (1996). Number affected/10 examined. Data were obtained from Text Tables on pages 37 and 41 of the study report.

Table B.7. Parental Kidney Weights in S-D Rats Exposed to Benzenethiol via Gavage[a]

Parameter	Exposure Group (mg/kg-day)			
	0	**9**	**18**	**35**
F0 Males				
Terminal body weights (g)	777.3 ± 16.7[b]	808.4 ± 32.7	777.3 ± 33.9	666.0 ± 16.8* (↓14)[c]
Kidney				
Absolute (mg)	4390.1 ± 130	5920.2 ± 216* (↑35)	6719.7 ± 258* (↑53)	7717.6 ± 586* (↑76)[c]
Relative (mg/g bw)	5.7 ± 0.14	7.4 ± 0.40* (↑30)	8.7 ± 0.37* (↑53)	11.6 ± 0.74* (↑104)[c]
F0 Females				
Terminal body weights (g)	464.8 ± 11.2	441.8 ± 12.0	451.8 ± 16.1	428.8 ± 12.4
Kidney				
Absolute (mg)	2715.2 ± 50.4	2803.6 ± 62.4	2784.9 ± 77.1	3033.0 ± 103* (↑12)[c]
Relative (mg/g bw)	5.9 ± 0.11	6.4 ± 0.12* (↑8)	6.2 ± 0.26 (↑5)	7.1 ± 0.31* (↑20)[c]
F1 Males				
Terminal body weights (g)	639.0 ± 17.1	670.4 ± 14.9	608.6 ± 7.7	528.8 ± 13.2* (↓17)[c]
Kidney				
Absolute (mg)	3991.7 ± 110	6482.6 ± 588* (↑62)	6407.6 ± 193* (↑61)	8703.8 ± 1093* (↑118)[c]
Relative (mg/g bw)	6.3 ± 0.07	9.6 ± 0.80* (↑52)	10.5 ± 0.33* (↑67)	16.6 ± 2.3* (↑163)[c]
F1 Females				
Terminal body weights (g)	371.2 ± 8.2	358.0 ± 16.7	363.1 ± 8.7	350.9 ± 15.9
Kidney				
Absolute (mg)	2446.7 ± 71.1	2626.7 ± 77.1	2550.9 ± 83.0	2855.2 ± 95.3* (↑17)[c]
Relative (mg/g bw)	6.6 ± 0.12	7.4 ± 0.28* (↑12)	7.0 ± 0.21* (↑6)	8.3 ± 0.42* (↑26)[c]

[a]NTP (1996). Data were obtained from Tables 3-3, 3-5, 4-5, and 4-7 on pages 59, 61, 75, and 77 and text table on page 34 of the study report.
[b]Means ± SE, () = percent change compared to control.
[c]Significant linear trend.
*Significantly different from control ($p \leq 0.05$) by pair-wise comparison.

Table B.8. Incidences of Gross Findings in the Kidneys of S-D Rats Exposed to Benzenethiol via Gavage[a]

Macroscopic finding	Exposure Group (mg/kg-day)			
	0	**9**	**18**	**35**
F0 Males				
Number examined	20	10	10	10
Kidneys, enlarged	0	0	0	2
Pitted	1	0	1	4
F1 Males				
Number examined	20	10	10	10
Kidneys, enlarged	0	2	1	4
Pale	0	9	10	9
Soft	0	0	0	2

[a]NTP (1996). Number affected. Data were obtained from Table 3-7 on page 63 and Table 4-9 on page 79 of the study report.

Table B.9. Incidences of Renal Tubule Degeneration in the Kidneys of S-D Rats Exposed to Benzenethiol via Oral Gavage for 2 Generations[a]

Generation/Sex	Exposure Group (mg/kg-day)			
	0	**9**	**18**	**35**
F0 Males Total	**5**	**10**	**10**	**10**
Minimal	2	---	---	---
Mild	3	8	2	---
Moderate	---	2	8	6
Marked	---	---	---	4
F0 Females Total	**1**	**2**	**3**	**4**
Minimal	1	2	2	---
Mild	---	---	1	4
F1 Males Total	**0**	**10**	**10**	**10**
Minimal	---	---	1	---
Mild	---	6	5	1
Moderate	---	3	4	3
Marked	---	1	---	6
F1 Females Total	**0**	**0**	**1**	**4**
Minimal	---	---	1	---
Mild	---	---	---	3
Moderate	---	---	---	1

[a]NTP (1996). Number affected/10 examined. Data were obtained from Text Tables on pages 37 and 41 of the study report.

Table B.10. Computer-Assisted Sperm Analysis of the Epididymis and Microscopic Examination of Testis Sperm in S-D Rats Exposed to Benzenethiol via Gavage[a]

Parameter	Exposure Group (mg/kg-day)			
	0	9	18	35
F0 Males				
Sperm motility (% motile)	89.2 ± 1.3[b]	88.1 ± 1.5	83.9 ± 2.5* (↓6)	84.8 ± 1.9* (↓5)[c]
Velocity (μm/sec)	198.9 ± 4.0	187.4 ± 4.6	183.2 ± 7.2	186.5.5.0[c]
F1 Males				
Sperm motility (% motile)	89.8 ± 0.88	86.4 ± 2.7	88.3 ± 0.74	85.8 ± 2.2
Velocity (μm/sec)	210.1 ± 6.1	206.8 ± 6.6	210.0 ± 6.1	196.1 ± 7.8
Inhibited spermiation of the Stage VIII-X tubules (# affected/10)	0	6	6	9

[a]NTP (1996). Data were obtained from text table on page 41, Table 3-4 on page 60, and Table 4-6 on page 76 of the study report. Spermatid head count was determined from the right testis. Sperm density, morphology, and motion analyses (computer-assisted) were evaluated from the right cauda epididymis. Sperm parameters included: motility, velocity (μm/sec); linearity; ALH max (μm); ALH mean (μm); beat/cross frequency (Hz/sec); average radius (μm); circular cells; circular over motile cells (%); circular over all cells (%); epididymal sperm density (1000 sperm/mg caudal tissue) and morphology (% abnormal); spermatids/mg testis; and total spermatids/testis. Aside from sperm motility in the F0 gernation and inhibited spermiation in the F1 males, none of these parameters were affected by treatment.

[b]Means ± SE, () = percent change compared to control.

[c]Significant ($p \leq 0.05$) linear trend.

*Significantly different from control ($p \leq 0.05$) by pair-wise comparison.

Table B.11. Selected Live Pup Body Weights of S-D Rats Exposed to Benzenethiol via Gavage[a]

Time Point/Interval	Exposure Group (mg/kg-day)			
	0	9	18	35
F1 Pups				
Absolute body weight (g)				
Males	6.67 ± 0.08[b]	6.38 ± 0.07* (↓4)	6.50 ± 0.09	6.35 ± 0.07* (↓5)[c]
Females	6.36 ± 0.09	6.06 ± 0.09* (↓5)	6.16 ± 0.08	6.05 ± 0.08* (↓5)[c]
Combined	6.51 ± 0.08	6.22 ± 0.08* (↓4)	6.33 ± 0.09	6.20 ± 0.07* (↓5)[c]
Adjusted[d]				
Males	6.68 ± 0.08	6.40 ± 0.08* (↓4)	6.50 ± 0.08	6.31 ± 0.08* (↓6)[c]
Females	6.37 ± 0.08	6.09 ± 0.08* (↓4)	6.16 ± 0.08	6.01 ± 0.08* (↓6)[c]
Combined	6.52 ± 0.08	6.24 ± 0.08* (↓4)	6.33 ± 0.08	6.16 ± 0.08* (↓6)[c]
F2 Pups				
Absolute body weight (g)				
Males	7.18 ± 0.24	6.71 ± 0.32	6.50 ± 0.19	6.30 ± 0.20* (↓12)[c]
Females	6.86 ± 0.21	6.38 ± 0.30	6.23 ± 0.16* (↓9)	5.99 ± 0.15* (↓13)[c]
Combined	6.99 ± 0.21	6.53 ± 0.30	6.35 ± 0.17* (↓9)	6.16 ± 0.17* (↓12)[c]
Adjusted[d]				
Males	7.26 ± 0.25	6.56 ± 0.21	6.44 ± 0.24	6.49 ± 0.26
Females	6.92 ± 0.24	6.28 ± 0.20	6.20 ± 0.22	6.12 ± 0.24
Combined	7.06 ± 0.23	6.41 ± 0.19	6.31 ± 0.22	6.32 ± 0.24

[a]NTP (1996). Data were obtained from Table 2-2 on page 48 and Table 4-2 on page 71 of the study report.
[b]Means ± SE, () = percent change compared to control.
[c]Significant linear trend.
[d]Least squares estimate of mean pup weight adjusted for average litter size ± SE (number of fertile pairs producing live pups).
*Significantly different from control ($p \leq 0.05$) by pair-wise comparison.

APPENDIX C. BMD MODELING OUTPUTS FOR BENZENETHIOL

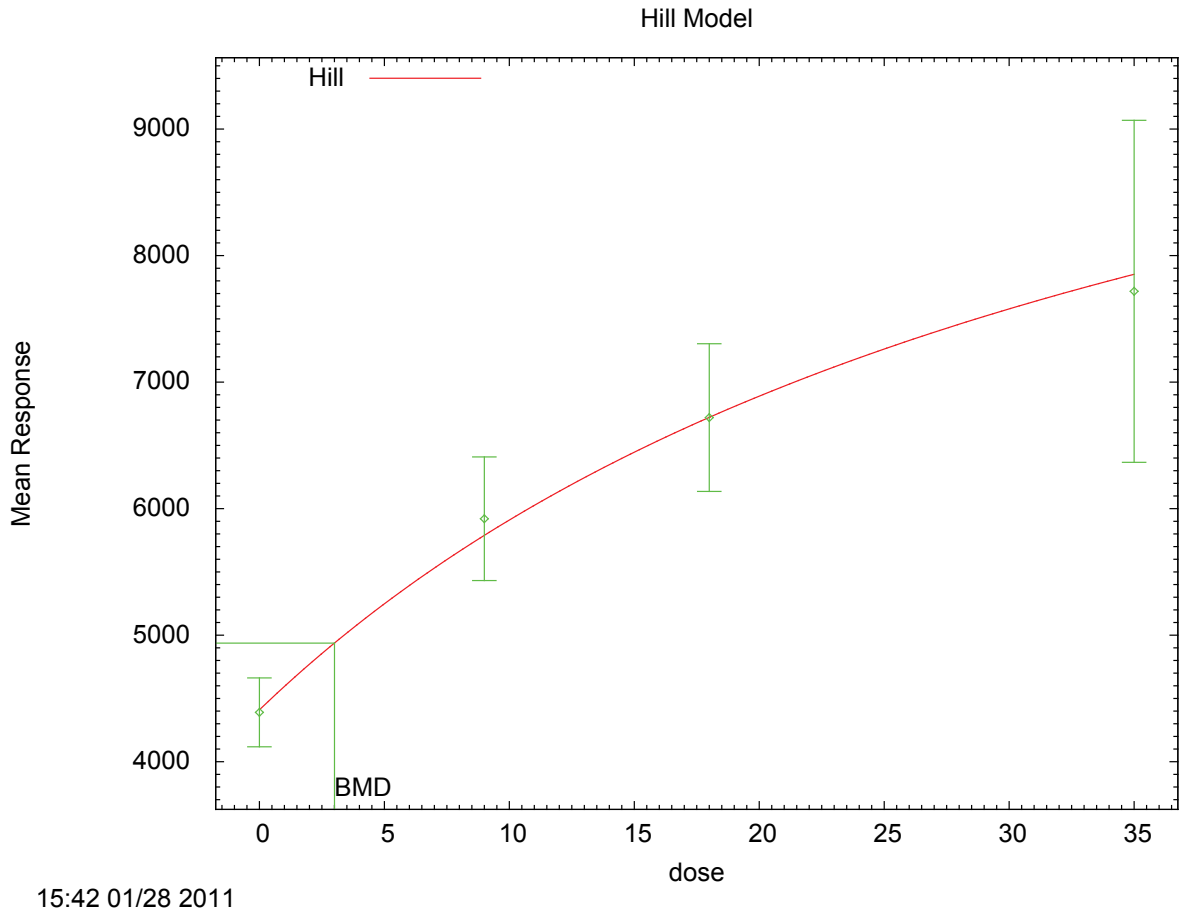

Figure C-1. Hill BMD Model for Absolute Kidney Weight Data (NTP, 1996)

Text Output for Hill BMD Model for Absolute Kidney Weight Data (NTP, 1996)

```
 ======================================================================
          Hill Model. (Version: 2.15;  Date: 10/28/2009)
          Input Data File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Abs_Kidney_Wt_Hill_1.(d)
          Gnuplot Plotting File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Abs_Kidney_Wt_Hill_1.plt
                                                Fri Jan 28 15:42:37 2011
 ======================================================================

 F0_M_Abs_Kidney_Wt
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)
```

Dependent variable = Mean
Independent variable = Dose
Power parameter restricted to be greater than 1
The variance is to be modeled as Var(i) = exp(lalpha + rho * ln(mean(i)))

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	13.7306
rho =	0
intercept =	4390.1
v =	3327.5
n =	0.0773128
k =	25.4955

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	intercept	v	k
lalpha	1	-1	-0.2	0.022	-0.037
rho	-1	1	0.19	-0.023	0.037
intercept	-0.2	0.19	1	0.12	0.23
v	0.022	-0.023	0.12	1	0.98
k	-0.037	0.037	0.23	0.98	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-14.4795	7.24771	-28.6848	-0.274303
rho	3.21979	0.839143	1.5751	4.86448
intercept	4408.97	118.57	4176.57	4641.36
v	7140.96	3342.24	590.281	13691.6
n	1	NA		
k	37.5881	27.807	-16.9126	92.0888

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	20	4.39e+003	4.41e+003	581	528	-0.16
9	10	5.92e+003	5.79e+003	683	819	0.509
18	10	6.72e+003	6.72e+003	816	1.04e+003	-0.00481
35	9	7.72e+003	7.85e+003	1.76e+003	1.34e+003	-0.302

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-358.813074	5	727.626149
A2	-349.267070	8	714.534141
A3	-351.141284	6	714.282567
fitted	-351.238144	5	712.476288
R	-385.485941	2	774.971882

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	72.4377	6	<.0001
Test 2	19.092	3	0.0002617
Test 3	3.74843	2	0.1535
Test 4	0.193721	1	0.6598

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

```
The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =       3.00245


BMDL computation failed.
```

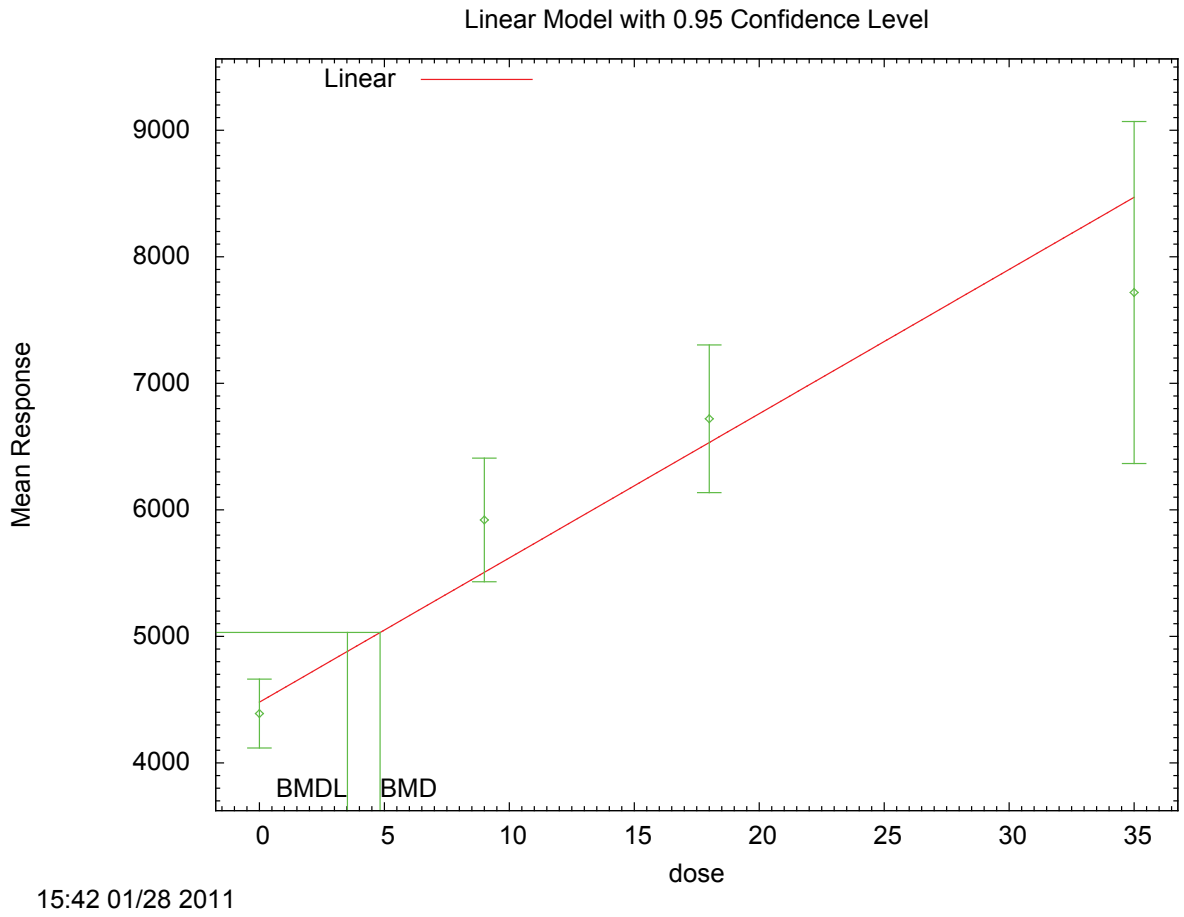

Figure C-2. Linear BMD Model for Absolute Kidney Weight Data (NTP, 1996)

Text Output for Linear BMD Model for Absolute Kidney Weight Data (NTP, 1996)

```
 ======================================================================
          Polynomial Model. (Version: 2.16;  Date: 05/26/2010)
          Input Data File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Abs_Kidney_Wt_Linear_1.(d)
          Gnuplot Plotting File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Abs_Kidney_Wt_Linear_1.plt
                                                Fri Jan 28 15:42:44 2011
 ======================================================================

 F0_M_Abs_Kidney_Wt
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
```

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	13.7306
rho =	0
beta_0 =	4779.05
beta_1 =	90.829

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	beta_0	beta_1
lalpha	1	-1	0.24	-0.39
rho	-1	1	-0.24	0.39
beta_0	0.24	-0.24	1	-0.53
beta_1	-0.39	0.39	-0.53	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-15.7807	7.45899	-30.4	-1.16134
rho	3.37767	0.862526	1.68715	5.06819
beta_0	4481.6	120.702	4245.03	4718.17
beta_1	113.816	13.4425	87.4689	140.163

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	20	4.39e+003	4.48e+003	581	549	-0.745
9	10	5.92e+003	5.51e+003	683	778	1.68
18	10	6.72e+003	6.53e+003	816	1.04e+003	0.577
35	9	7.72e+003	8.47e+003	1.76e+003	1.61e+003	-1.39

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)

```
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                     Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1         -358.813074            5     727.626149
              A2         -349.267070            8     714.534141
              A3         -351.141284            6     714.282567
          fitted         -353.138785            4     714.277570
               R         -385.485941            2     774.971882


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              72.4377          6          <.0001
   Test 2               19.092          3       0.0002617
   Test 3              3.74843          2          0.1535
   Test 4                3.995          2          0.1357

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


              Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95
```

BMD = 4.82763

BMDL = 3.52106

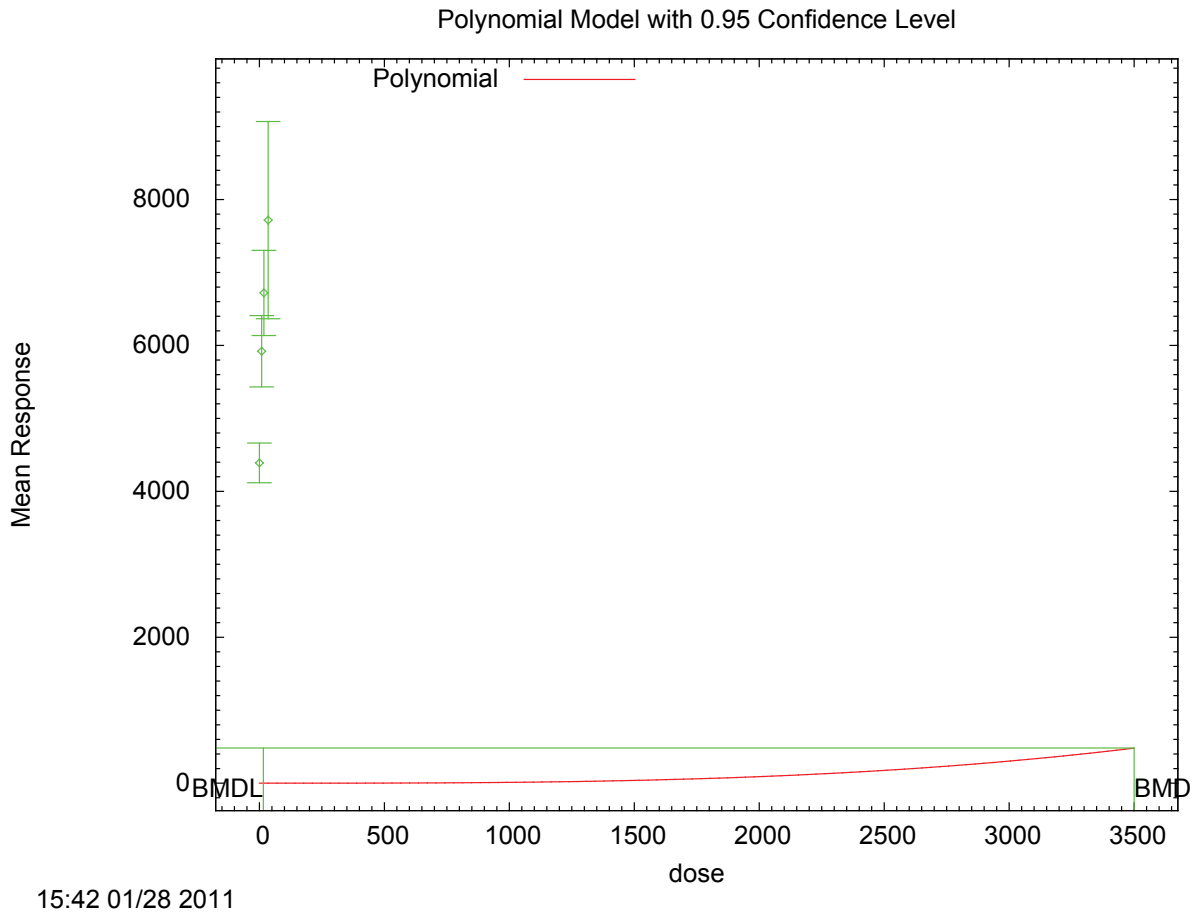

Figure C-3. Poly3 BMD Model for Absolute Kidney Weight Data (NTP, 1996)

Text Output for Poly3 BMD Model for Absolute Kidney Weight Data (NTP, 1996)

```
 ================================================================
          Polynomial Model. (Version: 2.16;  Date: 05/26/2010)
          Input Data File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Abs_Kidney_Wt_Poly3_1.(d)
          Gnuplot Plotting File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Abs_Kidney_Wt_Poly3_1.plt
                                                Fri Jan 28 15:42:44 2011
 ================================================================

 F0_M_Abs_Kidney_Wt
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   The polynomial coefficients are restricted to be positive
```

```
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                         lalpha =      13.7306
                            rho =            0
                         beta_0 =       4390.1
                         beta_1 =       226.11
                         beta_2 =            0
                         beta_3 =    0.0957401


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -beta_2
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                 lalpha          rho       beta_0       beta_1       beta_3

    lalpha            1         0.99      NA             NA              0.0065

       rho         0.99            1      NA             NA              0.0064

    beta_0      NA             NA             NA             NA             NA

    beta_1      NA             NA             NA             NA             NA

    beta_3       0.0065       0.0064      NA             NA                   1


                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
         lalpha          20.4374              NA                  NA
NA
            rho         0.431539              NA                  NA
NA
         beta_0      0.000213826              NA                  NA
NA
         beta_1     6.92766e-005              NA                  NA
NA
         beta_2     6.49404e-030              NA
         beta_3     1.12497e-008              NA                  NA
NA

At least some variance estimates are negative.
THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!
Try again from another starting point.
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	20	4.39e+003	0.000214	581	4.43e+003	4.44
9	10	5.92e+003	0.000846	683	5.96e+003	3.14
18	10	6.72e+003	0.00153	816	6.76e+003	3.14
35	9	7.72e+003	0.00312	1.76e+003	7.89e+003	2.93

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-358.813074	5	727.626149
A2	-349.267070	8	714.534141
A3	-351.141284	6	714.282567
fitted	-448.286301	5	906.572601
R	-385.485941	2	774.971882

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	72.4377	6	<.0001
Test 2	19.092	3	0.0002617
Test 3	3.74843	2	0.1535
Test 4	194.29	1	<.0001

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

```
The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model

BMD computation failed for BMR =        4426.54
Setting BMD = 100*(maximum dose)

             Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

              BMD =          -9999


            BMDL =        15.6802
```

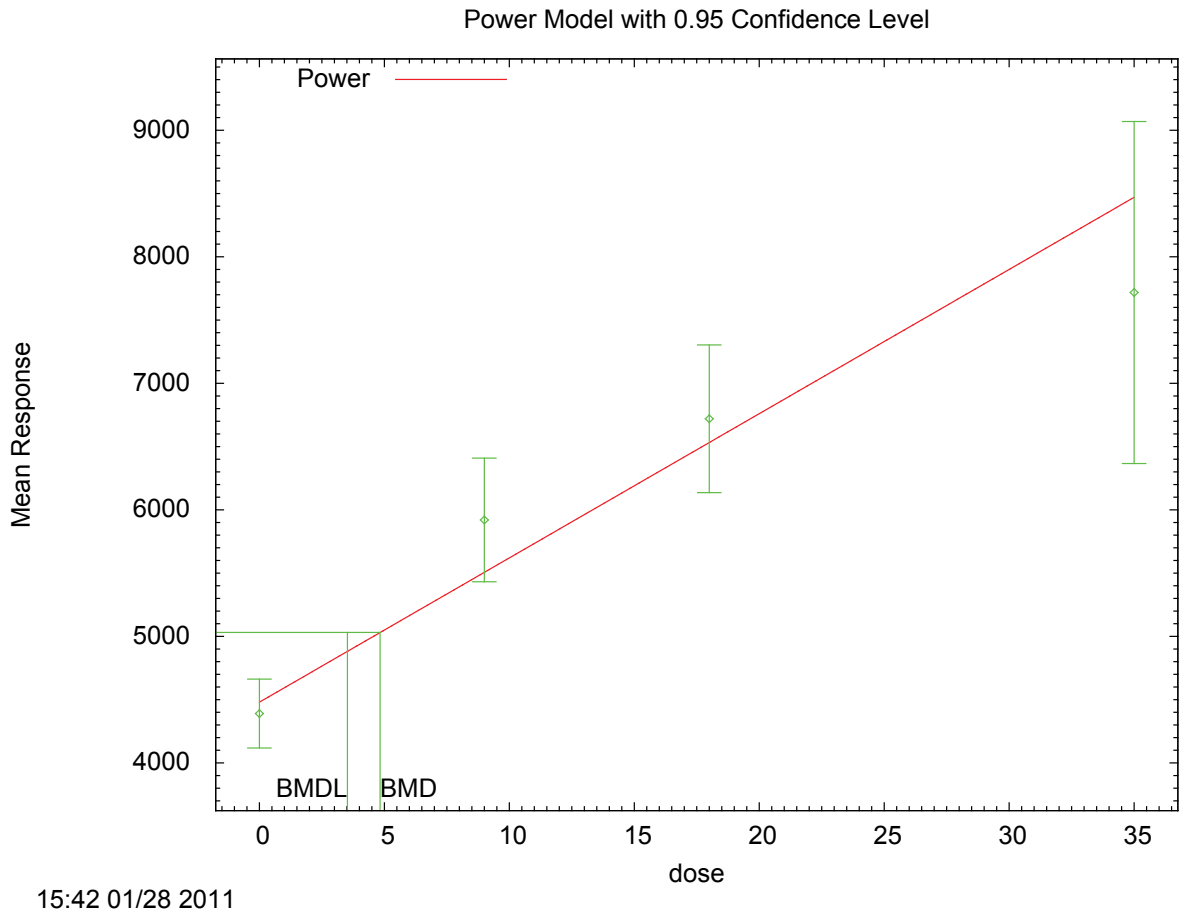

Figure C-4. Power BMD Model for Absolute Kidney Weight Data (NTP, 1996)

Text Output for Power BMD Model for Absolute Kidney Weight Data (NTP, 1996)

```
 ======================================================================
          Power Model. (Version: 2.16;  Date: 10/28/2009)
          Input Data File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Abs_Kidney_Wt_Power_1.(d)
          Gnuplot Plotting File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Abs_Kidney_Wt_Power_1.plt
                                                  Fri Jan 28 15:42:45 2011
 ======================================================================

 F0_M_Abs_Kidney_Wt
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   The power is restricted to be greater than or equal to 1
```

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	13.7306
rho =	0
control =	4390.1
slope =	435
power =	0.572274

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -power
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	control	slope
lalpha	1	-1	-0.062	0.039
rho	-1	1	0.056	-0.045
control	-0.062	0.056	1	-0.51
slope	0.039	-0.045	-0.51	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-15.7807	6.86996	-29.2456	-2.3158
rho	3.37767	0.794332	1.82081	4.93453
control	4481.6	119.67	4247.05	4716.15
slope	113.816	12.9506	88.433	139.198
power	1	NA		

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.

0	20	4.39e+003	4.48e+003	581	549	-0.745
9	10	5.92e+003	5.51e+003	683	778	1.68
18	10	6.72e+003	6.53e+003	816	1.04e+003	0.577
35	9	7.72e+003	8.47e+003	1.76e+003	1.61e+003	-1.39

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-358.813074	5	727.626149
A2	-349.267070	8	714.534141
A3	-351.141284	6	714.282567
fitted	-353.138785	4	714.277570
R	-385.485941	2	774.971882

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	72.4377	6	<.0001
Test 2	19.092	3	0.0002617
Test 3	3.74843	2	0.1535
Test 4	3.995	2	0.1357

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems

to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 4.82763

BMDL = 3.52106

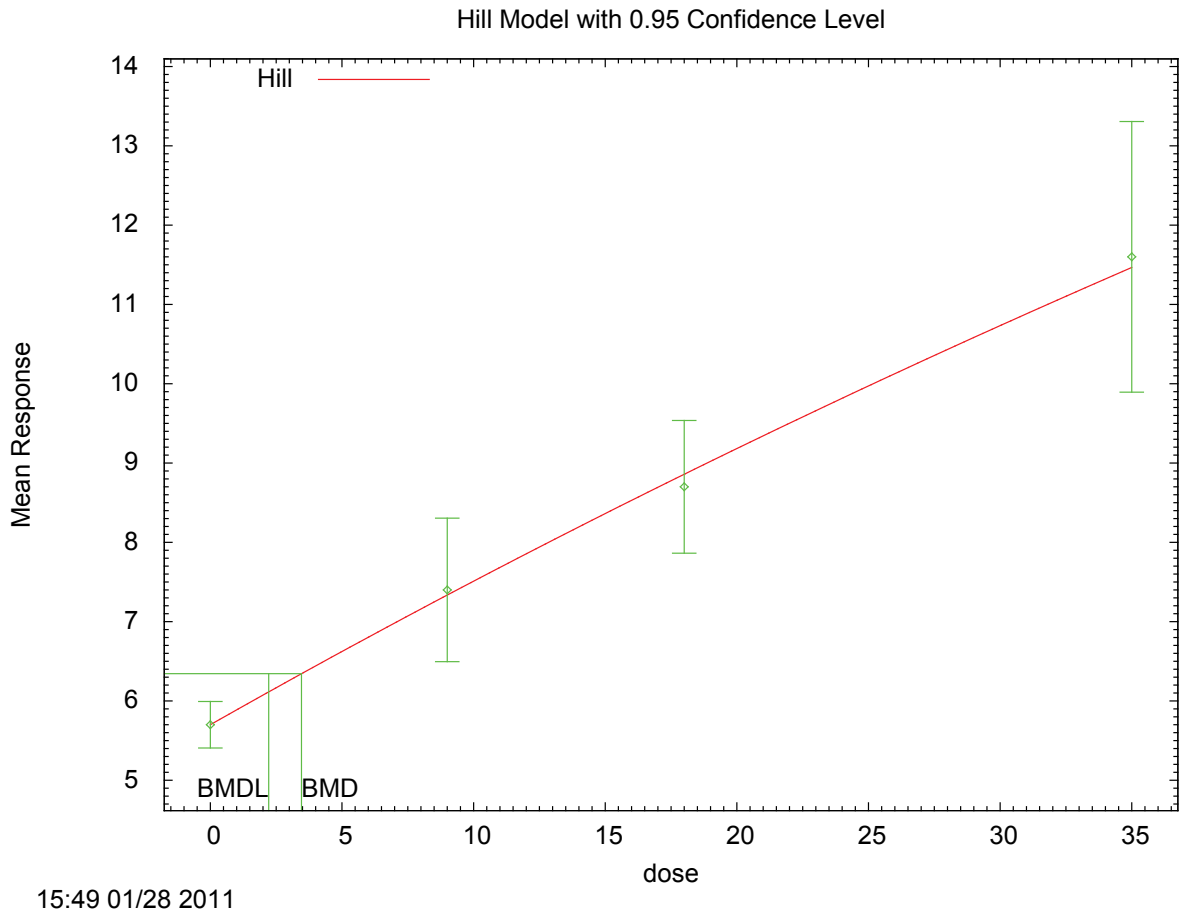

Figure C-5. Hill BMD Model for Relative Kidney Weight Data (NTP, 1996)

Text Output for Hill BMD Model for Relative Kidney Weight Data (NTP, 1996)

```
 ================================================================================
          Hill Model. (Version: 2.15;  Date: 10/28/2009)
          Input Data File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Rel_Kidney_Wt_Hill_1.(d)
          Gnuplot Plotting File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Rel_Kidney_Wt_Hill_1.plt
                                                    Fri Jan 28 15:49:30 2011
 ================================================================================

 F0_M_Rel_Kidney_Wt
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
```

The variance is to be modeled as Var(i) = exp(lalpha + rho * ln(mean(i)))

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	0.491931
rho =	0
intercept =	5.7
v =	5.9
n =	0.634978
k =	18.3462

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	intercept	v	k
lalpha	1	-0.99	-0.16	0.24	0.22
rho	-0.99	1	0.14	-0.24	-0.23
intercept	-0.16	0.14	1	0.22	0.24
v	0.24	-0.24	0.22	1	1
k	0.22	-0.23	0.24	1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-6.71853	1.72728	-10.1039	-3.33313
rho	3.35383	0.856645	1.67483	5.03282
intercept	5.70044	0.142801	5.42055	5.98033
v	45.8435	95.3867	-141.111	232.798
n	1	NA		
k	243.146	557.504	-849.542	1335.83

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	20	5.7	5.7	0.626	0.644	-0.00306
9	10	7.4	7.34	1.26	0.983	0.203
18	10	8.7	8.86	1.17	1.35	-0.376
35	9	11.6	11.5	2.22	2.08	0.189

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.465942	5	78.931884
A2	-24.136490	8	64.272980
A3	-24.749829	6	61.499659
fitted	-25.092897	5	60.185795
R	-68.998702	2	141.997404

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	89.7244	6	<.0001
Test 2	20.6589	3	0.0001239
Test 3	1.22668	2	0.5415
Test 4	0.686136	1	0.4075

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

```
The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =       3.46268

            BMDL =       2.21795
```

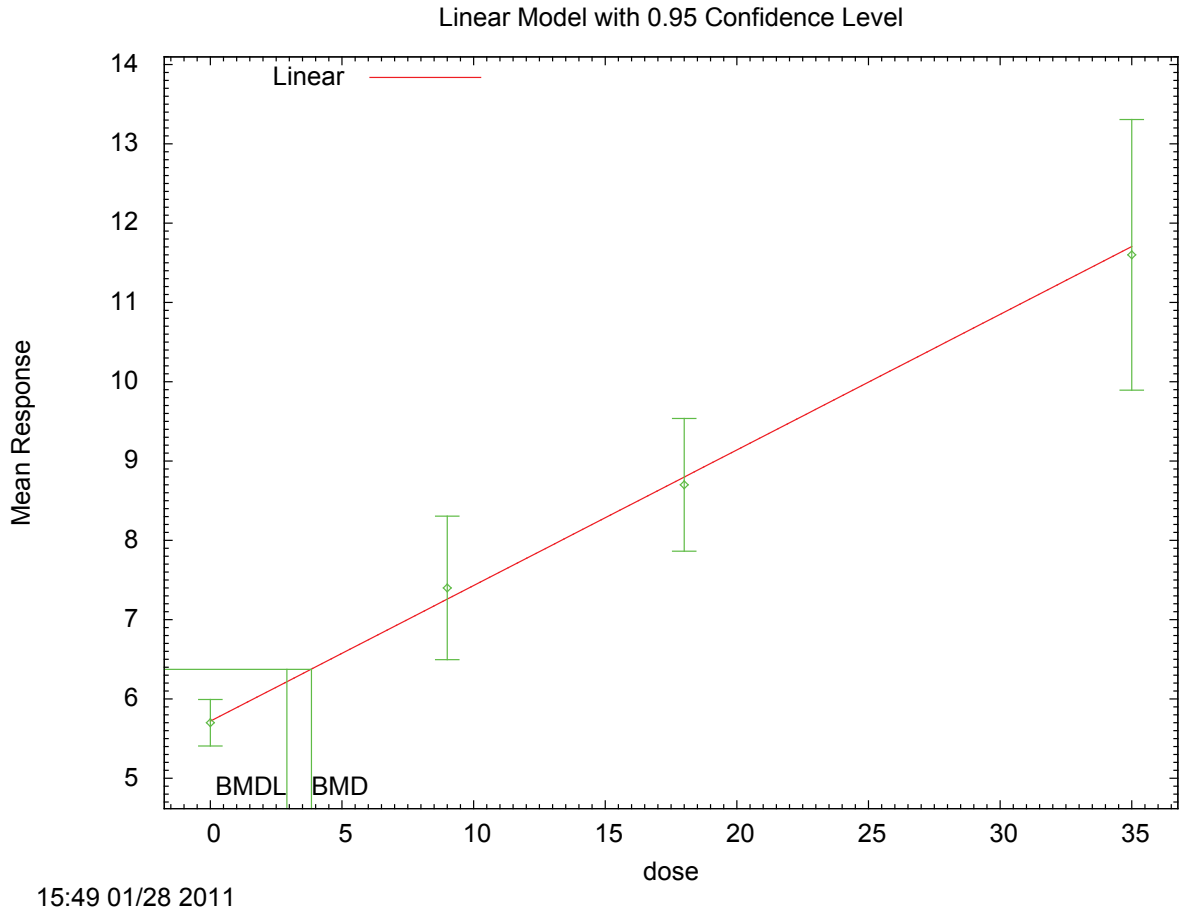

Figure C-6. Linear BMD Model for Relative Kidney Weight Data (NTP, 1996)

Text Output for Linear BMD Model for Relative Kidney Weight Data (NTP, 1996)

```
 ======================================================================
          Polynomial Model. (Version: 2.16;  Date: 05/26/2010)
          Input Data File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Rel_Kidney_Wt_Linear_1.(d)
          Gnuplot Plotting File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Rel_Kidney_Wt_Linear_1.plt
                                                Fri Jan 28 15:49:31 2011
 ======================================================================

 F0_M_Rel_Kidney_Wt
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
```

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	0.491931
rho =	0
beta_0 =	5.76667
beta_1 =	0.166667

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	0.011	-0.031
rho	-0.99	1	-0.012	0.032
beta_0	0.011	-0.012	1	-0.46
beta_1	-0.031	0.032	-0.46	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-6.55592	1.59871	-9.68933	-3.4225
rho	3.27401	0.788556	1.72847	4.81955
beta_0	5.71843	0.139691	5.44464	5.99222
beta_1	0.170536	0.0156231	0.139915	0.201156

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	20	5.7	5.72	0.626	0.655	-0.126
9	10	7.4	7.25	1.26	0.966	0.48
18	10	8.7	8.79	1.17	1.32	-0.211
35	9	11.6	11.7	2.22	2.11	-0.124

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)

```
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                     Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1          -34.465942            5      78.931884
              A2          -24.136490            8      64.272980
              A3          -24.749829            6      61.499659
          fitted          -25.204867            4      58.409735
               R          -68.998702            2     141.997404


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              89.7244          6          <.0001
   Test 2              20.6589          3       0.0001239
   Test 3              1.22668          2          0.5415
   Test 4             0.910076          2          0.6344

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


              Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95
```

BMD = 3.8393

BMDL = 2.90725

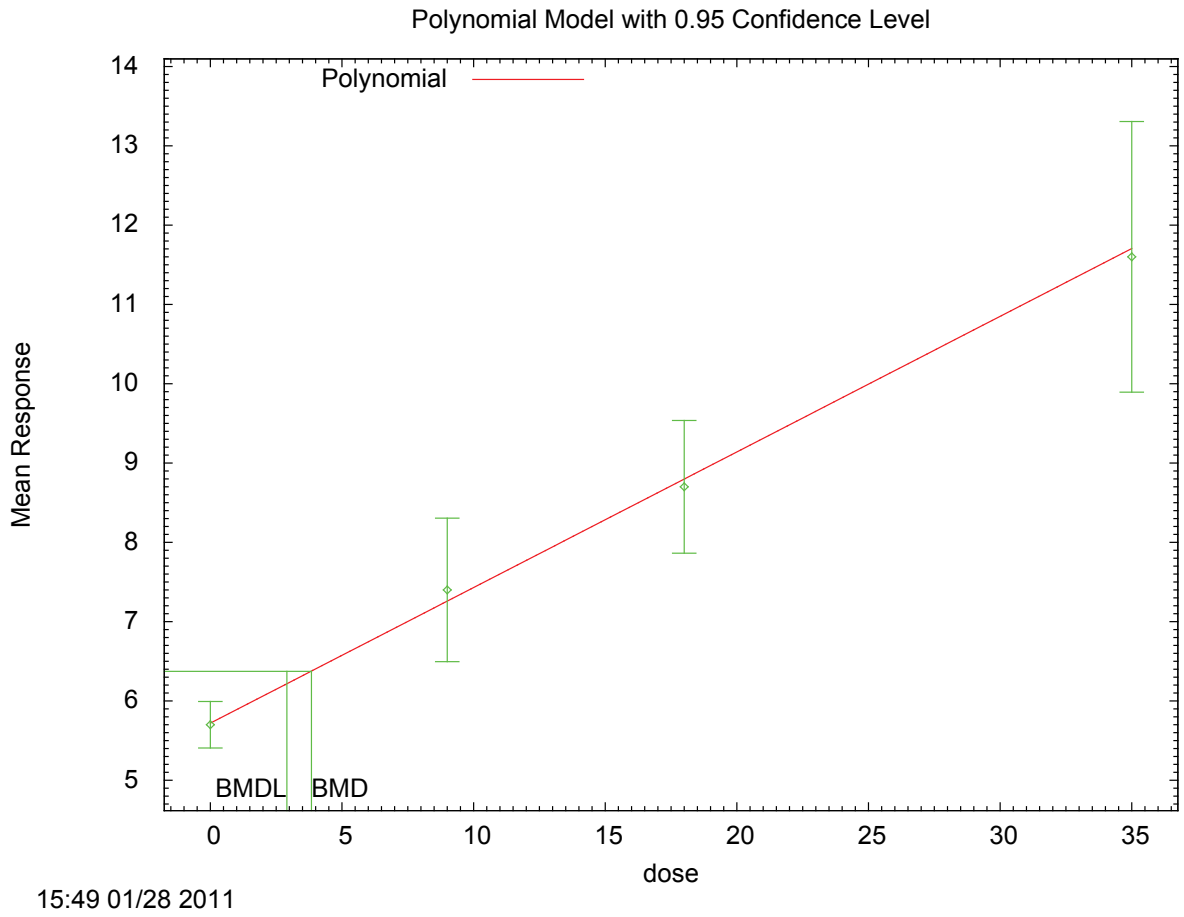

Figure C-7. Poly3 BMD Model for Relative Kidney Weight Data (NTP, 1996)

Text Output for Poly3 BMD Model for Relative Kidney Weight Data (NTP, 1996)

```
 ======================================================================
          Polynomial Model. (Version: 2.16;  Date: 05/26/2010)
          Input Data File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Rel_Kidney_Wt_Poly3_1.(d)
          Gnuplot Plotting File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Rel_Kidney_Wt_Poly3_1.plt
                                                Fri Jan 28 15:49:31 2011
 ======================================================================

 F0_M_Rel_Kidney_Wt
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   The polynomial coefficients are restricted to be positive
```

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	0.491931
rho =	0
beta_0 =	5.7
beta_1 =	0.227194
beta_2 =	0
beta_3 =	9.92762e-005

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -beta_2 -beta_3
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	0.011	-0.031
rho	-0.99	1	-0.012	0.032
beta_0	0.011	-0.012	1	-0.46
beta_1	-0.031	0.032	-0.46	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-6.55592	1.59871	-9.68933	-3.4225
rho	3.27401	0.788556	1.72847	4.81955
beta_0	5.71843	0.139691	5.44464	5.99222
beta_1	0.170536	0.0156231	0.139915	0.201156
beta_2	0	NA		
beta_3	0	NA		

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.

0	20	5.7	5.72	0.626	0.655	-0.126
9	10	7.4	7.25	1.26	0.966	0.48
18	10	8.7	8.79	1.17	1.32	-0.211
35	9	11.6	11.7	2.22	2.11	-0.124

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.465942	5	78.931884
A2	-24.136490	8	64.272980
A3	-24.749829	6	61.499659
fitted	-25.204867	4	58.409735
R	-68.998702	2	141.997404

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	89.7244	6	<.0001
Test 2	20.6589	3	0.0001239
Test 3	1.22668	2	0.5415
Test 4	0.910076	2	0.6344

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
to be appropriate here

```
The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


             Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

              BMD =         3.8393


             BMDL =        2.90725
```

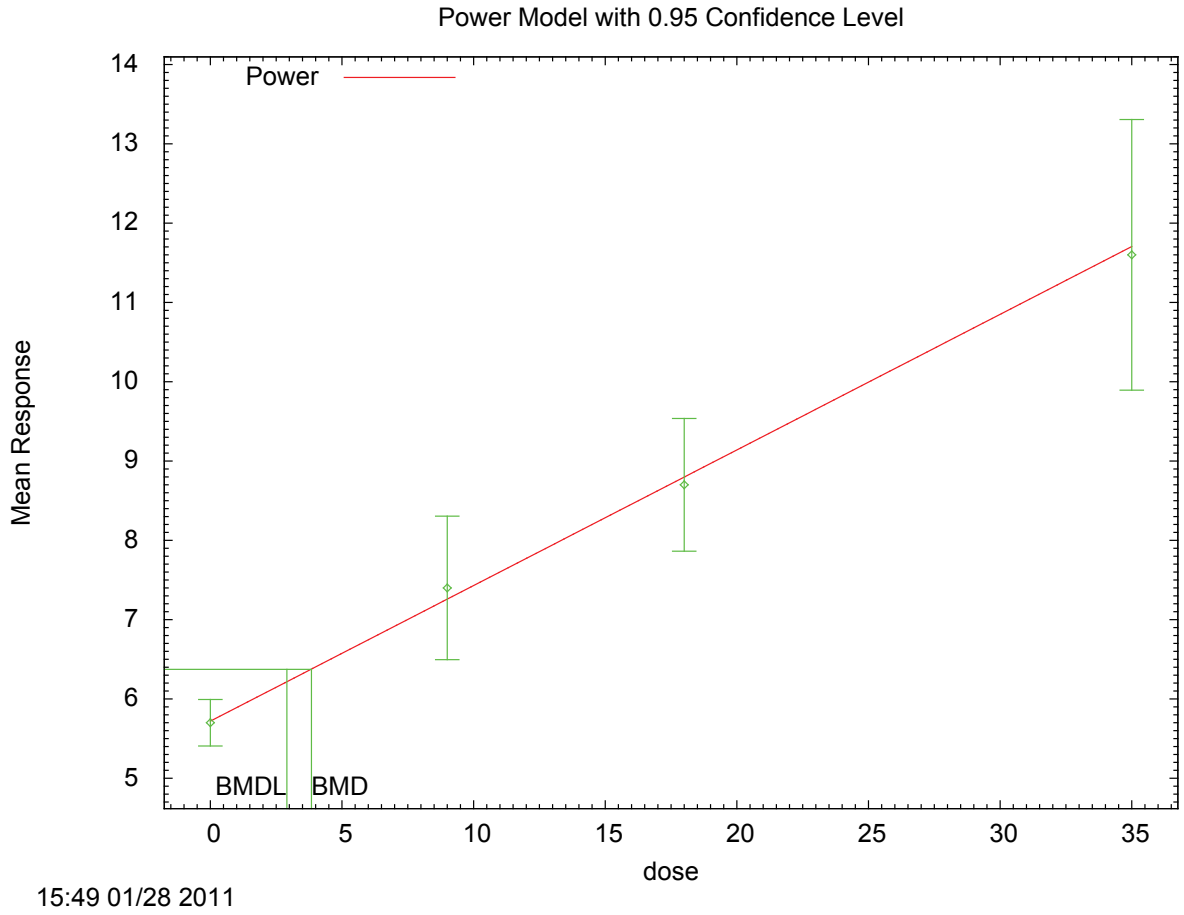

Figure C-8. Power BMD Model for Relative Kidney Weight Data (NTP, 1996)

Text Output for Power BMD Model for Relative Kidney Weight Data (NTP, 1996)

```
 ================================================================
          Power Model. (Version: 2.16;  Date: 10/28/2009)
          Input Data File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Rel_Kidney_Wt_Power_1.(d)
          Gnuplot Plotting File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Rel_Kidney_Wt_Power_1.plt
                                                Fri Jan 28 15:49:31 2011
 ================================================================

 F0_M_Rel_Kidney_Wt
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   The power is restricted to be greater than or equal to 1
```

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	0.491931
rho =	0
control =	5.7
slope =	0.227624
power =	0.915525

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -power
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	control	slope
lalpha	1	-0.99	-0.18	0.22
rho	-0.99	1	0.16	-0.24
control	-0.18	0.16	1	-0.47
slope	0.22	-0.24	-0.47	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-6.55592	1.64504	-9.78013	-3.3317
rho	3.27401	0.81337	1.67983	4.86818
control	5.71843	0.140126	5.44379	5.99308
slope	0.170536	0.0156782	0.139807	0.201264
power	1	NA		

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.

0	20	5.7	5.72	0.626	0.655	-0.126
9	10	7.4	7.25	1.26	0.966	0.48
18	10	8.7	8.79	1.17	1.32	-0.211
35	9	11.6	11.7	2.22	2.11	-0.124

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.465942	5	78.931884
A2	-24.136490	8	64.272980
A3	-24.749829	6	61.499659
fitted	-25.204867	4	58.409735
R	-68.998702	2	141.997404

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	89.7244	6	<.0001
Test 2	20.6589	3	0.0001239
Test 3	1.22668	2	0.5415
Test 4	0.910076	2	0.6344

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems

to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 3.8393

BMDL = 2.90725

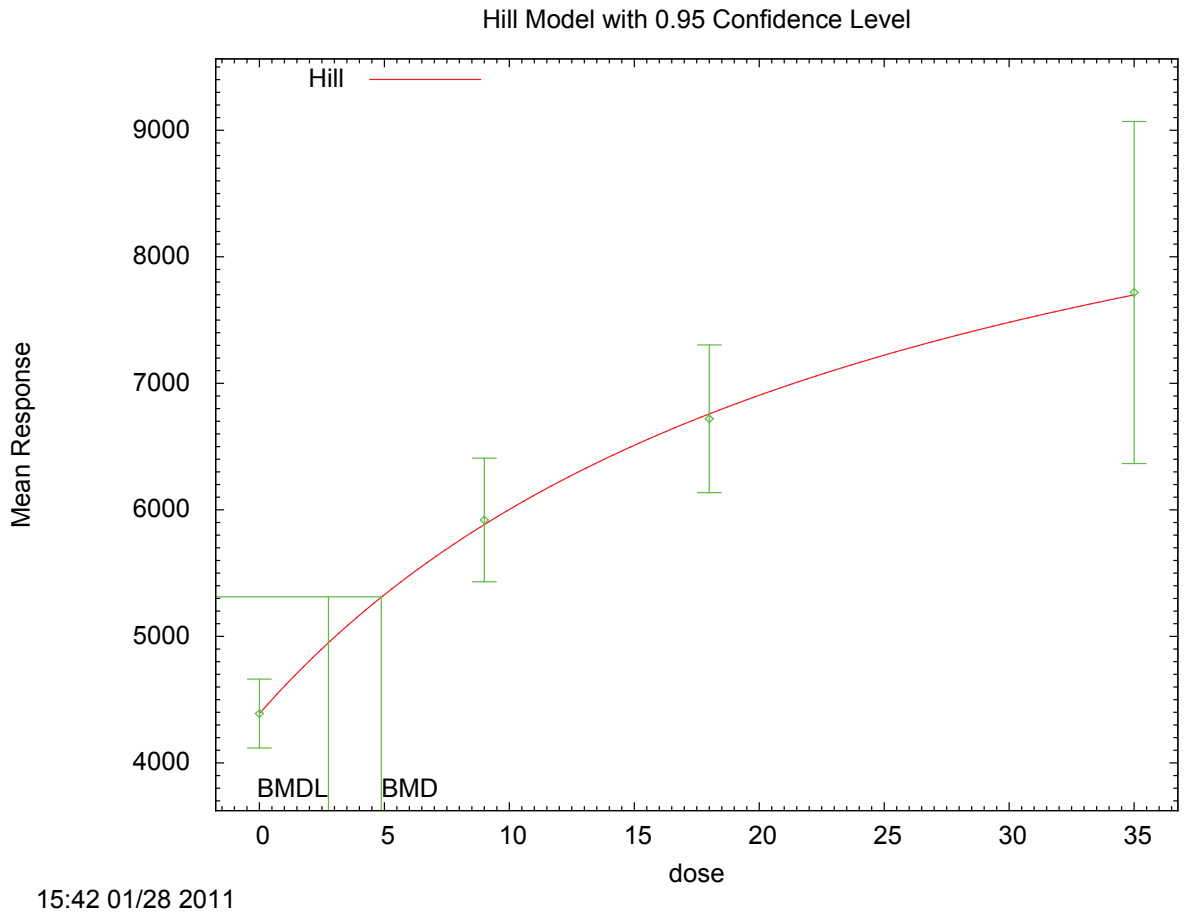

Figure C-9. Hill_CV BMD Model for Absolute Kidney Weight Data (NTP, 1996)

Text Output for Hill_CV BMD Model for Absolute Kidney Weight Data (NTP, 1996)

```
 ================================================================
          Hill Model. (Version: 2.15;  Date: 10/28/2009)
          Input Data File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Abs_Kidney_Wt_HillCV_1.(d)
          Gnuplot Plotting File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Abs_Kidney_Wt_HillCV_1.plt
                                                Fri Jan 28 15:42:45 2011
 ================================================================

 F0_M_Abs_Kidney_Wt
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
```

```
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =       918585
                            rho =            0   Specified
                      intercept =       4390.1
                              v =       3327.5
                              n =    0.0773128
                              k =      25.4955


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho    -n
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                    alpha    intercept            v            k

     alpha              1     6.3e-008    -1.2e-007    -7.3e-008

 intercept     6.3e-008            1        0.097         0.33

         v    -1.2e-007        0.097            1         0.95

         k    -7.3e-008         0.33         0.95            1


                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
          alpha           844225           170559              509935
1.17852e+006
      intercept          4393.52           204.94             3991.85
4795.2
              v          5713.26          1860.57              2066.6
9359.91
              n                1               NA
              k          25.4422           16.633            -7.15783
58.0422

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
```

0	20	4.39e+003	4.39e+003	581	919	-0.0167
9	10	5.92e+003	5.89e+003	683	919	0.116
18	10	6.72e+003	6.76e+003	816	919	-0.141
35	9	7.72e+003	7.7e+003	1.76e+003	919	0.0514

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-358.813074	5	727.626149
A2	-349.267070	8	714.534141
A3	-358.813074	5	727.626149
fitted	-358.831281	4	725.662562
R	-385.485941	2	774.971882

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	72.4377	6	<.0001
Test 2	19.092	3	0.0002617
Test 3	19.092	3	0.0002617
Test 4	0.0364132	1	0.8487

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. Consider running a non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider a different variance model

```
The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        4.8758

            BMDL =        2.7624
```

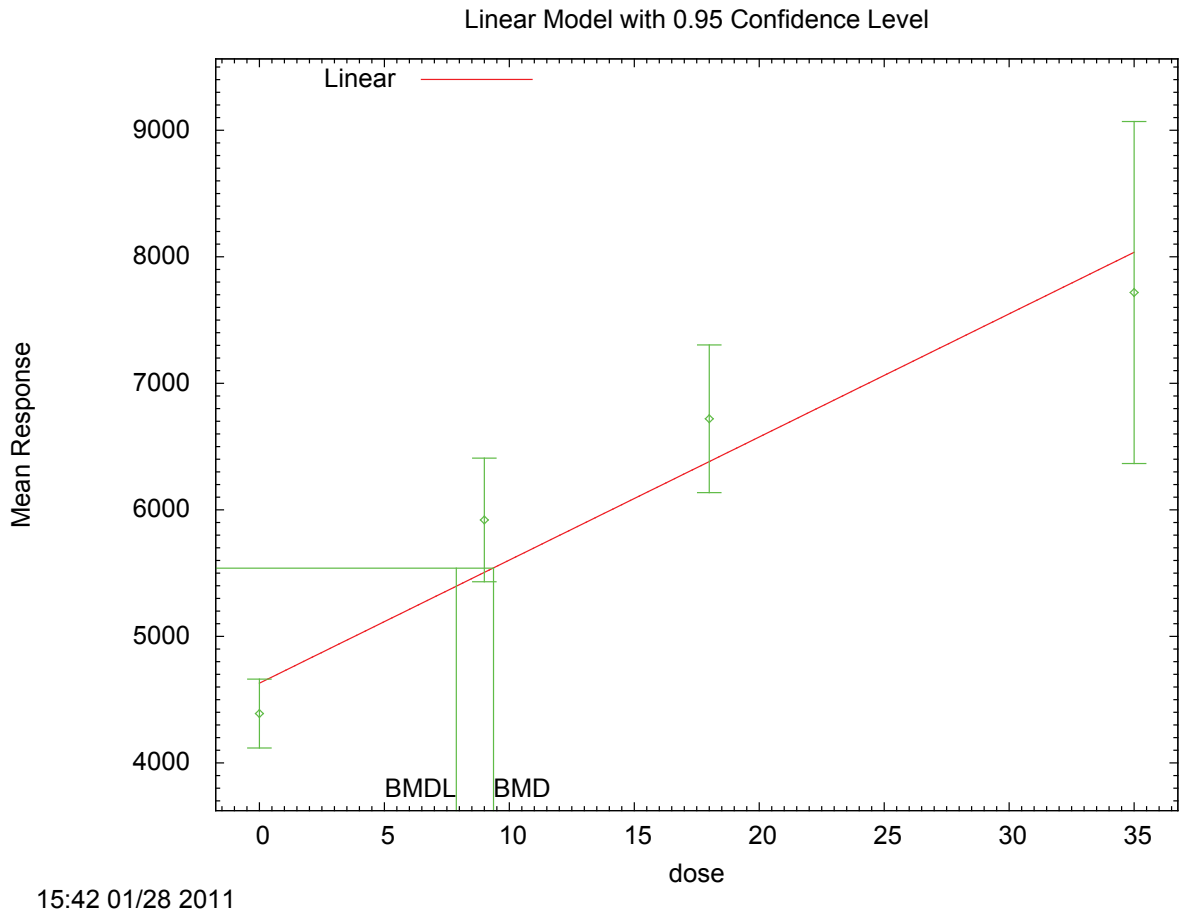

Figure C-10. Linear_CV BMD Model for Absolute Kidney Weight Data (NTP, 1996)

Text Output for Linear_CV BMD Model for Absolute Kidney Weight Data (NTP, 1996)

```
 ================================================================
          Polynomial Model. (Version: 2.16;  Date: 05/26/2010)
          Input Data File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Abs_Kidney_Wt_LinearCV_1.(d)
          Gnuplot Plotting File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Abs_Kidney_Wt_LinearCV_1.plt
                                                Fri Jan 28 15:42:46 2011
 ================================================================

 F0_M_Abs_Kidney_Wt
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
```

```
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =            1
                            rho =            0   Specified
                         beta_0 =      4779.05
                         beta_1 =       90.829


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                   alpha       beta_0       beta_1

     alpha             1     8.6e-007    -2.5e-006

    beta_0     8.6e-007            1        -0.68

    beta_1    -2.5e-006        -0.68            1


                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
          alpha           829883           148474              538880
1.12089e+006
         beta_0          4627.88          177.641             4279.71
4976.05
         beta_1          97.2536          10.1277             77.4036
117.104


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    20  4.39e+003    4.63e+003          581          911          -1.17
    9    10  5.92e+003     5.5e+003          683          911           1.45
   18    10  6.72e+003    6.38e+003          816          911           1.18
   35     9  7.72e+003    8.03e+003    1.76e+003          911          -1.03


 Model Descriptions for likelihoods calculated
```

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                     Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1         -358.813074            5     727.626149
            A2         -349.267070            8     714.534141
            A3         -358.813074            5     727.626149
        fitted         -361.782335            3     729.564669
             R         -385.485941            2     774.971882


                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              72.4377          6          <.0001
   Test 2               19.092          3        0.0002617
   Test 3               19.092          3        0.0002617
   Test 4              5.93852          2          0.05134

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  Consider running a
non-homogeneous variance model

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is less than .1.  You may want to try a different
model


              Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean
```

```
Confidence level =          0.95

             BMD =       9.36705

            BMDL =         7.879
```

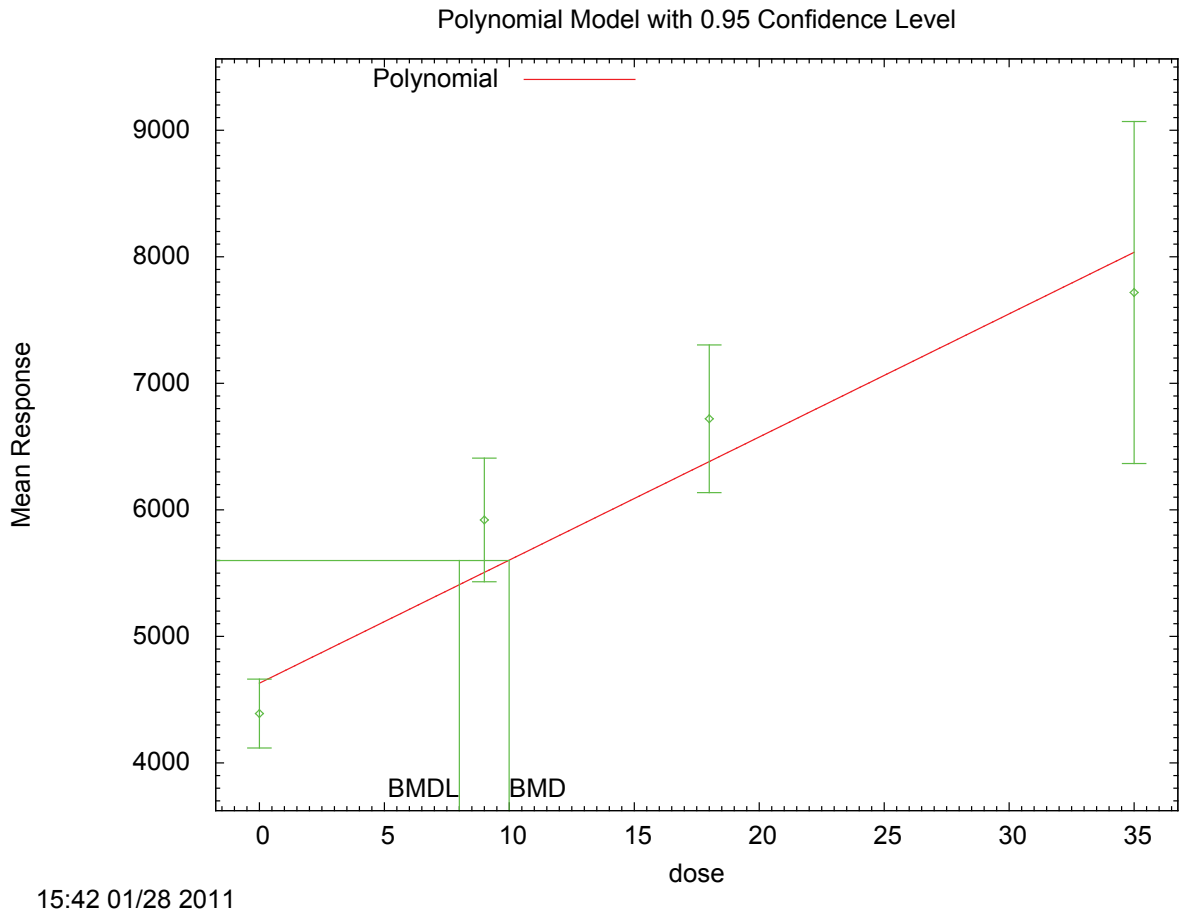

Figure C-11. Poly3_CV BMD Model for Absolute Kidney Weight Data (NTP, 1996)

Text Output for Poly3_CV BMD Model for Absolute Kidney Weight Data (NTP, 1996)

```
 ======================================================================
          Polynomial Model. (Version: 2.16;  Date: 05/26/2010)
          Input Data File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Abs_Kidney_Wt_PolyCV3_1.(d)
          Gnuplot Plotting File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Abs_Kidney_Wt_PolyCV3_1.plt
                                                  Fri Jan 28 15:42:46 2011
 ======================================================================

 F0_M_Abs_Kidney_Wt
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
```

```
   The polynomial coefficients are restricted to be positive
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =            1
                            rho =            0   Specified
                         beta_0 =       4390.1
                         beta_1 =       226.11
                         beta_2 =            0
                         beta_3 =    0.0957401


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho    -beta_2    -beta_3
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                    alpha       beta_0       beta_1

     alpha              1     5.1e-005     1.5e-005

    beta_0     5.1e-005            1        -0.68

    beta_1     1.5e-005        -0.68            1


                                  Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
          alpha           944168           190772              570262
1.31807e+006
         beta_0          4627.92          189.478             4256.55
4999.29
         beta_1          97.2545          10.8026             76.0818
118.427
         beta_2                0               NA
         beta_3                0               NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     20  4.39e+003    4.63e+003          581          972          -1.09
```

9	10	5.92e+003	5.5e+003	683	972	1.36
18	10	6.72e+003	6.38e+003	816	972	1.11
35	9	7.72e+003	8.03e+003	1.76e+003	972	-0.97

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-358.813074	5	727.626149
A2	-349.267070	8	714.534141
A3	-358.813074	5	727.626149
fitted	-361.569737	3	729.139475
R	-385.485941	2	774.971882

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	72.4377	6	<.0001
Test 2	19.092	3	0.0002617
Test 3	19.092	3	0.0002617
Test 4	5.51333	2	0.0635

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. Consider running a non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider a different variance model

The p-value for Test 4 is less than .1. You may want to try a different model

```
             Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        9.99114


            BMDL =        7.99895
```

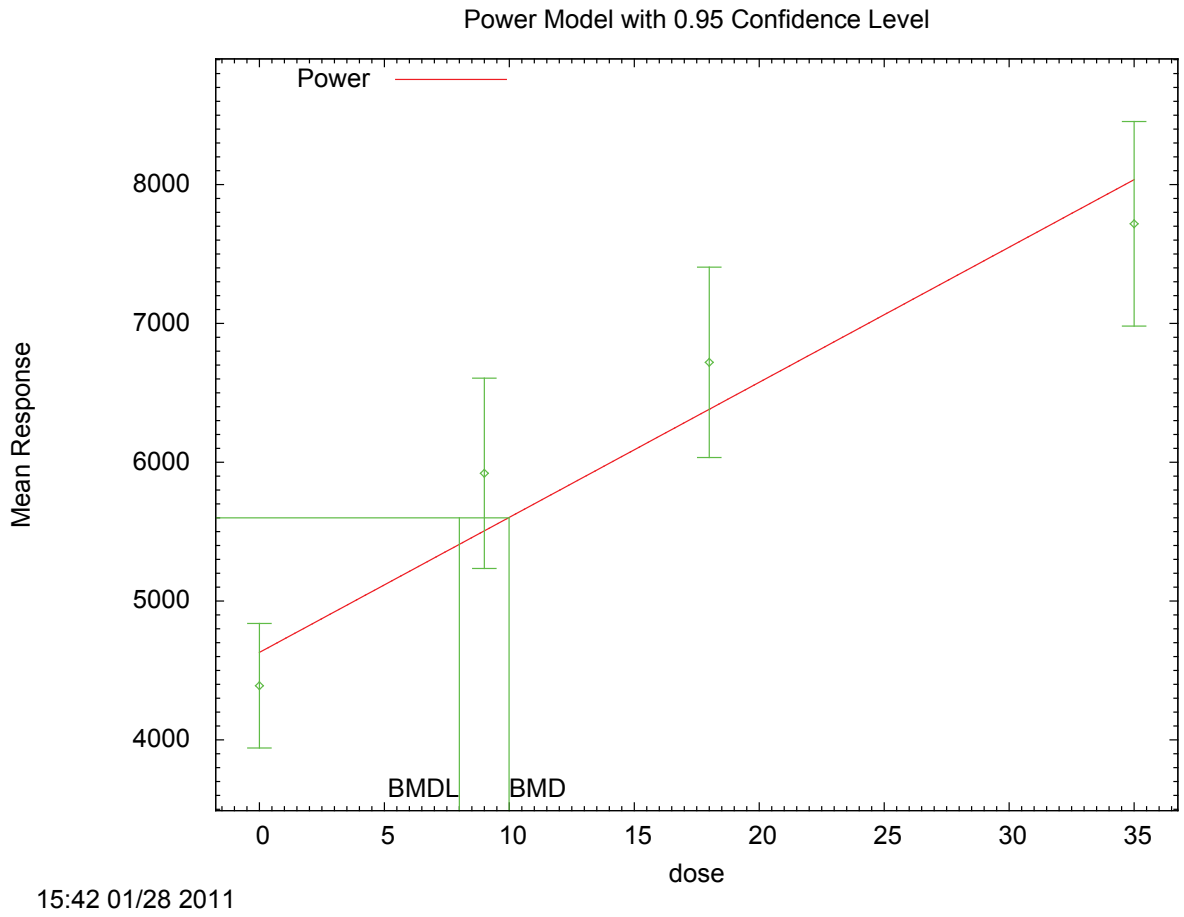

Figure C-12. Power_CV BMD Model for Absolute Kidney Weight Data (NTP, 1996)

Text Output for Power_CV BMD Model for Absolute Kidney Weight Data (NTP, 1996)

```
 ======================================================================
          Power Model. (Version: 2.16;  Date: 10/28/2009)
          Input Data File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Abs_Kidney_Wt_PowerCV_1.(d)
          Gnuplot Plotting File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Abs_Kidney_Wt_PowerCV_1.plt
                                                  Fri Jan 28 15:42:46 2011
 ======================================================================

 F0_M_Abs_Kidney_Wt
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
```

```
   The power is restricted to be greater than or equal to 1
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =       918585
                            rho =            0   Specified
                        control =       4390.1
                          slope =          435
                          power =     0.572274


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho    -power
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                    alpha      control        slope

     alpha              1     2.7e-009    -9.7e-010

   control     2.7e-009            1        -0.68

     slope    -9.7e-010        -0.68            1


                                 Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
          alpha           944063           190730              570240
1.31789e+006
        control          4627.88          189.468             4256.53
4999.23
          slope          97.2537           10.802             76.0822
118.425
          power                1               NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     20  4.39e+003    4.63e+003          581          972          -1.09
    9     10  5.92e+003     5.5e+003          683          972           1.36
   18     10  6.72e+003    6.38e+003          816          972           1.11
```

```
  35     9  7.72e+003    8.03e+003    1.76e+003          972          -0.97


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1         -358.813074            5     727.626149
              A2         -349.267070            8     714.534141
              A3         -358.813074            5     727.626149
          fitted         -361.569737            3     729.139474
               R         -385.485941            2     774.971882


                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              72.4377          6          <.0001
   Test 2               19.092          3        0.0002617
   Test 3               19.092          3        0.0002617
   Test 4              5.51333          2           0.0635

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  Consider running a
non-homogeneous variance model

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is less than .1.  You may want to try a different
model
```

```
              Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 9.99066


            BMDL = 7.99895
```

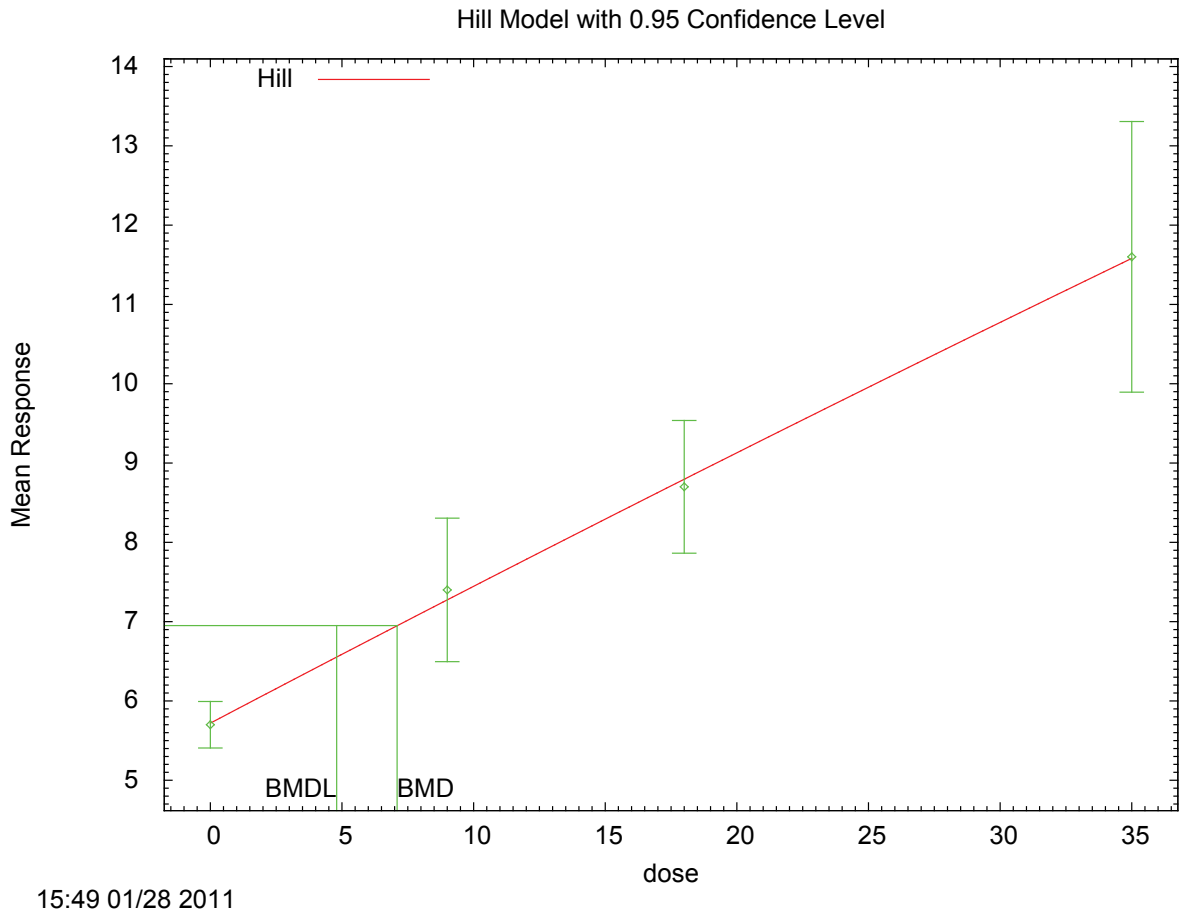

Figure C-13. Hill_CV BMD Model for Relative Kidney Weight Data (NTP, 1996)

Text Output for Hill_CV BMD Model for Relative Kidney Weight Data (NTP, 1996)

```
 ========================================================================
          Hill Model. (Version: 2.15;  Date: 10/28/2009)
          Input Data File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Rel_Kidney_Wt_HillCV_1.(d)
          Gnuplot Plotting File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Rel_Kidney_Wt_HillCV_1.plt
                                                  Fri Jan 28 15:49:32 2011
 ========================================================================

 F0_M_Rel_Kidney_Wt
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
```

Power parameter restricted to be greater than 1
A constant variance model is fit

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha =	1.63547	
rho =	0	Specified
intercept =	5.7	
v =	5.9	
n =	0.634978	
k =	18.3462	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	k
alpha	1	3.4e-006	6.8e-006	6.9e-006
intercept	3.4e-006	1	0.45	0.46
v	6.8e-006	0.45	1	1
k	6.9e-006	0.46	1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	1.50727	0.304514	0.91043	2.1041
intercept	5.72246	0.270183	5.19292	6.25201
v	141.882	921.029	-1663.3	1947.07
n	1	NA		
k	812.759	5492.34	-9952.03	11577.5

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.

0	20	5.7	5.72	0.626	1.23	-0.0818
9	10	7.4	7.28	1.26	1.23	0.318
18	10	8.7	8.8	1.17	1.23	-0.249
35	9	11.6	11.6	2.22	1.23	0.0486

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.465942	5	78.931884
A2	-24.136490	8	64.272980
A3	-34.465942	5	78.931884
fitted	-34.552287	4	77.104573
R	-68.998702	2	141.997404

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	89.7244	6	<.0001
Test 2	20.6589	3	0.0001239
Test 3	20.6589	3	0.0001239
Test 4	0.172689	1	0.6777

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. Consider running a
non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider a
different variance model

```
The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        7.09421

            BMDL =       4.79931
```

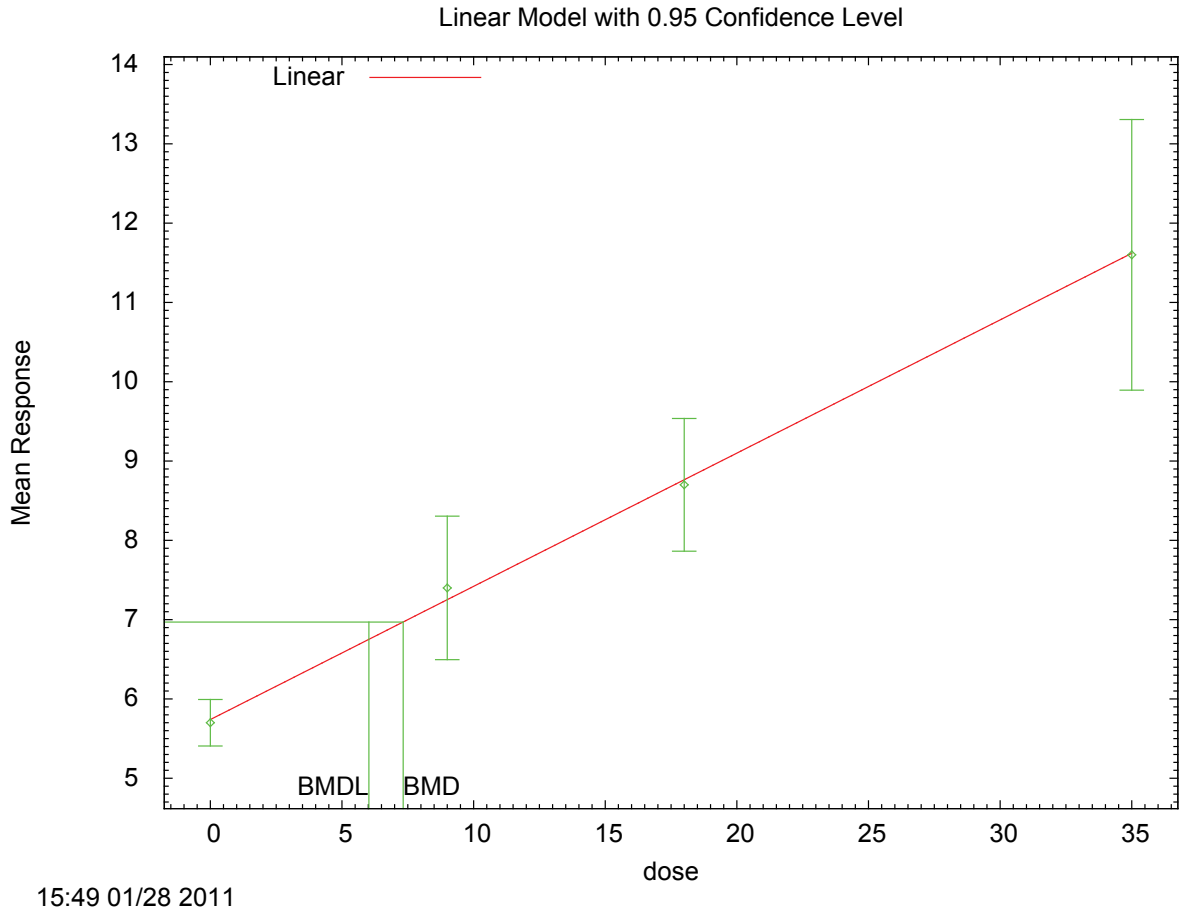

Figure C-14. Linear_CV BMD Model for Relative Kidney Weight Data (NTP, 1996)

Text Output for Linear_CV BMD Model for Relative Kidney Weight Data (NTP, 1996)

```
 ======================================================================
          Polynomial Model. (Version: 2.16;  Date: 05/26/2010)
          Input Data File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Rel_Kidney_Wt_LinearCV_1.(d)
          Gnuplot Plotting File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Rel_Kidney_Wt_LinearCV_1.plt
                                                Fri Jan 28 15:49:32 2011
 ======================================================================

 F0_M_Rel_Kidney_Wt
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
```

```
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =      1.63547
                            rho =            0   Specified
                         beta_0 =      5.76667
                         beta_1 =     0.166667


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                    alpha       beta_0       beta_1

     alpha              1    -1.8e-008    -9.9e-009

    beta_0    -1.8e-008            1        -0.68

    beta_1    -9.9e-009        -0.68            1


                                 Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
          alpha          1.50797         0.304655            0.910854
2.10508
         beta_0          5.74132         0.239459             5.27199
6.21065
         beta_1          0.16765        0.0136521            0.140893
0.194408


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    20        5.7         5.74        0.626         1.23          -0.15
    9    10        7.4         7.25         1.26         1.23          0.386
   18    10        8.7         8.76         1.17         1.23         -0.152
   35     9       11.6         11.6         2.22         1.23        -0.0222


 Model Descriptions for likelihoods calculated
```

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                     Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1          -34.465942            5      78.931884
            A2          -24.136490            8      64.272980
            A3          -34.465942            5      78.931884
        fitted          -34.563689            3      75.127378
             R          -68.998702            2     141.997404


                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              89.7244          6          <.0001
   Test 2              20.6589          3        0.0001239
   Test 3              20.6589          3        0.0001239
   Test 4             0.195494          2           0.9069

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  Consider running a
non-homogeneous variance model

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


              Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean
```

```
Confidence level =          0.95

             BMD =       7.32473

            BMDL =       6.02296
```

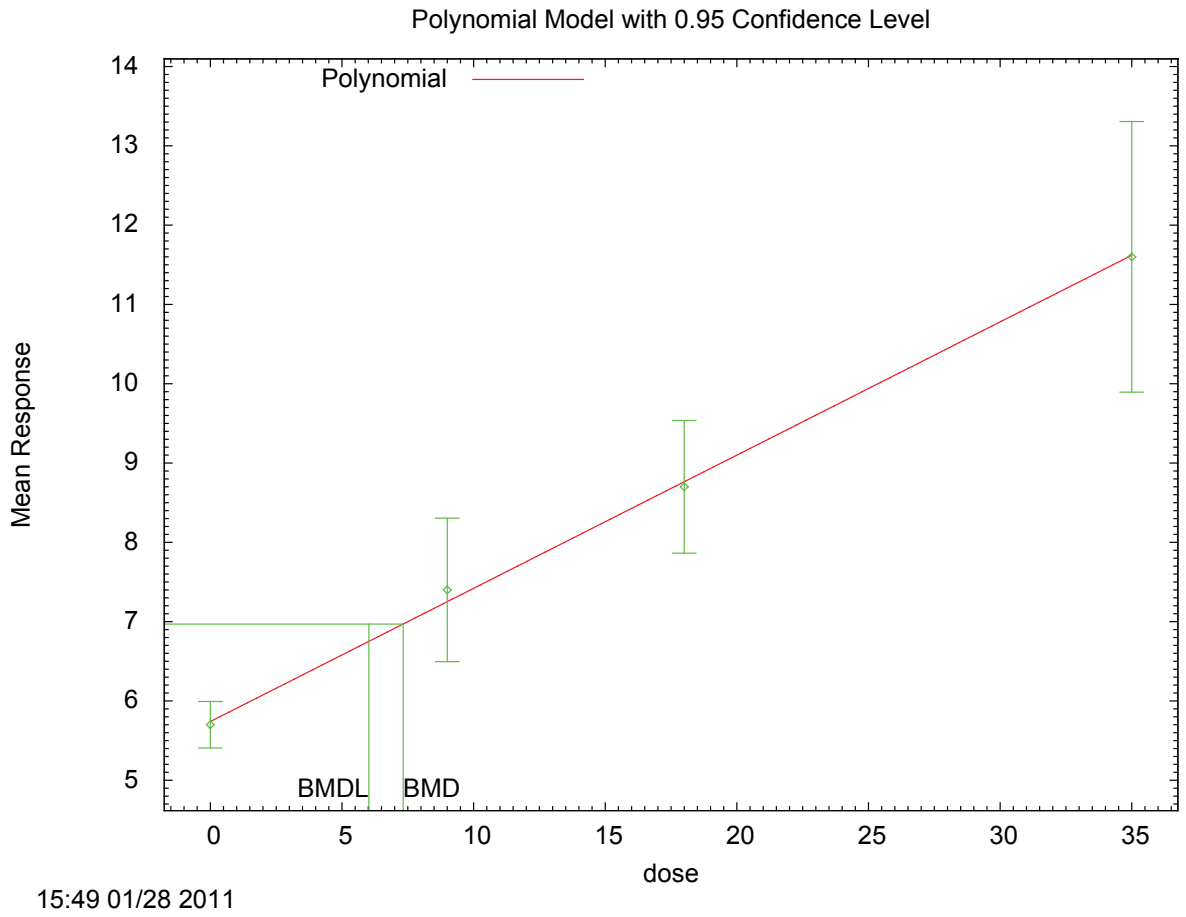

Figure C-15. Poly3_CV BMD Model for Relative Kidney Weight Data (NTP, 1996)

Text Output for Poly3_CV BMD Model for Relative Kidney Weight Data (NTP, 1996)

```
 ======================================================================
          Polynomial Model. (Version: 2.16;  Date: 05/26/2010)
          Input Data File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Rel_Kidney_Wt_PolyCV3_1.(d)
          Gnuplot Plotting File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Rel_Kidney_Wt_PolyCV3_1.plt
                                                Fri Jan 28 15:49:32 2011
 ======================================================================

 F0_M_Rel_Kidney_Wt
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
```

```
   The polynomial coefficients are restricted to be positive
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =      1.63547
                            rho =            0   Specified
                         beta_0 =          5.7
                         beta_1 =     0.227194
                         beta_2 =            0
                         beta_3 = 9.92762e-005


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho    -beta_2    -beta_3
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                    alpha       beta_0       beta_1

     alpha              1      -4e-009    -3.2e-009

    beta_0      -4e-009            1        -0.68

    beta_1    -3.2e-009        -0.68            1


                                 Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
          alpha          1.50797         0.304655            0.910854
2.10508
         beta_0          5.74132         0.239459             5.27199
6.21065
         beta_1          0.16765        0.0136521            0.140893
0.194408
         beta_2                0              NA
         beta_3                0              NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    20        5.7         5.74        0.626         1.23          -0.15
```

9	10	7.4	7.25	1.26	1.23	0.386
18	10	8.7	8.76	1.17	1.23	-0.152
35	9	11.6	11.6	2.22	1.23	-0.0222

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-34.465942	5	78.931884
A2	-24.136490	8	64.272980
A3	-34.465942	5	78.931884
fitted	-34.563689	3	75.127378
R	-68.998702	2	141.997404

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	89.7244	6	<.0001
Test 2	20.6589	3	0.0001239
Test 3	20.6589	3	0.0001239
Test 4	0.195494	2	0.9069

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. Consider running a non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider a different variance model

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 7.32473

BMDL = 6.02296

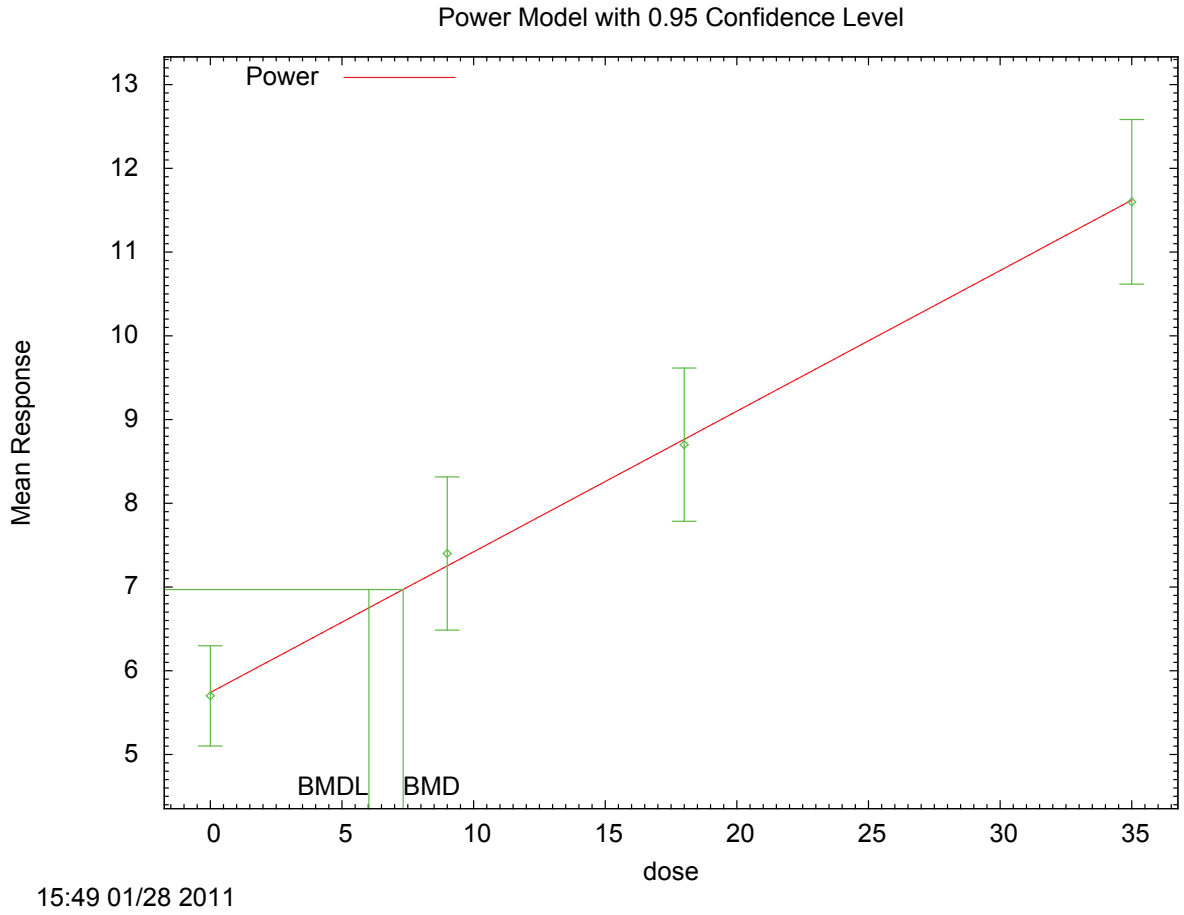

Figure C-16. Power_CV BMD Model for Relative Kidney Weight Data (NTP, 1996)

Text Output for Power_CV BMD Model for Relative Kidney Weight Data (NTP, 1996)

```
 ======================================================================
          Power Model. (Version: 2.16;  Date: 10/28/2009)
          Input Data File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Rel_Kidney_Wt_PowerCV_1.(d)
          Gnuplot Plotting File:
C:/USEPA/BMDS212/Allran2/NTP_1996_F0_M_Rel_Kidney_Wt_PowerCV_1.plt
                                                Fri Jan 28 15:49:33 2011
 ======================================================================

 F0_M_Rel_Kidney_Wt
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
```

The power is restricted to be greater than or equal to 1
A constant variance model is fit

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha =	1.63547	
rho =	0	Specified
control =	5.7	
slope =	0.227624	
power =	0.915525	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho -power
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	control	slope
alpha	1	4.1e-009	-1.5e-009
control	4.1e-009	1	-0.68
slope	-1.5e-009	-0.68	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	1.50797	0.304655	0.910854	2.10508
control	5.74132	0.239459	5.27199	6.21065
slope	0.16765	0.0136521	0.140893	0.194408
power	1	NA		

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	20	5.7	5.74	0.626	1.23	-0.15
9	10	7.4	7.25	1.26	1.23	0.386
18	10	8.7	8.76	1.17	1.23	-0.152

```
  35     9       11.6         11.6         2.22         1.23        -0.0222


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1          -34.465942            5      78.931884
            A2          -24.136490            8      64.272980
            A3          -34.465942            5      78.931884
        fitted          -34.563689            3      75.127378
             R          -68.998702            2     141.997404


                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              89.7244          6          <.0001
   Test 2              20.6589          3        0.0001239
   Test 3              20.6589          3        0.0001239
   Test 4             0.195494          2           0.9069

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  Consider running a
non-homogeneous variance model

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data
```

```
              Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 7.32473


            BMDL = 6.02296
```

APPENDIX D. REFERENCES

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