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Provisional Peer-Reviewed Toxicity Values for

Bis(2-chloro-1-methylethyl)ether
(CASRN 108-60-1)

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Questions regarding the contents of this document may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

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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
POD	point of departure
p-OSF	provisional oral slope factor
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 BIS(2-CHLORO-1-METHYLETHYL)ETHER (CASRN 108-60-1)

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 EPA's IRIS. 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 adverse 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

Bis(2-chloro-1methylethyl)ether (BCMEE) is used in paint and varnish removers as an intermediate in dyes, resins, and pharmaceuticals, as a solvent for natural and synthetic resins, as a soil fumigant, and as a nematocide in Japan (HSDB, 2010; NCI, 1979; IARC, 1986). It is also used in spotting agents, cleaning solutions, and as a soap adjuvant in the textile industry (OEHHA, 1999). It is reported to be formed as a by-product in some propylene oxide/propylene glycol production processes (OEHHA, 1999; IARC, 1986). The empirical formula for BCMEE is $C_6H_{12}Cl_2O$ (see Figure 1). Table 1 provides the physical properties of BCMEE.

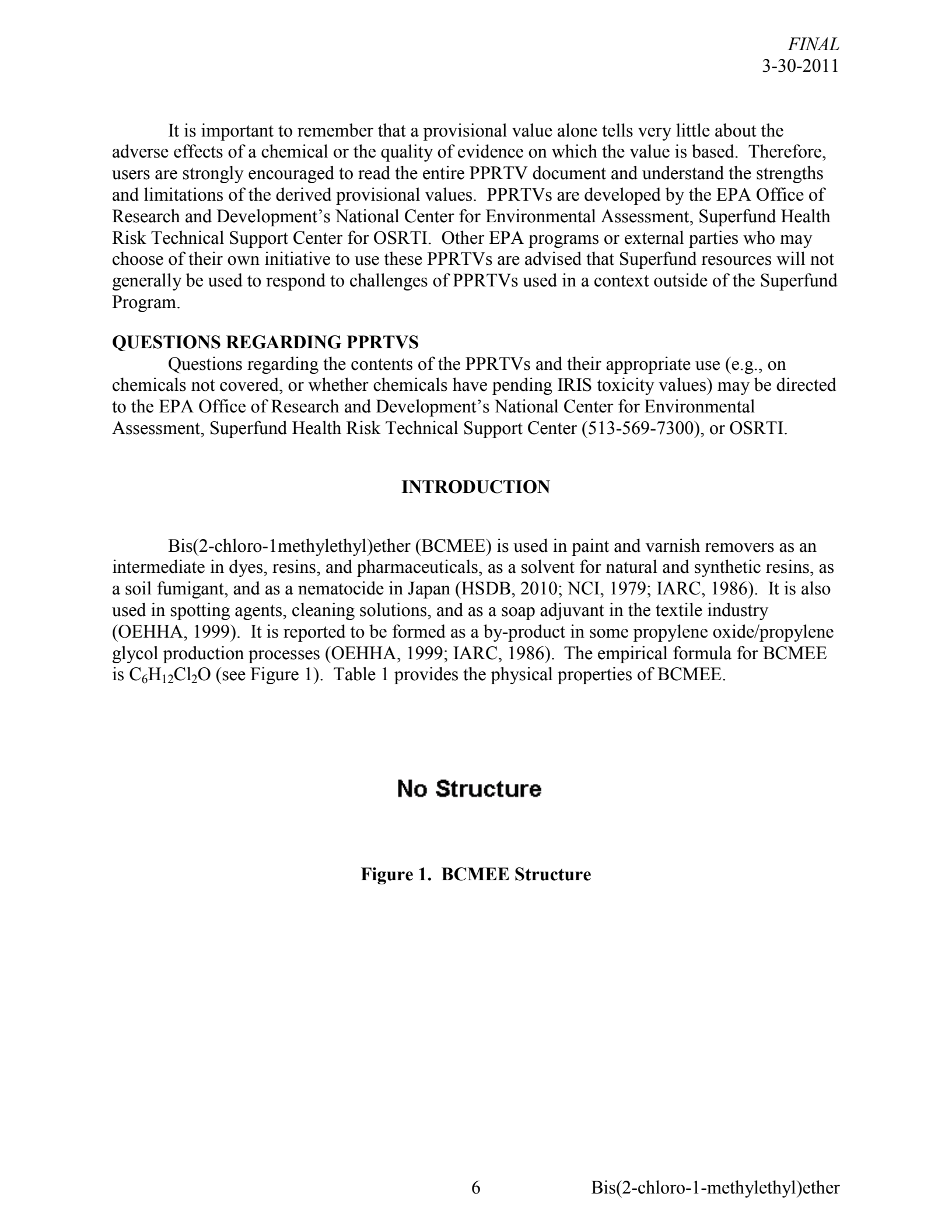

Figure 1. BCMEE Structure

Table 1. Physical Properties Table (BCMEE)	
Property (unit)	**Value**
Boiling point (ºC)	187[a]
Melting point (ºC)	-9.7×10^{1}[a]
Density (g/cm^3 at 20ºC)	1.103[b]
Vapor pressure (Pa at 20ºC)	74.7[a]
pH (unitless)	Not available
Solubility in water (mg/L at 20ºC)	1700[a]
Relative vapor density (air = 1)	5.9[b]
Molecular weight (g/mol)	171.1[a]
Octanol/water partition coefficient (unitless)	2.48[a]

[a]Values from ChemIDPlus Advanced;
http://chem.sis.nlm.nih.gov/chemidplus/jsp/common/ChemFull.jsp?calledFrom=null.
[b]Values from http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

The U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS) (U.S. EPA, 2010a) does not list a chronic reference concentration (RfC) or a cancer assessment for 2(chloro-1-methyl)ether (CAS No. 108-60-1). A chronic oral reference dose (RfD) of 4×10^{-2} mg/kg-day is included in the IRIS database (U.S. EPA, 2010a) based on the critical endpoint of decreased hemoglobin and possible erythrocyte destruction in SPF-ICR mice observed in a 104-week dietary BCMEE (purity 98.5%) study (Mitsumori et al, 1979). A Federal Drinking Water Guideline of 300 μg/L is published by EPA Office of Water (OW) (U.S. EPA, 2006). No subchronic or chronic RfD or RfC values are reported in the HEAST; (U.S. EPA, 2010b). CalEPA (OEHHA, 1999) has not derived toxicity values for exposure to BCMEE. The toxicity of BCMEE has not been reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR, 2008) or the World Health Organization (WHO, 2010). A Health and Environmental Effects Profile (HEEP) (U.S. EPA, 1987) has not been developed for BCMEE. No occupational exposure limits for BCMEE have been derived by the American Conference of Governmental Industrial Hygienists (ACGIH, 2009), the National Institute of Occupational Safety and Health (NIOSH, 2003), or the Occupational Safety and Health Administration (OSHA, 1997).

The HEAST (U.S. EPA, 2010b) reports an EPA cancer weight-of-evidence (WOE) classification of Group C (*Possible Human Carcinogen*), an oral slope factor (OSF) of 7×10^{-2} (mg/kg-day)$^{-1}$ and an inhalation slope factor (ISF) of 3.5×10^{-2} (mg/kg-day)$^{-1}$ for BCMEE. Both values were based on increased incidences of liver and lung tumors in male and female $B6C3F_1$ mice in a 103-week gavage study (NTP, 1982). The ISF was derived via route-to-route extrapolation from the oral dose in mice and assuming 50% inhalation absoroption. The HEAST (U.S. EPA, 2010b) also reported oral unit risk (UR) and inhalation UR values of 2×10^{-6} per μg/L and 1×10^{-5} per μg/m^3, respectively, for BCMEE. The inhalation values (ISF and IUR) were derived by a route-to-route extrapolation from the oral mouse doses (NTP, 1982) and assuming 50% absorption via the lungs. The chemical BCMEE has not been evaluated under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005).

The International Agency for Research on Cancer (IARC, 2000) has classified BCMEE as a Group 3 agent (*Not Classifiable as to Its Carcinogenicity to Humans*). CalEPA (OEHHA, 1999) has developed a qualitative document outlining evidence for the carcinogenicity of technical grade BCMEE based on the development of liver and lung tumors in male mice and lung tumors in female $B6C3F_1$ mice treated with BCMEE by gavage.

Literature searches were conducted from 1900 through November 2010, for studies relevant to the derivation of provisional toxicity values for BCMEE, CAS No. 108-60-1. The EPA Health and Environmental Research Online (HERO) database of scientific literature that searches the following databases was used: 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 among others); 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; Hazardous Substances Data Bank (HSDB); IRIS; ITER; LactMed; Multi-Database Search; NIOSH; NTIS; PESTAB; PPBIB; RISKLINE; TRI; and TSCATS); Virtual Health Library; Web of Science (searches Current Content database among others); World Health Organization; 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. A final search of the published literature was conducted from January 2010 through November 2010 for recent studies.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides information for all of the potentially relevant studies. Entries for the principal studies are bolded and are labeled "PS".

Table 2. Summary of Potentially Relevant Data for BCMEE (CASRN 108-60-1)

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]					
			None					
			2. Inhalation (mg/m^3)[b]					
			None					
Animal								
			1. Oral (mg/kg-day)[b]					
PS	**Subchronic**	**56M/56F SPF-ICR mice in the diet, 7 d/wk, total 104 weeks; 7/7 sacrificed at 13 weeks for analysis**	**0, 9.69, 48.42, 242.18, 984.9 (males) and 0, 11.99, 60.26, 305.80, 1211.7 (females); intake was author determined**	**Decreased RBC count, hematocrit, hemoglobin, and particularly in total leukocyte counts in male mice and blood biochemical parameters**	**Not identifiable**	**Run; however, results not suitable for POD determination**	**9.69 (male mice)**	**Mitsumori et al., 1979**
		10M/10F F344 rats by gavage, 7 d/wk, 13 weeks	0, 10, 25, 50, 100, 250 Purity 69.4%	Reduction in body weight in the high dose group, particularly in males	None	Not run	None	NCI, 1979
		10M/10F B6C3F$_1$ mice by gavage, 7 d/wk, 13 weeks	0, 10, 25, 50, 100, 250 Purity approx. 69.4%	Respiratory lesions and focal pneumonitis were seen in the three highest doses	None	Not run	None	NTP, 1982
	Chronic	50M/50F F344 rats by gavage, 5 d/wk, 103 weeks	0, 71.4, 142.9 Purity approx. 69.4%	Reduction in body weight and survival was noted in the high dose group	71.4	Not run	142.9	NCI, 1979
U.S. EPA, 2010a		56M/56FSPF- ICR mice in the diet, 7 d/wk, 104 weeks	0, 8.41, 40.1, 198, 927 (males) and 0, 7.58, **35.8**, 194, 961 (females); intake was author determined	Hemosiderin deposition in spleen, decrease in hemoglobin, and erythrocyte (red blood cell [RBC]) count	198 (males); 35.8 (females); reported by study authors	Not run	927 (males); 194 (females)	Mitsumori et al., 1979

Table 2. Summary of Potentially Relevant Data for BCMEE (CASRN 108-60-1)

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)
		50M/50F B6C3F$_1$ mice gavage, 5d/wk, 103 weeks	0, 71.4, 142.9 Purity approx. 69.4%	No clinical observations; body-weight changes were comparable to the control group	None	Not run	None	NTP, 1982
	Developmental	None						
	Reproductive	None						
	Carcinogenic	50M/50F F344 rats by gavage, 5d/wk, 103 weeks	0, 71.4, 142.9 Purity 69.4%	Significant dose-response trends in tumor incidences were not noted in either male or female rats	None	Not run	None	NCI, 1979 In most instances, the number of tumors was higher in the control group compared to the low and high dose BCMEE treated groups; the study authors concluded that these results may partly be due to lower survival rates in the high-dose group

Table 2. Summary of Potentially Relevant Data for BCMEE (CASRN 108-60-1)

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)
		50M/50F B6C3F$_1$ mice by gavage, 5d/wk, 103 weeks	0, 71.4, 142.9 Purity approx. 69.4%	A dose-related, statistically significant increase in incidence of alveolar/bronchiolar adenomas were noted in male and female mice (males: 5/50, 13/50, 11/50 in the control, low, and high dose groups, respectively; females: 1/50, 4/50, 8/50 in the control, low, and high dose groups, respectively); a statistically significant increase in the incidence of hepatocellular carcinomas was noted in male mice (5/50, 13/50, 17/50 in the control, low-, and high-dose groups, respectively)	None	Not run	None	NTP, 1982
	Carcinogenic	56M/56F SPF-ICR mice in the diet, 7 d/wk, 104 weeks	0, 8.41, 40.1, 198, 927 (males) and 0, 7.58, 35.8, 194, 961 (females); intake was author determined	No significant ($p < 0.05$) difference between controls and treated mice for any tumor type	927 (males); 961 (females)	Not run	None	Mitsumori et al., 1979 This was the only chronic-duration study that used relatively pure BCMEE (98.5%)
2. Inhalation (mg/m^3)[b]								
None								

[a]IRIS = utilized by IRIS, date of last update; **PS** = principal study in bold text; POD dose also in bold font.
[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). Noncancer oral data are only adjusted for continuous exposure.
[c]Not reported by the study author but determined from data.

HUMAN STUDIES

Oral and Inhalation Exposure

No published studies investigating the effects of subchronic- or chronic-duration oral or inhalation exposure to BCMEE in humans have been identified. HSDB (2010) reports that the toxicity of BCMEE is less than that of dichloroethyl ether (isomer not specified). Damage is reported to occur in the liver and kidneys rather than in the lungs. The report also stated that the central nervous system (CNS) depressant action of chlorinated ethers leads to loss of consciousness following high exposures (concentration estimates not provided).

ANIMAL STUDIES

Oral Exposure

The effects of oral exposures to BCMEE have been evaluated in subchronic- and chronic-duration animal studies (NCI, 1979; NTP, 1982; Mitsumori et al., 1979). Published studies pertaining to developmental and reproductive effects of BCMEE have not been identified.

Short-term Study

NTP (1982) conducted a short-term 14-day study as part of its chronic-duration carcinogenesis assay using an isomeric mixture of 69.4% BCMEE and 30% 2-chloro-1-methylethyl(2-chloropropyl)ether. Groups of five male and five female B6C3F_1 mice were administered this mixture of BCMEE isomers at 17.8-, 31.6-, 56.2-, 100-, 178-, 316-, or 562-mg/kg-body weight (BW) per day (mg/kg-day) via corn oil gavage for 14 consecutive days. A control group was not used in this study. Mice were observed daily for mortality and were weighed on Days 0, 7, and 14. Necropsies were performed on all animals at study termination. Compound-related deaths were noted at the two highest doses (316 and 562 mg/kg-day). One male mouse dosed with 56.2-mg/kg-day BCMEE was found dead on Day 7, and five male mice died following the first 562-mg/kg-day dose of BCMEE. One female mouse each in the 100- and 316-mg/kg-day dose groups were found dead on Days 8 and 6, respectively, and all 5 female mice were dead on Day 1 following treatment with 562-mg/kg-day BCMEE. Animals (number not specified) receiving 562 mg/kg-day exhibited a hunched appearance. No other signs of overt toxicity were observed at the other dose levels. No compound-related gross lesions were noted at any of the administered doses at necropsy (data not provided). Body-weight changes as result of BCMEE exposure were not reported. Because an isomeric mixture of BCMEE was used in this assay and detailed results from short-term BCMEE exposures were not reported in the technical report, this study is of limited use for deriving toxicity values.

Subchronic-duration Studies

The study by Mitsumori et al. (1979) is selected as the principal study for deriving the subchronic p-RfD. Mitsumori et al. (1979) conducted a 104-week chronic-duration toxicity study in which groups of 56 male and 56 female specific-pathogen-free (SPF)-ICR mice were fed a diet containing 0-, 80-, 400-, 2000-, or 10,000-ppm BCMEE (purity 98.5%) for 104 weeks. Adjusted for continuous exposure, these levels correspond to doses of 0, 9.69, 48.42, 242.18, and 984.9 mg/kg-day in human males and 0, 11.99, 60.26, 305.80, and 1211.7 mg/kg-day in human females. Animal body weights were determined weekly from Weeks 0 to 26, once every 2 weeks from Weeks 27 to 52, and once every 4 weeks from Weeks 52 to 104. During Week 13, 7 mice/sex/group were sacrificed after removing blood for testing. Blood for hematological and biochemical testing was obtained from the posterior vena cava while the animals were under anesthesia. Hematological examinations included determination of erythrocyte count,

hemoglobin concentration, leukocyte count, and hematocrit measurement. Tail vein blood was collected for the determination of differential leukocyte count (%). Blood biochemical examinations included determination of plasma glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), alkaline phosphatase (ALP), glucose, total protein (TP), urea nitrogen (UN), cholesterol, and bilirubin. Urinalysis included determination of pH, protein, glucose, ketone bodies, and occult blood. Mice that were moribund were euthanized and examined in a manner similar to that which was used for mice sacrificed by design. All animals that were euthanized by design or in extremis received a necropsy examination. Following necropsy, the following organs were weighed: brain, pituitary, thyroid, heart, thymus, liver, kidneys, spleen, adrenals, gonads (testes and ovaries), and muscle (triceps surae muscle of hind leg). In addition to these organs, the salivary glands, lungs, lymph nodes, pancreas, stomach, duodenum, jejunum, ileum, cecum, colon, seminal vesicles, prostrate, uterus, bladder, bone marrow (femur), and other regions considered to present abnormalities following necropsy were fixed for further examination.

Treatment-related mortalities occurred in both sexes in the 10,000-ppm dose group at 8 weeks after BCMEE administration. At Week 13, in the 10,000-ppm dose group, besides the 7 males and females that were euthanized by design, 8 male and 12 female mice were either dead or euthanized in extremis. In contrast, besides the 7 males and females that were euthanized by design, none of the animals in the other dose groups were dead or euthanized in extremis. Although the duration of the observation period was not specified, the authors reported that the general condition of animals in the 10,000-ppm dose group revealed smaller body size and emaciation, which they primarily attributed to undernutrition due to food aversion rather than an effect of BCMEE toxicity. Hematological examinations performed at 13 weeks indicated dose-related reductions in the erythrocyte (red blood cell [RBC]) count, percent hematocrit (Ht), and hemoglobin (Hb) levels in male mice, but this trend was not observed in female mice. As outlined in Table B.1, the authors reported statistically significant drops in RBC counts ($p < 0.05$), percent Ht ($p < 0.05$), and Hb ($p < 0.01$) levels in males beginning at the lowest administered dose when compared to the control group. In contrast, statistically significant drops in percent Ht ($p < 0.05$) and Hb ($p < 0.01$) levels were reported only at the highest dose in female mice when compared to the concurrent controls.

Leukocyte counts exhibited a decreasing and statistically significant ($p < 0.05$, $p < 0.01$, or $p < 0.001$) dose-response in males (see Table B.1); however, this trend was not noted in females. The study authors reported a statistically significant ($p < 0.05$) increase in leukocyte counts in the 2,000-ppm females compared to controls and a statistically significant ($p < 0.01$) decrease in neutrophils in the 10,000-ppm females (see Table B.1). Because a clear dose-response trend was not observed in females, the toxicological significance of changes in these leukocyte measurements in the female mice is unclear. In contrast to the hematological results, blood biochemical examinations indicated a statistically significant ($p < 0.05$ or $p < 0.01$) difference in GOT, GPT, ALP(males only), glucose, TP, and UN(females only) mainly in the 10,000-ppm males and females when compared to the control group (see Table B.2).

Absolute and relative organ weights and histopathological examination results of animals euthanized by design or in extremis at 13 weeks were not reported by the study authors. The LOAEL for the 13-week oral exposure is identified as an average daily dose of 80 ppm (9.69 mg/kg-day) in male SPF-ICR mice for significant changes in hematological endpoints,

including significant reduction in total number of leukocytes. A NOAEL is not established for this study.

NCI (1979) conducted a 13-week rat study as part of its chronic carcinogenesis assay. Groups of 10 Fisher 344 (F344) rats/sex were administered 0, 10, 25, 50, 100, or 250 mg/kg-day of 69.4% BCMEE, 2.1% bis(2-chloro-*n*-propyl)ether, and 28.5% of the mixed iso- and normal ether (referred to as BCMEE mixture in the study summary below) in corn oil 7 days/week via gavage for 13 weeks. A control group composed of 10 rats/sex received only corn oil. All animals were checked daily for mortality; body-weight data were also collected. At the end of 13 weeks, all surviving animals were sacrificed, and necropsies were performed on all animals.

No treatment-related mortalities occurred. An adverse effect on body weight was observed only at the 250-mg/kg-day dose, with males exhibiting a 20% drop and females exhibiting an 8% drop in mean body weight compared with the corresponding controls. Detailed results on histopathological evaluations, if conducted, were not presented in the NCI (1979) technical report. A statistical analysis of these results could not be performed because body-weight data for control animals were not provided in the study report. Because detailed results from the 13-week exposure to the BCMEE mixture are not presented in the technical report, and, also, because an isomeric mixture containing only 69.4% BCMEE was used in this assay, a LOAEL and a NOAEL for the pure compound cannot be identified from this study. Studies using chemicals of high purity are preferred because of the possibility that the observed effects of exposure are caused by an impurity or by an interaction between BCMEE and the impurity.

In a 13-week study conducted by the National Toxicology Program (NTP, 1982) as part of its chronic carcinogenesis assay, groups of 10 $B6C3F_1$ mice/sex were administered 0, 10, 25, 50, 100, or 250 mg/kg-day of 69.4% BCMEE and 30% 2-chloro-1-methylethyl(2-chloropropyl)ether (referred to as BCMEE mixture in the study summary below) in corn oil 7 days/week via gavage for 13 weeks. All animals were checked daily for mortality and morbidity and were observed weekly for overt signs of toxicity. Body-weight data were collected on a weekly basis. At the end of 13 weeks, all surviving animals were sacrificed, and necropsies were performed on all mice. Gross lesions, tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, bone marrow, sternebrae, femur, thymus, larynx, trachea, lungs and bronchi, and other organs from the control and high-dose groups (high-dose groups not specified) were preserved for analysis.

The study authors stated that no compound-related changes in mean body weights were observed in any of the animals. None of the treated animals died as a result of exposure to the BCMEE mixture. While detailed results of histopathological evaluations were not presented in the NTP (1982) technical report, histopathological changes were noted in the respiratory system. Focal pneumonitis was observed in 3/10 males and 1/10 females, 2/10 males and 3/10 females, and 8/10 males and 4/10 females in the 50-, 100-, and 250-mg/kg-day exposure groups, respectively. Statistical analysis of these data indicates that the incidence of focal pneumonitis was statistically significant ($p = 0.0349$) only in the high-dose male mice compared to the low-dose male mice. Statistical analysis between the dosed and control groups could not be performed because control data were not provided. Because an isomeric mixture containing only 69.4% BCMEE was used in this assay and detailed results from the 13-week exposure to the

BCMEE mixture are not presented in the technical report, the LOAEL and NOAEL for the mixture (see Table 2) cannot represent pure BCMEE in a quantitative toxicity assessment.

Chronic-duration Studies

NCI (1979) conducted a 103-week chronic-duration toxicity and carcinogenicity study in F344 rats. Groups of 50 F344 rats/sex were administered 0, 100, or 200 mg/kg-day of 69.4% BCMEE, 2.1% bis(2-chloro-n-propyl)ether, and 28.5% of the mixed iso- and normal ether (referred to as BCMEE mixture in the study summary below) in corn oil 5 days/week via gavage for 103 weeks. The corresponding daily average doses for continuous exposure to the BCMEE mixture were 0, 71.4, or 142.9 mg/kg-day, respectively. Two control groups composed of 50 animals/sex served as corn oil and untreated controls. All animals were observed twice daily for overt signs of toxicity, and the presence of palpable masses was recorded on a weekly basis. Mean body weights of the animals were recorded once every 2 weeks for the first 12 weeks of the study, then monthly until Week 72, and then every 2 weeks until study termination. Animals that were moribund and those that survived until study termination were sacrificed, and gross and microscopic examinations were performed on major tissues. Presence of gross lesions was not reported for animals that were sacrificed or animals that died during the study. Microscopic examinations were performed on many tissues including sections from the lungs, bronchi, trachea, kidneys, and liver.

Mean body weights of the male and female rats exhibited a dose-related trend, and dosed animals had lower mean body weights than those of the control groups throughout the exposure duration. Additionally, animals treated with the BCMEE mixture exhibited a hunched appearance. The study authors stated that a departure from linear trend was noted in each sex due to a relatively steep decrease in survival in the 200-mg/kg-day dose group. In male rats, 56% of animals in the high-dose group were alive at Week 78 of the study compared to 92% in the low-dose group and 88% in the corresponding control groups. In females, 50% of animals in the high-dose group were alive at Week 78 of the study compared to 88% in the low-dose group and 96% in the corresponding control groups. The study authors also reported that, except in the high-dose group males and females, there were sufficient numbers of rats of each sex that were at risk for the development of late-appearing tumors. As outlined in Table B.3, a notable increase in the incidence of esophageal hyperkeratosis (82% and 65% in male and female rats, respectively) was noted in male and female rats dosed with 200 mg/kg-day compared to the corresponding control groups. Additionally, 10% of females treated with 200 mg/kg-day had an increased incidence of esophageal acanthosis. In contrast, the incidence of gastric hyperkeratosis was higher in vehicle controls compared to animals dosed with the BCMEE mixture. In addition to these effects, a dose-related increase in the incidence of aspiration pneumonia was noted in low- and high-dose male and female rats. Males exhibited a 14% and 24% increase in aspiration pneumonia at the low- and high-doses, respectively, compared to 2% in vehicle control animals. Females exhibited a 33% and 46% increase at the low- and high-doses, respectively, compared to 2% in the vehicle controls. Because an isomeric mixture of BCMEE was used in this assay and the effects described above cannot be attributed exclusively to BCMEE exposure, a LOAEL and a NOAEL cannot be identified for the pure compound from this study.

Evidence of carcinogenic activity of BCMEE was not observed in male or female F344 rats. Tumor incidences in dosed groups were not significantly higher than those noted in the vehicle controls. Significant results, using the one-tailed Fisher's exact test in the *negative* direction, were reported in the incidences of hematopoietic tumors, tumors of the adrenal,

preputial gland, and testes in the males, and in the tumors of the pituitary gland, uterus, and pancreatic islets in females. The NCI (1979) report stated that the apparent negative dose-response relationships may be attributed to the relatively low survival of rats in the 200-mg/kg-day group. The study authors stated that, although tumors outlined above were noted in animals dosed with the BCMEE mixture, the incidences of these tumors were lower in the dosed groups than in the corresponding control groups.

Two male rats, one in the high-dose group and one in the low-dose group, died during Week 15 of the study with malignant lymphoma affecting multiple organs. The NCI (1979) report stated that these early deaths with tumors were not considered to be treatment related because F344 rats are known to be prone to juvenile lymphoid tumors. The NCI (1979) concluded that, under the conditions of the bioassay, BCMEE was not carcinogenic to F344 rats of either sex. However, the NCI report also stated that BCMEE cannot be considered adequately tested until additional bioassays have been conducted in other animal species.

NTP (1982) conducted a 103-week chronic-duration toxicity and carcinogenicity study in $B6C3F_1$ mice. Groups of 50 mice/sex were administered 0, 100, or 200 mg/kg-day of 69.4% BCMEE and 30% 2-chloro-1-methylethyl(2-chloropropyl)ether (referred to as BCMEE mixture in the study summary below) in corn oil 5 days/week via gavage for 103 weeks. Groups of 50 mice/sex received corn oil alone and served as vehicle controls. The corresponding daily average doses adjusted for continuous exposure were 0, 71.4, or 142.9 mg/kg-day, respectively, for the BCMEE mixture. All animals were observed twice daily for mortality and morbidity. Clinical signs were recorded on a monthly basis. Body weights were recorded on a weekly basis for the first 13 weeks and once a month thereafter until study termination. Moribund animals and animals surviving until the end of study were sacrificed and necropsied. All major tissues and organs were examined for grossly visible lesions. Microscopic examinations were also performed on the mammary gland, salivary gland, bone marrow, thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, liver, gallbladder, pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/prostate/testes (males) or ovaries/uterus (females), brain, and pituitary. Additionally, sections of the nasal turbinates were examined in male mice treated with 200 mg/kg-day of the BCMEE mixture.

Treatment with the BCMEE mixture had no effects on clinical observations or body weights throughout the duration of the study. Although there were no significant differences in animal survival between the dosed groups and control group, in males, 82%, 88%, and 74% of animals survived until study termination in the control, low-dose, and high-dose groups, respectively. In females, 62%, 68%, and 56% of animals survived until study termination in the control, low-dose, and high-dose groups, respectively. Nonneoplastic lesions observed included a 60% increase in chronic inflammation of the nasal cavity in male mice treated with 200 mg/kg-day of the BCMEE mixture, as well as a 12% and 28% increase in fatty metamorphosis of the liver in the 100- and 200-mg/kg-day dose groups, respectively, compared to a 2% increase in the control group (per data reported by NTP). Additionally, a 56% increase in chronic inflammation was noted in the naso-lacrimal duct of male mice treated with 200 mg/kg-day of the BCMEE mixture. A similar analysis of nonneoplastic lesions in females indicated a 71% increase in the incidence of cystic hyperplasia in the uterus/endometrium of the 100- and 200-mg/kg-day treated female mice, but the effect was comparable to a 61% increase in the control group (per data reported in NTP [1982]). Because an isomeric mixture of BCMEE

was used in this assay and the effects described above cannot be attributed to BCMEE exposure, a LOAEL and a NOAEL cannot be identified for the pure substance from this study.

Evidence of carcinogenic activity was well supported in both male and female mice (see Table B.4). Statistical significance was evaluated by the authors using both the Incidental Tumor Test and the Fischer Exact Test (see Table B.5). In the lung, statistically significant ($p < 0.05$) increases in alveolar/bronchiolar adenomas occurred in male and female mice with a positive trend. In male mice, 13/50 and 11/50 exhibited these tumors in the 100- and 200-mg/kg-day groups, respectively, compared to 5/50 in the control group. In female mice, 4/50 and 8/50 exhibited these tumors in the 100- and 200-mg/kg-day groups, respectively, compared to 1/50 in the control group. The tumor incidence was significantly ($p < 0.029$) higher in the high-dose females than in the control group. The combined incidence of alveolar/ bronchiolar adenomas and carcinomas indicated a significant (males, $p \leq 0.062$; females $p \leq 0.004$; high dose group) positive trend with the males and females treated with the BCMEE mixture exhibiting significantly (males, $p < 0.035$; females, $p < 0.008$; high dose group) higher incidences of the combined tumors compared to the control group (see Table B.5). In the liver, hepatocellular carcinomas exhibited a statistically significant ($p \leq 0.004$; high dose group) positive trend in male mice with the incidence of tumors significantly ($p \leq 0.007$) higher in mice treated with 200-mg/kg-day BCMEE mixture compared to the corresponding control group (see Table B.5). The combined incidence of hepatocelluar adenomas and carcinomas was significant ($p \leq 0.003$) in trend tests in male mice, with male mice treated with the 200-mg/kg-day BCMEE mixture exhibiting a significantly ($p \leq 0.005$ in all tests) higher incidence of these tumors compared to the control group (see Table B.5). Metastases to the lung was reported in 1/50, 4/50, and 3/50 mice in the control, low dose, and high dose groups, respectively. In contrast, incidences of livers tumors in female mice were not statistically significant. In the hematopoietic system, incidence of histiocytic lymphoma was noted in 3/50 (6%) male micei treated with 200 mg/kg-day with a positive trend ($p \leq 0.086$). However, incidences of other types of lymphoma were not observed in the male mice, and female mice did not exhibit any type of malignant lymphoma at a statistically significant level. Additionally, squamous-cell papillomas were seen in 2/49 female mice treated with 200 mg/kg-day of the BCMEE mixture and in 1/50 low-dose and 1/50 high-dose male mice. Squamous-cell carcinoma was observed in one high-dose female mouse that did not have squamous-cell papillomas.

Mistumori et al. (1979) investigated the chronic toxicity of BCMEE using SPF-ICR mice. Groups of 56 mice/sex were fed a diet containing 0-, 80-, 400-, 2000-, or 10,000-ppm BCMEE (purity 98.5%) seven days/week for 104 weeks. The total average daily intake of BCMEE as calculated by the study authors was 0, 8.41, 40.1, 198, and 927 mg/kg-day in male mice and 0, 7.58, 35.8, 194, and 961 mg/kg-day in female mice. Body weights were determined weekly from Weeks 0 to 26, once every 2 weeks from Weeks 27 to 52, and once every 4 weeks from Weeks 53 to 104. After study initiation, following the removal of blood samples for analysis, 7 mice/sex/group were sacrificed by design at Weeks 13, 26, and 52, and 6 mice/sex/group were sacrificed at Week 78. All remaining surviving animals were followed through Week 104 prior to sacrifice. Blood samples obtained prior to sacrifice were used for hematological and biochemical examinations. Necropsies were performed on all animals that were sacrificed by design and in extremis. Animals that died during the course of the study were also necropsied. Organs weights for brain, pituitary, thyroid, heart, thymus, liver, kidneys, spleen, adrenals, gonads (testes, ovaries), and muscle (triceps surae muscle of hind leg) were recorded. In addition to these organs, the salivary gland, lungs, lymph nodes, pancreas, stomach, duodenum,

jejunum, ileum, cecum, colon, seminal vesicles, prostrate, uterus, bladder, bone marrow, and other regions were examined for chemical-specific abnormalities.

The study authors reported smaller body size and emaciation in both male and female mice in the 10,000-ppm dose group, which they attributed to undernutrition. At Week 52, the cumulative death in the 10,000-ppm BCMEE dose group was 14 males and 22 females, compared to 3 males and 4 females in the control group. There was a remarkable inhibition in weight gain beginning Week 1 in the 10,000-ppm treatment group that continued until study termination at 104 weeks. A similar tendency of lower body-weight gain was also noted in female mice treated with 2000-ppm BCMEE. Additionally, the study authors also reported a significant (significance level not reported) difference in body weight during certain weeks (weeks not specified) in other treated groups. Food consumption was markedly lower in male and female mice treated with 10,000-ppm BCMEE throughout the study period. In contrast, in other treatment groups, generally stable values in consumption were observed throughout the study period, though some fluctuations were noted. Based on the study authors' evaluation, food aversion is the likely cause of reduced body weight in the 10,000-ppm dose group and not due to the toxicity of BCMEE.

Evaluation of hematological parameters indicated a mild, but statisitically significant ($p < 0.05$) decrease in erythrocyte count in males beginning at the lowest dose level of 80 ppm at Weeks 13 and 26, and in females during Weeks 26 and 52 (significance level $p < 0.05$ at Week 52 beginning at 2000 ppm; see Table B.1 for 13-week results). Mild depression of hematocrit levels, compared to the control group, was noted in both sexes of the same dose groups at Weeks 13 (see Table B.1) and 52 (see Table B.6), and in females at Week 26 (data not provided in article). Additionally, hemoglobin concentration in the 10,000-ppm group was reduced in male and female mice at Weeks 13 (see Table B.1) and 26, and in females at Week 52 (see Table B.6). Leukocyte counts exhibited a decreasing trend in 10,000-ppm males at each assigned period of sacrifice by design. Additionally, 400- and 2000-ppm group male mice and 10,000-ppm group female mice showed a small decrease in leukocyte counts at Weeks 13 (see Table B.1). Differential leukocyte counts exhibited reduction in leukocytes and increases in polymorphonuclear neutrophils in 10,000-ppm males at Weeks 13 (see Table B.1) and 26 and in females euthanized in extremis during the first 13 weeks of treatment (see Tables B.1).

Blood biochemical examination showed a significant ($p < 0.01$) increase in plasma GOT and GPT levels in both male and female mice treated with 10,000-ppm BCMEE during Week 13. UN levels were significantly ($p < 0.05$ or $p < 0.01$) increased in female mice treated with 10,000-ppm BCMEE during Weeks 13 and 52. In male mice, statistically significant ($p < 0.0.1$ or $p < 0.05$) increases in UN levels were seen only during Week 52 at the 400-, 2000-, and 10,000-ppm dose levels. In addition to GOT and GPT levels, ALP levels were increased in male mice during Week 13 and in both sexes during Weeks 26 and 52 (data not provided in article). Minor decreases in total protein were also seen in both sexes, primarily in animals treated with 10,000-ppm BCMEE during Weeks 13 (males only), 26, and 52. The study authors also reported reductions in blood glucose levels in both sexes during Weeks 13 (see Table B.2), 26, and 52 (see Table B.8), and in females during Week 78 (data not provided in article). Though some significant changes in organ weights in male mice treated with 10,000-ppm BCMEE were noted, in general, the absolute and relative organ weights of animals treated with BCMEE did not show marked adversity and weight changes corresponding to decreased body

weights. Table B.9 presents absolute and relative organ weights for select organs in SPF-ICR mice.

Examination of nonneoplastic endpoints indicated an increased incidence of hemosiderin deposition in the spleen. Seventeen males and 17 females in the 10,000-ppm dose group exhibited increased hemosiderin deposition in the spleen compared to only 1 male and 2 females in the control group. Additionally, splenic hemosiderin deposition was also noted in females during Week 13 and in males during Weeks 13, 26, and 52. The study authors also reported mild-to-moderate increases in extramedullary hematopoieses in the spleen in males during Week 13 (numerical data not reported). Though not statisitically significant, this effect was associated with a high number of mice exhibiting erythroblastic hyperplasia compared to the control group at 104 weeks (see Table B.10). The study authors identified a NOAEL for BCMEE of 2,000 ppm (198 mg/kg-day) in male mice and 400 ppm (35.8 mg/kg-day) in females for hematological changes. Based on these results, a chronic LOAEL of 10,000 ppm (927 mg/kg-day) for males and 2,000 ppm (194 mg/kg-day) for females is identified in this study.

No evidence of BCMEE-related carcinogenicity was observed in either male or female mice. Adenomas of the lung, lymphatic leukemia, reticulum cell sarcomas, and other types of tumors were observed at a relatively high incidence in each of the groups. However, there was no difference in the incidence of these tumors, age of onset, and histological findings between the treatment groups and the control group. Sporadic tumors, such as benign papilloma of the forestomach in one male mouse, and a granulose cell tumor, two adenomas of the ovary, three pituitary adenomas, and a uterine leiomyoma in females were observed, but the incidences of these tumors in male and female mice were low and independent of BCMEE dose. Similarly, the occurrences of malignant tumors such as carcinoma of the lung, subcutaneous leiomyosarcoma, subcutaneous osteogenic sarcoma, and subcutaneous undifferentiated tumor in males, and undifferentiated tumors in the uterus or peritoneum in females were sporadic, and the incidences were low. The study authors concluded that because the occurrence of benign and malignant tumors were sporadic with low incidence, the evidence of carcinogenic activity in male and female SPF-ICR mice was negative.

Inhalation Exposure

No studies investigating the effects of subchronic- or chronic-duration inhalation exposure to BCMEE in animals were identified.

Other Studies

Developmental and Reproductive Toxicity Studies

No studies pertaining to the developmental and reproductive toxicity of BCMEE were identified.

Other Data (Short-Term Tests, Other Examination)

Little information is available on the toxicokinetics of BCMEE. Results of available studies (i.e., U.S. EPA, 1987; Smith et al., 1978) show evidence of saturation of absorption mechanisms at high doses, with concentrations of radioactivity peaking in blood 2–4 hours after treatment at the lower doses. A $t_{1/2}$ for the elimination of BCMEE and its metabolites from blood in monkeys was reported to be about 5 hours in the α-phase, while, in rats, the $t_{1/2}$ was approximately 48 days. Beyond 24 hours, elimination curves for blood in monkeys and rats

were stated to be identical (Smith et al., 1978). Smith et al. (1978) also studied tissue distribution of BCMEE by administering a single parenteral dose of 30 mg/kg to rats and monkeys. In rats, a significant (exact percentage not reported in study summary) amount of BCMEE was excreted via the bile with reabsorption into the intestine. In contrast, in monkeys, there seemed to be a statisitically significant (28.8 mg/kg) accumulation of BCMEE in the liver with very little excretion of BCMEE or its metabolites, via the bile into the intestines. Additionally, much higher concentrations of radioactivity were noted in the brain and muscle mass (3.3 mg/kg in both tissues) of the monkeys compared to the rats. Elimination of BCMEE is primarily in urine and is rapid, and is composed of BCMEE and its metabolites (1-chloro-2-propanol [CIP], and propylene) with the rats excreting approximately twice (63.36% of the administered dose) as much BCMEE compared to the monkeys (28.61% of the administered dose). Excretion in the feces ranged from 1% in the monkeys to 6% in the rats.

The genotoxicity of BCMEE has been tested in a select number of studies (e.g. Zeiger, 1987; Moriya et al., 1983; Mirsalis et al., 1989; Jorgenson et al., 1977; and McGregor et al., 1988) using in vitro and in vivo test systems. Test results were equivocal, with some results indicating genotoxicity, while others were negative.

Table 3 summarizes the toxicokinetics and genotoxicity studies for BCMEE.

Table 3. Other Studies				
Tests	**Materials and Methods**	**Results**	**Conclusions**	**References**
Toxicokinetic	Three female CD rats were administered (route not specified) a single dose of 0.2 µg/kg to 300 mg/kg of BCMEE (purity >95%); tissue distribution was studied by treating three rats with 30 mg/kg of BCMEE via intraperitoneal injection and treating one monkey with 30 mg/kg of BCMEE via intravenous injection. Tail vein blood from rats was collected at specified intervals between 15 minutes and 48 hours after BCMEE administration, and animals were sacrificed after 48 hours; monkey blood was also collected (intervals not specified); tissues from various organs were collected from rats and monkeys that were sacrificed 7 days after BCMEE administration; urine and feces were collected up to 168 hours after BCMEE administration along with expired air (collection times not specified).	There was evidence of saturation of absorption mechanisms at high doses. In the rat, a large proportion of material seemed to be excreted via the bile, with reabsorption by the intestine. Tissue distribution indicated that monkeys had an accumulation of 28.8 mg/kg of BCMEE in the liver. Monkeys also had substantially higher concentrations in the brain and muscle mass (3.3 mg/kg in both tissues) compared to rats. Elimination of BCMEE was primarily in urine and was rapid, and was composed of BCMEE and its metabolites, with the rats excreting approximately twice as much (63.36% of the administered dose) BCMEE compared to the monkeys (28.61% of the administered dose). Excretion in the feces ranged from 1% in the monkeys to 6% in the rats. Two metabolites of BCMEE were identified in the urine: 1-chloro-2-propanol (CIP) and propylene oxide (PO).	BCMEE is well absorbed from the gastrointestinal tract in the rats—but not monkeys. Tissue distribution indicated higher levels of BCMEE in the fat, urine, and feces of the rat, whereas higher quantities were found in the muscle and liver of the monkey. Elimination is rapid, predominantly as BCMEE and its metabolites in urine. Excretion in feces was minimal.	Smith et al., 1978

Table 3. Other Studies

Tests	Materials and Methods	Results	Conclusions	References
Toxicokinetic	Seven adult male Sprague-Dawley rats were administered ^{14}C BCMEE in corn oil at 90 mg/kg via gavage. Radioactivity was measured in expired air, urine, feces, carcass, and cage wash 48 hours after BCMEE administration.	Total ^{14}C recovery was 73.3 ± 7.7% of the administered BCMEE dose. Fecal excretion accounted for 3.8% of the administered BCMEE dose. Excretion rates in expired air and urine were not provided.	The authors state that the results suggest that gastrointestinal absorption of BCMEE was nearly complete.	U.S. EPA, 1987
Genotoxicity	*Salmonella* mutagenicity study results for BCMEE were obtained from two programs. In one program, *Salmonella* strains TA98, TA100, TA1535, and TA1537 were used in a standard plate assay without metabolic activation and with activation by liver S9 preparations from uninduced and Aroclor 1254-induced male Fischer 344 rats, $B6C3F_1$ mice, and Syrian hamsters. In the second program, strains TA98, TA100, TAI535, and either TA97 or TAI537 were used in a preincubation assay without activation and with liver S9 preparations from Aroclor 1254-induced male Sprague-Dawley rats and Syrian hamsters.	The author concluded that BCMEE is mutagenic. BCMEE was reported to be mutagenic in TA98 and TA100—but not mutagenic in TA97, TA1535, and TA1537 strains. The study does not state whether mutagenicity was observed both with and without S9 activation.	This is a review article outlining the carcinogenicity and mutagenicity of 224 chemicals. BCMEE was characterized as a bacterial mutagen by the review author.	Zeiger, 1987

Table 3. Other Studies				
Tests	**Materials and Methods**	**Results**	**Conclusions**	**References**
Genotoxicity	Ames mutagenicity assay was used to test for mutagenic potential. *Salmonella* strains, TA98, TA100, TA1535, TA1537, and TA1538 were used along with a WP2 hcr strain of *Escherichia coli* with and without S9 activation. Though specific tested doses are not reported, the authors state that BCMEE, along with several other pesticides, was tested up to a dose of 5000 µg/plate.	The authors concluded that BCMEE had a negative response in the mutagenicity assay (strain-specific information not provided).	The article reports mutagenicity results for 228 pesticides including BCMEE. The study authors concluded that BCMEE is not mutagenic in the Ames assay.	Moriya et al., 1983
Genotoxicity	Male F344 and male and female B6C3F$_1$ mice were treated with BCMEE in corn oil as a single bolus dose via gavage. Doses of 20, 100, and 400 mg/kg were used in male and female mice to study unscheduled DNA synthesis (UDS) induction. Induction of S-phase synthesis (SPS) in male and female mice was examined using doses of 75-, 300-, and 400-mg/kg BCMEE.	Induction of UDS was not observed in mice treated with BCMEE. The study authors reported that the SPS induction was positive, particularly at higher doses in male mice, but equivocal in female mice.	In this study, 19 chemicals were evaluated for their potential to cause UDS and SPS. UDS was not induced in either male or female mice as a result of BCMEE exposure. SPS induction was positive in male mice but equivocal in female mice.	Mirsalis et al., 1989

Table 3. Other Studies

Tests	Materials and Methods	Results	Conclusions	References
Genotoxicity	Male mice (strain not specified) were treated daily via gavage for 8 weeks with three doses of BCMEE (doses not specified) to examine the mutagenic potential of BCMEE via the heritable translocation test. After treatment, each male was mated with two virgin females to produce an F1 generation. Upon maturity, 100 F1 males per treatment group then were selected and bred to three virgin females. Pregnant females were evaluated against a set of predetermined selection criteria (not specified) to identify compromised males. These males were rebred with three additional virgin females. Presumptive F1 males were examined cytogenetically after two breedings.	Preliminary evaluations indicated that heritable translocations did not occur in animals exposed to BCMEE.	Detailed results were unavailable because the study results were retrieved from an abstract. A publication outlining detailed study results could not be located.	Jorgenson et al., 1977
Genotoxicity	Mouse lymphoma L5178 tk^+/tk^- cells were used to test the mutagenic potential of BCMEE. Cultures cells (6×10^6) were treated with BCMEE (0, DMSO, 62.5, 125, 250, 500, 1000, 2000 µg/ml) without S9 activation.	Mutant-forming colonies were significantly elevated ($p < 0.05$) at 250, 500, and 1000 µg/ml in a significant ($p < 0.05$) dose-response trend.	BCMEE is mutagenic under the conditions of the test.	McGregor et al., 1988

DERIVATION OF PROVISIONAL VALUES

Table 4 presents a summary of noncancer reference values. Table 5 presents a summary of cancer values. The toxicity values were converted to HEC/HED units, and the conversion process is presented in the text below. IRIS data are indicated in the table if available.

DERIVATION OF ORAL REFERENCE DOSE

Derivation of Subchronic p-RfD

Three publications (NTP, 1982; NCI, 1979; and Mitsumori et al., 1979) were considered as principle studies. Both NCI (1979) and NTP (1982) used a mixture of approximately 69.4% BCMEE with about 30% of related compounds, thus making them unsuitable for evaluating the effects of high purity BCMEE. Because they used relatively high purity (98.5%) BCMEE, the study by Mistumori et al. (1979) is selected as the principal study for the derivation of the subchronic p-RfD. The critical endpoints are statistically significant ($p < 0.05$) changes in RBC count, hematocrit, hemoglobin, and total leukocytes in male SPF-ICR mice at the lowest dose tested (9.96 mg/kg-day). This study, published in a peer-reviewed journal, was conducted with multiple doses (0, 80, 400, 2000, 10,000 ppm in the diet) with a variety of toxicologic endpoints that demonstrated a statistically significant dose response in male and female rats, with interim sacrifice of seven animals per sex per dose at 13, 26, 52, and 104 weeks. Among the available subchronic-duration studies, the Mitsumori et al. (1979) study is the only one that provides information for the determination of a credible point of departure (POD) for deriving a subchronic p-RfD using relatively pure BCMEE. Thus, the Mitsumori et al. (1979) study provides a LOAEL (9.69 mg/kg-day) as the only POD.

Table 4. Summary of Noncancer Reference Values for BCMEE (CASRN 108-60-1)							
Toxicity Type (Units)	**Species/ Sex**	**Critical Effect**	**p-Reference Value**	**POD Method**	**POD**	**UF_C**	**Principal Study**
Subchronic p-RfD (mg/kg-day)— Screening Value	Mouse/M	**Decreased RBC count, hematocrit, hemoglobin, and particularly in total leukocyte counts in male mice and blood biochemical parameters**	1×10^{-3}	LOAEL	9.69	10,000	Mitsumori et al. (1979)
Chronic RfD[a] (mg/kg-day) (IRIS)	Mouse/F	Decreased hemoglobin concentration and possible erythrocyte destruction	4×10^{-2}	NOAEL	35.8	1000	Mitsumori et al. (1979)
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]Value from IRIS (EPA, 2010a).

Table 5. Summary of Cancer Values for BCMEE (CASRN 108-60-1)				
Toxicity Type	**Species/Sex**	**Tumor Type**	**Cancer Value**	**Principal Study**
p-OSF	None	None	None	None
p-IUR	None	None	None	None

Table 6. Summary of Potentially Relevant Oral Systemic Subchronic Toxicity Studies for BCMEE

#/Sex (M/F)	Critical Endpoint	Exposure (ppm)	Frequency/ Duration	$NOAEL_{ADJ}$[a] (mg/kg-day)	$LOAEL_{ADJ}$[a] (mg/kg-day)	References
56/56, mice; 7/7 evaluated at 13 weeks	**Decreased RBC count, hematocrit, hemoglobin, and particularly in total leukocyte counts in male mice and blood biochemical parameters**	0, 80, 400, 2000, 10,000	Daily for a total of 104 weeks	None	9.69 (males)	Mitsumori et al., 1979
10/10, F344 rats	Adverse effect on body weight at the highest dose; an isomeric mixture of BCMEE was used which precludes the identification of a NOAEL and LOAEL	0, 10, 25, 50, 100, 250	7 d/wk for 13 weeks	None	None	NCI, 1979
10/10, $B6C3F_1$ mice	Focal pneumonitis at the three highest doses administered; an isomeric mixture of BCMEE was used which precludes the identification of a NOAEL and LOAEL	0, 10, 25, 50, 100, 250	7 d/wk for 13 weeks	None	None	NTP, 1982

[a]$NOAEL_{ADJ}$ or $LOAEL_{ADJ}$ = Dose (NOAEL or LOAEL) × Food Consumption Value ÷ day × (1 ÷ BW Value) × Days Dosed ÷ Total Days in Study.

A benchmark dose (BMD) analysis of the various hematological and biochemical parameters was conducted for the Mitsumori et al. (1979) study to determine if a credible benchmark dose lower bound (BMDL) could be established for the derivation of a p-RfD. Modeling was performed with—and without—the highest dose (984.9 mg/kg-day) because the reduced body weight at that dose may not represent an effect of BCMEE toxicity. BMD models were run, but an adequate fit could not be attained because, in most instances, consistent, monotonic dose-response relationships were not observed at the doses that were modeled. All model runs failed a visual inspection and one or more of the four BMD model test. Additionally, not all BMD modeling criteria were met with many of the resulting BMDLs being extremely small (e.g., BMDL = 7.4×10^{-6} mg/kg-day; Table C.1 shows these values as a zero). This can occur when the dose range in the study does not adequately cover the selected benchmark response level (BMR_{1SD}). This was true in the Mitsumori et al. (1979) study. Consequently, a traditional NOAEL/LOAEL approach has been used for the derivation of a subchronic p-RfD. A POD of 80 ppm or 9.69 mg/kg-day in male SPF-ICR mice has been identified using the conventional NOAEL/LOAEL approach from the Mitsumori et al. (1979) study.

Since a NOAEL could not be determined from the Mitsumori et al. (1979) study, the BMD analysis did not provide an acceptable POD, and because no acceptable multigeneration reproduction or developmental studies were identified, the composite uncertainty factor (UF_C) exceeds 3000 (see Table A.1). A very high level of uncertainty ($UF_C > 3000$) precludes derivation of a subchronic p-RfD. Hence, a screening value is presented in Appendix A.

Derivation of a Chronic RfD

A chronic RfD of 4×10^{-2} is included in the IRIS database (U.S. EPA, 2010a) based on the critical endpoint of decreased hemoglobin and possible erythrocyte destruction observed in a 104-week study, in which SPF-ICR mice were exposed to BCMEE in the diet. A NOAEL of 35.8 mg/kg-day and a LOAEL of 198 mg/kg-day were identified by the study authors (Mitsumori et al., 1979) with the NOAEL serving as a POD for chronic RfD derivation.

It should be noted that the screening subchronic p-RfD value (1×10^{-3} mg/kg-day; see Appendix A) is lower than the chronic RfD (4×10^{-2} mg/kg-day) because hematopoietic effects were more significant during the 13-week observation period compared to the observations at 104 weeks (see Table B.1) that were used to derive the chronic RfD (U.S. EPA, 2010a). After 13 weeks of exposure, significant changes in hematological endpoints in the male mice appeared at the lowest administered BCMEE dose, precluding the identification of a NOAEL. This led to the application of an additional uncertainty factor (UF_L) of 10 in the derivation of a subchronic p-RfD. The chronic RfD is based on the chronic-duration study of Mitsumori et al. (1979) in SPF-ICR mice. The chronic-duration study does not show direct evidence of hematological effects after 52 weeks of the study, but does provide a description of splenic effects—namely hemosiderin deposition. Although hemosiderin deposition may be regarded as a sequelae of hematological effects, the dose-response relationship between them is not characterized. Also, other chronic-duration studies of BCMEE exposure in mice, most notably that of the NTP (1982) study that used $B6C3F_1$ mice, showed no evidence of chemical-related effects in the spleen. This observation raises the possibility of a species-specific effect whose relevance to other strains of mice, and to humans, may also be uncertain.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No published studies investigating the effects of subchronic- or chronic-duration inhalation exposure to BCMEE in humans or animals were identified. This precludes the derivation of subchronic and chronic inhalation toxicity values.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 7 identifies the cancer WOE descriptor for BCMEE.

Table 7. Cancer WOE Descriptor for BCMEE			
Possible WOE Descriptor	**Designation**	**Route of Entry (Oral, Inhalation, or Both)**	**Comments**
"Carcinogenic to Humans"	N/A	N/A	No human studies are available.
"Likely to be Carcinogenic to Humans"	N/A	N/A	No strong animal cancer data are available.
"Suggestive Evidence of Carcinogenic Potential"	**X**	**Oral administration by gavage only**	**Under the 2005 *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 2005), the available evidence from oral exposure to BCMEE is suggestive of carcinogenic potential based on evidence of carcinogenicity in male and female mice in the NTP (1982) gavage bioassay. Results of NTP (1982) show statistically significant increases in incidences of alveolar/bronchiolar adenomas and carcinomas in treated male and female mice compared to study and historical controls. Additionally, incidences of hepatocellular adenomas and carcinomas were significantly increased in treated males compared to the control group, with metastases occurring in the lung. Rare forms of squamous cell papillomas were seen in the stomach or forestomach of females and males. The NTP study authors report that because these stomach tumors are rare in $B6C3F_1$ mice, the presence of these tumors, particularly in high-dose female mice, were probably related to administration of BCMEE. Because this study utilized an isomeric mixture of 69.4% BCMEE and 30% 2-chloro-1-methylethyl (2-chloropropyl)ether, tumor occurrence in $B6C3F_1$ mice cannot be firmly associated with exposure to BCMEE. Exposure-related tumors have not been observed in male and female rats exposed via gavage to BCMEE for 103 weeks (NCI, 1979). There was no evidence of carcinogenicity in male and female SPF-ICR mice fed diets containing high purity (98.5%) BCMEE (Mitsumori et al., 1979). Studies evaluating the carcinogenic potential of inhaled BCMEE in humans or animals were not located.**
"Inadequate Information to Assess Carcinogenic Potential"	N/A	N/A	Available information adequate to assess carcinogenic potential.
"Not Likely to be Carcinogenic to Humans"	N/A	N/A	No strong evidence of noncarcinogenicity in humans is available.

MODE-OF-ACTION DISCUSSION

The *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 2005) define mode-of-action as "a sequence of key events and processes starting with the interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. Because the mechanism of potential carcinogenicity of BCMEE has not yet been investigated, a discussion of the mode-of-action is not applicable.

DERIVATION OF ORAL SLOPE FACTOR

No published studies demonstrating carcinogenic effects of chronic-duration oral exposure to relatively pure BCMEE in humans or animals were identified. An obsolete oral slope factor (OSF), of 7×10^{-2} reported in the HEAST (U.S. EPA, 2010b), was derived from an NTP (1982) gavage study in mice. Existing studies showing a positive dose-response relationship between BCMEE exposure and tumor formation in mice (NTP, 1982)—but not in rats (NCI, 1979)—used a mixture of 69.4% BCMEE and 30% other isomers and could not be used to derive an OSF for pure BCMEE. Consequently no p-OSF is developed.

DERIVATION OF INHALATION UNIT RISK

No published studies demonstrating carcinogenic effects of chronic-duration inhalation exposure to relatively pure BCMEE in humans or animals were identified. This precludes the derivation of inhalation unit risk (IUR) values. An obsolete IUR of 3.5×10^{-2}, reported in the HEAST (U.S. EPA, 2010b), is derived by route-to-route extrapolation from an NTP (1982) gavage study in mice. The EPA methodology (U.S. EPA, 2005) allows for such extrapolation—but sufficient information from metabolic studies and pharmacokinetic/pharmacodynamic studies is not available for reliable route-to-route extrapolation. Existing studies showing a positive dose-response relationship between BCMEE exposure and tumor formation in mice (NTP, 1982)—but not in rats (NCI, 1979)—used a mixture of 69.4% BCMEE and 30% other isomers and could not be extrapolated to an IUR for pure BCMEE. Consequently no p-IUR is developed.

APPENDIX A. PROVISIONAL SCREENING VALUES

DERIVATION OF SCREENING PROVISIONAL ORAL REFRENCE DOSES

Derivation of Screening Subchronic Provisional RfD (subchronic p-RfD)

For reasons noted in the main document, it is inappropriate to derive a provisional subchronic p-RfD for BCMEE. However, information is available which, although insufficient to support derivation of a provisional toxicity value under current guidelines, may be of limited to use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in a supplement and develops a screening value. Appendices receive the same level of internal and external scientific peer review as the main document to ensure their appropriateness within the limitation detailed in the document. Users of the screening toxicity values in a supplement to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of a supplement screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

The study by Mitusmori et al. (1979) is selected as the principal study for the derivation of a screening subchronic p-RfD. The critical endpoint is a statistically significant reduction in several hematological parameters, including significant reduction in the total number of leukocytes in male SPF-ICR mice. This study is a peer-reviewed journal publication and, though not stated in the article, seems to be performed in general accordance with good laboratory practice (GLP) principles. It was conducted with multiple doses (0, 80, 400, 2000, 10,000 ppm in the diet) with a variety of toxicologic endpoints that demonstrated a statistically significant dose response. Details on the study are provided in the **Review of Potentially Relevant Data** section. Among the available, acceptable studies (see Table 6), this study represents the lowest POD for developing a subchronic p-RfD.

Adjusted doses for daily exposure:

The following dosimetric adjustments were made for each dose in the principal study for food intake. Dosimetric adjustment for 80 ppm (mg/kg) is presented below.

$(DOSE_{ADJ})$ = $DOSE_{CITATION}$ × Food Consumption Value ÷ day × (1 ÷ BW Value) × Days Dosed ÷ Total Days in Study

= 80 ppm (mg/kg) × 4.6 g/day (males) × (1 ÷ 38.0228 g) × 91 days ÷ 91 days

$(DOSE_{ADJ})$ = 368 mg/kg-day × 0.0263

$(DOSE_{ADJ})$ = 9.69 mg/kg-day

Food consumption values and animal body weights were obtained by digitizing the food intake rates and body weights presented in Figure 2 in the Mitsumori et al. (1979) article using the GetData graph digitizer tool (http://www.getdata.com.ru). Average food intake values and body-weight values from these digitized results were used to determine the daily average dose of BCMEE. Because food intake rates at 80 and 400 ppm were not provided in Figure 2 (Mitsumori et al., 1979), average food intake rates from the 0-ppm dose level were used to calculated daily average doses for the 80- and 400-ppm dose groups.

The screening subchronic p-RfD for BCMEE based on the LOAEL of 9.69 mg/kg-day in the male ICR mouse (Mitsumori et al., 1979) is derived as follows:

Screening Subchronic p-RfD = LOAEL ÷ UF_C
= 9.69 ÷ 10,000
= **0.000969 mg/kg-day or 1×10^{-3} mg/kg-day**

Table A.1 summarizes the UFs for the subchronic p-RfD for BCMEE.

Table A.1. Uncertainty Factors for Subchronic p-RfD for BCMEE

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 mice and humans. There are no data to determine whether humans are more or less sensitive than mice to hematological effects of BCMEE.
UF_D	10	A UF_D of 10 is selected because there are no acceptable two-generation reproduction studies or developmental studies, and there is no indication of any other studies that may be relevant for the database UF.
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response to humans.
UF_L	10	A UF_L of 10 is applied for using a POD based on a LOAEL because a NOAEL cannot be determined from the available database.
UF_S	1	A UF_S of 1 is applied because results from a subchronic duration (Mitsumori et al., 1979) were utilized as the principal study.
UF_C	10,000	

APPENDIX B. DATA TABLES

Table B.1. Results of Hematological Examination in SPF-ICR Mice Fed BCMEE in the Diet for 13 Weeks[a,b,c]

Sex and Dose Group (mg/kg-BW)[d]	No. of Mice	Mean RBC ($\times 10^6$/mm^3)	Mean Ht (%)	Mean Hb (g/dl)	Leukocyte						
					Total ($\times 10^6$/mm^3)	Differential %					
						Mean L	Mean N		Mean M	Mean E	Mean Others
							Stab.	Seg.			
Males—13 Weeks											
0	7	7.2 ± 0.6	41.8 ± 3.1	14.1 ± 0.9	6.5 ± 1.7	78.1	2.1	17.0	1.9	0.9	0
9.69	7	6.3 ± 0.7* (5)	37.7 ± 2.8*	11.8 ± 1.2** (5)	4.3 ± 1.2*	73.1	1.3	22.7	1.4	1.4	0
48.42	7	6.2 ± 0.6*	38.3 ± 2.9*	12.5 ± 0.7**	3.4 ± 1.2**	69.9	2.3	22.9	2.4	2.6	0
242.18	7	6.8 ± 0.5	40.4 ± 2.0	13.0 ± 0.6*	3.4 ± 1.1**	68.1	2.0	24.9	2.6	2.3	0.1
984.9	7	5.1 ± 1.3**	34.9 ± 3.2**	11.5 ± 0.7***	1.5 ± 0.5***	63.3	4.0	29.1	2.1	1.4	0
Females—13 Weeks											
0	7	6.9 ± 0.7	36.9 ± 2.7	13.4 ± 1.0	6.8 ± 3.0	75.7	3.0	18.9	1.1	1.3	0
11.99	7	7.4 ± 0.5	37.6 ± 1.4	13.9 ± 0.5	8.5 ± 5.4	77.4	1.7	18.0	1.4	1.4	0
60.26	7	7.1 ± 0.5	37.8 ± 2.8	13.7 ± 1.0	6.9 ± 2.4	80.3	2.7	13.6	1.3	2.1	0
305.80	7	7.0 ± 0.5	39.0 ± 1.9	13.2 ± 0.3	3.9 ± 1.2	85.1*	1.6	11.1*	0.7	1.4	0
1211.7	7	6.2 ± 0.5	33.4 ± 2.8*	11.0 ± 1.1**	2.6 ± 1.1* (6)	80.7	0.9**	14.9	1.0	1.1	0
Males—52 Weeks											
0	7	7.9 ± 0.5	38.6 ± 3.4	13.4 ± 1.1	6.5 ± 2.1	53.4	1.1	43.6	0.9	0.6	0.4
9.69	7	7.7 ± 1.3	37.7 ± 3.0	12.7 ± 2.3	6.4 ± 1.5 (6)	69.3 (6)	2.2 (6)	26.3* (6)	1.0 (6)	1.2 (6)	0 (6)
48.42	7	7.9 ± 0.6	37.3 ± 1.7	13.3 ± 0.9	5.5 ± 1.2	50.1	0.4	47.3	1.3	0.9	0
242.18	7	7.8 ± 0.7	35.3 ± 3.5	12.5 ± 1.2	6.4 ± 3.8	72.6**	0.7	24.6**	0.3	1.7	0.1
984.9	7	7.3 ± 0.7	33.9 ± 3.0*	11.6 ± 1.1	5.7 ± 2.7	62.3	1.3	35.0	0.4	1.0	0

Table B.1. Results of Hematological Examination in SPF-ICR Mice Fed BCMEE in the Diet for 13 Weeks[a,b,c]

Sex and Dose Group (mg/kg-BW)[d]	No. of Mice	Mean RBC ($\times 10^6$/mm^3)	Mean Ht (%)	Mean Hb (g/dl)	Leukocyte						
					Total ($\times 10^6$/mm^3)	Differential %					
						Mean L	Mean N		Mean M	Mean E	Mean Others
							Stab.	Seg.			
Females—52 Weeks											
0	7	8.2 ± 0.5	38.9 ± 2.0	13.3 ± 0.9	4.3 ± 1.9	59.1	4.6	32.0	1.7	1.9	0.7
11.99	7	8.2 ± 0.5	38.5 ± 1.9	13.5 ± 0.9	3.9 ± 0.8	63.9	4.1	30.7	0.3*	0.9	0.1
60.26	7	7.7 ± 0.7 (6)	38.9 ± 2.5 (6)	13.4 ± 1.0 (6)	3.6 ± 1.3 (5)	61.1	4.6	32.7	0**	1.4	0.1
305.80	7	6.7 ± 1.3*	33.8 ± 5.6	11.2 ± 1.7*	3.9 ± 1.8 (6)	62.5 (6)	4.2 (6)	31.3 (6)	0.3* (6)	1.0 (6)	0.7 (6)
1211.7	7	6.7 ± 0.4*** (4)	32.9 ± 1.9*** (4)	11.0 ± 1.0** (4)	5.1 ± 1.6 (4)	67.4	5.0	24.4	0.1*	2.4	0.6
Males—104Weeks											
0	8	7.1 ± 0.9	36.3 ± 5.7	11.2 ± 1.5	5.8 ± 2.7	55.8	4.0	37.1	0.5	2.4	1.3
9.69	5	6.6 ± 1.1	35.5 ± 4.6	10.7 ± 1.3	7.6 ± 2.6	49.0	3.6	44.2	1.0	2.2	0
48.42	8	7.0 ± 0.7	35.7 ± 4.1	10.6 ± 1.4	5.2 ± 1.6	52.6	1.9	40.9	0.9	3.8	0
242.18	5	6.8 ± 0.5	35.1 ± 2.2	10.4 ± 0.7	4.0 ± 1.2	58.4	6.2	32.8	0.6	2.0	0
984.9	6	6.9 ± 0.6	34.4 ± 4.4	10.2 ± 0.9	3.4 ± 1.3	52.2	3.3	41.8	1.2	1.5	0
Females—104 Weeks											
0	5	7.3 ± 0.5	36.9 ± 3.8	10.8 ± 1.1	4.5 ± 2.4	63.2	4.0	30.0	2.2	0.6	0
11.99	9	7.2 ± 0.8	34.7 ± 2.3	10.5 ± 1.2	3.7 ± 1.4	49.1	5.3	40.3	2.8	1.3	1.1
60.26	9	6.4 ± 1.1 (8)	33.6 ± 5.1	10.0 ± 1.6 (8)	2.8 ± 0.8 (8)	47.7	7.6	42.7	1.1	0.7	0.3
305.80	7	6.6 ± 0.9	34.7 ± 5.0	10.0 ± 1.4	3.1 ± 2.3	47.7*	3.0	46.0	1.6	1.6	0.1
1211.7	1	6.8	34.0	9.8	3.2	86	1	13	0	0	0

[a]Mitsumori et al. (1979).
[b]Values are mean ± SD or means (differential leukocytes).
[c]Parentheses values: number of mice examined for that specific dose.
[d]Adjusted doses determined using digitized results for body weight and food intake from the graph provided by the authors; these doses were used in the BMD analysis for total leukocytes.

RBC: erythrocyte count; Ht: hematocrit; Hb: hemoglobin; L: leukocytes; N: neutrophils; M: monocytes; E: eosinophils.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ based on Student's *t*-test.

Table B.2. Results of Blood Biochemical Examination in Mice Fed BCMEE in the Diet for 13 Weeks[a,b]

Dose Group (mg/kg-day)	No. of Animals	Mean GOT (K-unit)	Mean GPT (K-unit)	Mean ALP (K-A unit)	Mean Glucose (mg/dl)	Mean TP (g/dl)	Mean UN (mg/dl)	Mean CHO (mg/dl)	Mean Bil (mg/dl)
Male									
0	7	45 ± 6	26 ± 7	4.0 ± 0.9	232 ± 13	5.0 ± 0.2	27 ± 3	110 ± 10	0.3 ± 0.05
9.69	7	44 ± 8(5)	24 ± 7(5)	3.7 ± 0.9(5)	218 ± 13(5)	4.8 ± 0.3(4)	24 ± 3(4)	121 ± 31(3)	0.2 ± 0.06(3)
48.42	7	45 ± 6	23 ± 6	3.6 ± 1.1	244 ± 45	4.9 ± 0.3	29 ± 3	123 ± 15	0.2 ± 0.04
242.18	7	53 ± 11	37 ± 18	4.4 ± 0.8	252 ± 30	4.9 ± 0.3	26 ± 4	102 ± 26	0.2 ± 0
984.9	7	87 ± 25**	64 ± 26**	11.8 ± 7.1*	184 ± 32*	4.5 ± 0.3** (6)	35 ± 12(6)	98 ± 12(4)	0.3 ± 0.07(2)
Female									
0	7	45 ± 3(6)	21 ± 3(6)	4.7 ± 1.3(6)	194 ± 29(6)	4.8 ± 0.4(6)	20 ± 3(6)	68 ± 24(4)	0.2 ± 0.05(4)
11.99	7	46 ± 6	24 ± 10	5.0 ± 0.8	216 ± 36	4.8 ± 0.1	20 ± 4	61 ± 14	0.2 ± 0.05
60.26	7	51 ± 15	26 ± 18	4.9 ± 0.5	217 ± 40(6)	4.8 ± 0.3	20 ± 3	63 ± 15(5)	0.2 ± 0(5)
305.8	7	48 ± 5	20 ± 3	4.7 ± 1.4	205 ± 19	4.8 ± 0.3	22 ± 5	79 ± 12(5)	0.2 ± 0.05(5)
1211.7	7	70 ± 14**	35 ± 14*	5.2 ± 1.8	147 ± 32*(6)	4.5 ± 0.3*(6)	28 ± 7*	106 ± 42(3)	0.2 ± 0.06(3)

[a]Values obtained from Mitsumori et al. (1979).
[b]Parentheses values: number of mice examined for that specific dose.

GOT: glutamic-oxaloacetic transaminase; GPT: glutamic-pyruvic transaminase; ALP: alkaline phosphatase; TP: total protein; UN: urea nitrogen; CHO: cholesterol; Bil: bilirubin.
*$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.(Student's *t* test)

Table B.3. Results of Microscopic Examination of Selected Tissues in F344 Rats Treated with BCMEE Mixture via Gavage for 103 Weeks[a]

	Male				Female			
Title	**Untreated Control**	**Vehicle Control**	**100 mg/kg-day**	**200 mg/kg-day**	**Untreated Control**	**Vehicle Control**	**100 mg/kg-day**	**200 mg/kg-day**
No. of tissues examined microscopically	47	50	50	49	49	50	49	48
Esophageal hyperkeratosis	0 (0%)	9 (18%)	10 (20%)	40 (82%)	0 (0%)	13 (26%)	10 (20%)	31 (65%)
Esophageal acanthosis	0 (0%)	0 (0%)	1 (2%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)	5 (10%)
Gastric hyperkeratosis	0 (0%)	13 (26%)	5 (10%)	10 (20%)	0 (0%)	21 (42%)	14 (29%)	11 (23%)
Gastric acanthosis	1 (2%)	6 (12%)	4 (8%)	9 (18%)	0 (0%)	8 (16%)	5 (10%)	9 (19%)

[a]Values obtained from NCI (1979).

Table B.4. Primary Tumors in B6C3F$_1$ Mice Administered BCMEE Mixture via Gavage for 103 Weeks[a]

Tumor Type	Vehicle Control[b]	Low Dose[b]—100 (71.4 mg/kg-day)	High Dose[b]—200 (142.9mg/kg-day)
Male			
Lung: Alveolar/Bronchiolar Adenomas	5/50	13/50	11/50
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma	6/50	15/50	13/50
Hematopoietic System: All Malignant Lymphoma	6/50	3/50	7/50
Liver Adenoma	8/50	10/50	13/50
Liver Carcinoma	5/50	13/50	17/50
Liver Adenoma or Carcinoma	13/50	23/50	27/50
Forestomach: Squamous Cell Papilloma	0/49	1/50	0/50
Female			
Lung: Alveolar/Bronchiolar Adenomas	1/50	4/50	8/50
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma	1/50	4/50	10/50
Stomach/Forestomach: Squamous Cell Papilloma/Carcinoma	0/50	0/49	3/49

[a]Values obtained from NTP (1982).
[b]Number of tumor-bearing animals/number of animals examined at the site.

Table B.5. Incidence of Neoplastic Tumors in a 103-Week Gavage Study of BCMEE Mixture in B6C3F$_1$ Mice[a]

Lesion Type	Exposure Group (Daily Average Dose, mg/kg-day)		
	0	100 (71.4)	200 (142.9)
Male			
Alveolar/Bronchiolar adenomas			
Tumor rates			
Overall[b]	5/50 (10%)	13/50 (26%)	11/50 (22%)
Adjusted[c]	12.2%	28.8%	28.9%
Terminal[d]	5/41 (12%)	12/44 (27%)	10/37 (27%)
Statistics: Incidental tumor test	$p = 0.045$	$p = 0.035$	$p = 0.067$
Statistics: Fisher's exact test	$p = 0.083$	$p = 0.033$	$p = 0.086$
Alveolar/Bronchiolar adenomas or carcinomas			
Tumor rates			
Overall[b]	6/50 (12%)	15/50 (30%)	13/50 (26%)
Adjusted[c]	14.1%	33.2%	34.2%
Terminal[d]	5/41 (12%)	14/44 (32%)	12/37 (32%)
Statistics: Incidental tumor test	$p = 0.024$	$p = 0.019$	$p = 0.035$
Statistics: Fisher's exact test	$p = 0.061$	$p = 0.024$	$p = 0.062$
Female			
Alveolar/Bronchiolar adenomas			
Tumor rates			
Overall[b]	1/50 (2%)	4/50 (8%)	8/50 (16%)
Adjusted[c]	2.8%	11.8%	24.2%
Terminal[d]	0/31 (0%)	4/34 (12%)	5/28 (18%)
Statistics: Incidental tumor test	$p = 0.016$	$p = 0.148$	$p = 0.029$
Statistics: Fisher's exact test	$p = 0.011$	$p = 0.181$	$p = 0.015$
Alveolar/Bronchiolar adenomas or carcinomas			
Tumor rates			
Overall[b]	1/50 (2%)	4/50 (8%)	10/50 (20%)
Adjusted[c]	2.8%	11.8%	30.8%
Terminal[d]	0/31 (0%)	4/34 (12%)	7/28 (25%)
Statistics: Incidental tumor test	$p = 0.004$	$p = 0.148$	$p = 0.008$
Statistics: Fisher's exact test	$p = 0.003$	$p = 0.181$	$p = 0.004$
Male			
Liver carcinomas			
Tumor rates			
Overall[b]	5/50 (10%)	13/50 (26%)	17/50 (34%)
Adjusted[c]	11.5%	27.6%	40.1%
Terminal[d]	3/41 (7%)	10/44 (23%)	12/37 (32%)
Statistics: Incidental tumor test	$p = 0.004$	$p = 0.023$	$p = 0.007$
Statistics: Fisher's exact test	$p = 0.004$	$p = 0.033$	$p = 0.004$

Table B.5. Incidence of Neoplastic Tumors in a 103-Week Gavage Study of BCMEE Mixture in B6C3F$_1$ Mice[a]

Lesion Type	Exposure Group (Daily Average Dose, mg/kg-day)		
	0	**100 (71.4)**	**200 (142.9)**
Female			
Liver adenoma or carcinoma			
Tumor rates			
Overall[b]	13/50	23/50	27/50
Adjusted[c]	29.5%	48.9%	64.0%
Terminal[d]	10/41 (24%)	20/44 (45%)	22/37 (59%)
Statistics: Incidental tumor test	p =0.003	p = 0.030	p = 0.005
Statistics: Fisher's exact test	p = 0.003	p = 0.030	p = 0.004

[a]Values obtained from NTP (1982).
[b]Number of tumor-bearing animals/number of animals examined at the site.
[c]Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
[d]Observed tumor incidence at terminal kill.

Table B.6. Results of Hematological Examination in SPF-ICR Mice Fed BCMEE in the Diet for 104 Weeks[a]

Sex and Dose Group (mg/kg-day)	No. of Mice	Mean RBC ($\times 10^6$/mm^3)	Mean Ht (%)	Mean Hb (g/dl)
Male–52 Weeks[b]				
0	7	7.9 ± 0.5	38.6 ± 3.4	13.4 ± 1.1
8.41	7	7.7 ± 1.3	37.7 ± 3.0	12.7 ± 2.3
40.1	7	7.9 ± 0.6	37.3 ± 1.7	13.3 ± 0.9
198	7	7.8 ± 0.7	35.3 ± 3.5	12.5 ± 1.2
927	7	7.3 ± 0.7	33.9 ± 3.0*	11.6 ± 1.1
Male–104 Weeks[b]				
0	8	7.1 ± 0.9	36.3 ± 5.7	11.2 ± 1.5
8.41	5	6.6 ± 1.1	35.5 ± 4.6	10.7 ± 1.3
40.1	8	7.0 ± 0.7	35.7 ± 4.1	10.6 ± 1.4
198	5	6.8 ± 0.5	35.1 ± 2.2	10.4 ± 0.7
927	6	6.9 ± 0.6	34.4 ± 4.4	10.2 ± 0.9
Female–52 Weeks[b]				
0	7	8.2 ± 0.5	38.9 ± 2.0	13.3 ± 0.9
7.58	7	8.2 ± 0.5	38.5 ± 1.9	13.5 ± 0.9
35.8	7	7.7 ± 0.7(6)	38.9 ± 2.5(6)	13.4 ± 1.0(6)
194	7	6.7 ± 1.3*	33.8 ± 5.6	11.2 ± 1.7*
961	7	6.7 ± 0.4***(4)	32.9 ± 1.9***(4)	11.0 ± 1.0**(4)
Female–104 Weeks[b]				
0	5	7.3 ± 0.5	36.9 ± 3.8	10.8 ± 1.1
7.58	9	7.2 ± 0.8	34.7 ± 2.3	10.5 ± 1.2
35.8	9	6.4 ± 1.1(8)	33.6 ± 5.1	10.0 ± 1.6(8)
194	7	6.6 ± 0.9	34.7 ± 5.0	10.0 ± 1.4
961	1	6.8	34.0	9.8

[a]Values obtained from Mitsumori et al. (1979). Results for males and females at 13 weeks are provided in Table B.1.
[b]Adjusted doses reported by the study authors.

Parentheses values = number of mice examined for that specific dose.
RBC: erythrocyte count; Ht: hematocrit; Hb: hemoglobin.
*$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table B.7. Results of Hematological Examination in SPF-ICR Mice Fed BCMEE in the Diet at 52 Weeks and 104 Weeks[a,b,c]

Sex and Dose Group (mg/kg-BW)	No. of Mice	Leukocyte						
		Total ($\times 10^6$/mm^3)	Differential %					
			Mean L	Mean N		Mean M	Mean E	Mean Others
				Stab.	Seg.			
Male–52 Weeks[d]								
0	7	6.5 ± 2.1	53.4	1.1	43.6	0.9	0.6	0.4
8.41	7	6.4 ± 1.5(6)	69.3(6)	2.2(6)	26.3*(6)	1.0(6)	1.2(6)	0(6)
40.1	7	5.5 ± 1.2	50.1	0.4	47.3	1.3	0.9	0
198	7	6.4 ± 3.8	72.6**	0.7	24.6**	0.3	1.7	0.1
927	7	5.7 ± 2.7	62.3	1.3	35.0	0.4	1.0	0
Male–104 Weeks[d]								
0	8	5.8 ± 2.7	55.8	4.0	37.1	0.5	2.4	0.3
8.41	5	7.6 ± 2.6	49.0	3.6	44.2	1.0	2.2	0
40.1	8	5.2 ± 1.6	52.6	1.9	40.9	0.9	3.8	0
198	5	4.0 ± 1.2	58.4	6.2	32.8	0.6	2.0	0
927	6	3.4 ± 1.3	52.2	3.3	41.8	1.2	1.5	0
Female–52 Weeks[d]								
0	7	4.3 ± 1.9	59.1	4.6	32.0	1.7	1.9	0.7
7.58	7	3.9 ± 0.8	63.9	4.1	30.7	0.3*	0.9	0.1
35.8	7	3.6 ± 1.3(5)	61.1	4.6	32.7	0**	1.4	0.1
194	7	3.9 ± 1.8(6)	62.5(6)	4.2(6)	31.3(6)	0.3*(6)	1.0(6)	0.7(6)
961	7	5.1 ± 1.6(4)	67.4	5.0	24.4	0.1*	2.4	0.6
Female–104 Weeks[d]								
0	5	4.5 ± 2.4	63.2	4.0	30.0	2.2	0.6	0
7.58	9	3.7 ± 1.4	49.1	5.3	40.3	2.8	1.3	1.1
35.8	9	2.8 ± 0.8(8)	47.7	7.6	42.7	1.1	0.7	0.3
194	7	3.1 ± 2.3	47.7*	3.0	46.0	1.6	1.6	0.1
961	1	3.2	86	1	13	0	0	0

[a]Mitsumori et al. (1979).
[b]Values are mean ± SD or means (differential leukocytes).
[c]Parentheses values: number of mice examined for that specific dose.
[d]Adjusted doses determined using digitized results for body weight and food intake from the graph provided by the authors; these doses were used in the BMD analysis for total leukocytes.

RBC: erythrocyte count; Ht: hematocrit; Hb: hemoglobin; L: Leukocytes; N: Neutrophils; M: Monocytes; E: Eosinophils.
*$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ based on Student's *t*-test.

Table B.8. Results of Blood Biochemical Examination in SPF-ICR Mice Fed BCMEE in the Diet for 104 Weeks[a, b]

Dose Group (mg/kg-BW)	No. of Animals	Mean GOT (K-unit)	Mean GPT (K-unit)	Mean ALP (K-A unit)	Mean Glucose (mg/dl)	Mean TP (g/dl)	Mean UN (mg/dl)	Mean CHO (mg/dl)	Mean Bil (mg/dl)
Male–52 Weeks									
0	7	62 ± 25	43 ± 49	2.3 ± 0.7	218 ± 34	5.3 ± 0.4	21 ± 4	125 ± 29	0.2 ± 0.22(5)
8.41	7	65 ± 21	57 ± 72	3.8 ± 1.5*	206 ± 50	5.2 ± 0.4	26 ± 6	112 ± 19	0.2 ± 0.19(6)
40.1	7	52 ± 14	27 ± 17	2.5 ± 1.1	196 ± 33	4.9 ± 0.4	29 ± 5**	119 ± 20	0.2 ± 0.05(6)
198	7	49 ± 14	22 ± 9	2.9 ± 1.0	184 ± 27	5.0 ± 0.2(6)	26 ± 4*	116 ± 9(6)	0.1 ± 0.08(6)
927	7	49 ± 13	18 ± 8	5.6 ± 2.3**	130 ± 35***	4.4 ± 0.3***	28 ± 8*	101 ± 28	0.1 ± 0(3)
Male–104 Weeks									
0	8	50 ± 10	37 ± 28	12.7 ± 25.6	143 ± 26	4.7 ± 0.7	24 ± 6	185 ± 97(7)	0.2 ± 0.11(7)
8.41	5	50 ± 8	31 ± 19	4.7 ± 0.9	166 ± 21	4.7 ± 0.2	27 ± 4	184 ± 68	0.2 ± 0.07
40.1	8	51 ± 5	29 ± 11	7.7 ± 7.1	164 ± 28	5.0 ± 0.3	28 ± 8	150 ± 30	0.2 ± 0.06
198	5	54 ± 8	24 ± 8	3.7 ± 1.0	169 ± 12	5.5 ± 0.2*	33 ± 11	139 ± 36	0.2 ± 0.07
927	6	59 ± 28	59 ± 87	6.5 ± 4.8	166 ± 35	4.9 ± 0.3	29 ± 5	129 ± 32	0.2 ± 0.04
Female–52 Weeks									
0	7	56 ± 6	18 ± 3(6)	4.0 ± 1.2(6)	172 ± 18(6)	5.4 ± 0.3(5)	22 ± 3(6)	86 ± 9(3)	-
7.58	7	67 ± 24	22 ± 11	3.2 ± 0.8	164 ± 15	5.4 ± 0.3	21 ± 7	78 ± 6(6)	-
35.8	7	122 ± 109	86 ± 117	4.0 ± 0.7	205 ± 42	5.0 ± 0.4*	25 ± 8	130 ± 74(5)	-
194	7	80 ± 47	23 ± 14	10.9 ± 16.3(6)	178 ± 18(6)	5.5 ± 0.3(6)	27 ± 9(6)	87 ± 13(4)	-
961	7	97 ± 54(5)	50 ± 6(5)	6.7 ± 1.5**(5)	124 ± 22**(5)	4.6 ± 0.3**(4)	32 ± 4**(5)	84 ± 18(4)	-

Table B.8. Results of Blood Biochemical Examination in SPF-ICR Mice Fed BCMEE in the Diet for 104 Weeks[a, b]

Dose Group (mg/kg-BW)	No. of Animals	Mean GOT (K-unit)	Mean GPT (K-unit)	Mean ALP (K-A unit)	Mean Glucose (mg/dl)	Mean TP (g/dl)	Mean UN (mg/dl)	Mean CHO (mg/dl)	Mean Bil (mg/dl)
Female–104 Weeks									
0	5	56 ± 21	41 ± 44	4.7 ± 1.5	152 ± 20	5.1 ± 0.3	26 ± 7	133 ± 51	0.2 ± 0.09
7.58	9	53 ± 12	33 ± 12	5.1 ± 2.3	142 ± 30	5.2 ± 0.4	25 ± 11	101 ± 27	0.2 ± 0.04
35.8	9	58 ± 22	37 ± 23(8)	5.0 ± 1.9	148 ± 17	5.1 ± 0.3	25 ± 8	120 ± 33(8)	0.2 ± 0.08(8)
194	7	60 ± 20	32 ± 14	4.6 ± 1.9	131 ± 29	5.1 ± 0.4	22 ± 6	102 ± 12	0.1 ± 0.05
961	1	42	17	3.6	129	4.6	28	93	0.1

[a]Values obtained from Mitsumori et al. (1979). Results for males and females at 13 weeks are provided in Table B.2.
[b]Parentheses values: number of mice examined for that specific dose.

GOT: glutamic-oxaloacetic transaminase; GPT: glutamic-pyruvic transaminase; ALP: alkaline phosphatase; TP: total protein; UN: urea nitrogen; CHO: cholesterol; Bil: bilirubin.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Table B.9. Absolute and Relative Organ Weights in SPF-ICR Mice Fed BCMEE in the Diet for 104 Weeks[a,b,c]

Dose Group (mg/kg-day)	No. of Animals	Body Weight (g)	Absolute and Relative Organ Weights (mg)[d]			
			Brain	Thyroid	Kidney	Heart
Male						
0	8	48.0 ± 6.4	485 ± 18 [1.02 ± 0.13]	3.1 ± 0.15(6) [0.006 ± 0.003]	796 ± 92 [1.67 ± 0.20]	212 ± 34 [0.44 ± 0.06]
8.41	5	43.7 ± 4.5	508 ± 9* [1.17 ± 0.11]	4.4 ± 0.2 [0.010 ± 0.001]	748 ± 78(4) [1.72 ± 0.08]	211 ± 22 [0.48 ± 0.02]
40.1	8	45.0 ± 3.2	495 ± 14 [1.11 ± 0.09]	3.1 ± 1.1(7) [0.007 ± 0.003]	742 ± 74 [1.65 ± 0.17]	203 ± 24 [0.45 ± 0.05]
198	5	44.2 ± 2.7	526 ± 27** [1.19 ± 0.06]	4.9 ± 0.7* [0.011 ± 0.002]	845 ± 89 [1.92 ± 0.25]	224 ± 29 [0.51 ± 0.10]
927	6	37.2 ± 2.6**	485 ± 38 [1.30 ± 0.07]	3.2 ± 1.1 [0.009 ± 0.003]	636 ± 21** [1.72 ± 0.14]	180 ± 21 [0.48 ± 0.05]
Female						
0	5	42.1 ± 6.5	518 ± 27 [1.25 ± 0.19]	3.1 ± 1(3) [0.008 ± 0.002]	506 ± 48(4) [1.22 ± 0.33]	179 ± 23 [0.44 ± 0.10]
7.58	9	38.1 ± 6.4	510 ± 45 [1.37 ± 0.27]	3.8 ± 0.7 [0.010 ± 0.003]	468 ± 58 [1.27 ± 0.32]	151 ± 23* [0.40 ± 0.08]
35.8	9	42.2 ± 2.6	517 ± 33 [1.23 ± 0.07]	3.4 ± 1.0 [0.008 ± 0.002]	474 ± 59 [1.12 ± 0.13]	157 ± 29 [0.37 ± 0.06]
194	7	36.5 ± 2.9	510 ± 35 [1.41 ± 0.15]	3.6 ± 1.0 [0.010 ± 0.003]	477 ± 67 [1.31 ± 0.17]	157 ± 18 [0.43 ± 0.06]
961	1	28.6	440 [1.54]	4.7 [0.016]	384 [1.34]	128 [0.45]

[a]Values obtained from Mitsumori et al. (1979).
[b]Values are means ± SD.
[c]Parentheses values: number of mice examined for that specific dose.
[d]Relative organ weight (100 × organ weight/body weight); presented in brackets [ ].

*$p < 0.05$, **$p < 0.01$.

Table B.10. Incidence of Nonneoplastic Histological Findings in Male and Female SPF-ICR mice Fed BCMEE for 104 Weeks[a,b]

Nonneoplastic Lesion	Dose Group									
	Male (Dose Groups, ppm)					Female (Dose Groups, ppm)				
	0	80	400	2000	10,000	0	80	400	2000	10,000
Spleen: Hemosiderin Deposition	1/56	0/56	0/56	3/56	17/56	2/56	3/56	1/56	8/56	17/56
Spleen: Increased Extramedullary Hematopoiesis	9/56	10/56	7/56	6/56	10/56	9/56	7/56	6/56	6/56	7/56

[a]Values obtained from Mitsumori et al. (1979).
[b]Groups of 56 mice/sex/group were examined. This includes animals sacrificed by design and animals euthanized in extremis or found dead.

APPENDIX C. BMD MODELING OUTPUTS FOR BCMEE

Table C.1. BMD Modeling Output Summary for BCMEE[a]

Endpoint	Species	Sex	Figure	Model	Homogeneity Variance *p*-Value	Goodness-of-Fit *p*-Value[b]	AIC for Fitted Model	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)	Conclusions
Hemoglobin (Hb)	Mouse	F	C.1	Power (nonconstant variance)	0.009	0.974	12.21	308.39	243.29	Lowest AIC Poor variance model
Hemoglobin (Hb)	Mouse	M	C.2	Hill (nonconstant variance)	0.381	0.041	27.03	0.00	0.00	Lowest BMDL p-score 4 < 0.1 Wrong variance model hit bound (n = 1)
Hematocrit (Ht)	Mouse	F	C.3.1	Linear (constant variance)	0.260	0.829	76.09	367.54	188.75	Lowest AIC Lowest BMDL
			C.3.2	Polynomial (constant variance)	0.260	0.829	76.09	367.54	188.75	Lowest AIC Lowest BMDL Maximum order beta = 0 β2 = 0 β3 = 0
			C.3.3	Power (constant variance)	0.260	0.829	76.09	367.54	188.75	Lowest AIC Lowest BMDL hit bound (power = 1)
Hematocrit (Ht)	Mouse	M	C.4	Hill (constant variance)	0.700	0.043	92.05	0.00	0.00	Lowest AIC Lowest BMDL p-score 4 < 0.1
Erythrocytes (RBC)	Mouse	F	C.5	Power (nonconstant variance)	0.726	0.352	-0.53	1032.70	307.91	Lowest AIC BMD/BMDL ratio > 3 Wrong variance model hit bound (power = 1)
Erythrocytes (RBC)	Mouse	M	C.6	Hill (constant variance)	0.906	0.038	6.95	0.00	0.00	Lowest AIC Lowest BMDL p-score 4 < 0.1

Table C.1. BMD Modeling Output Summary for BCMEE[a]

Endpoint	Species	Sex	Figure	Model	Homogeneity Variance *p*-Value	Goodness-of-Fit *p*-Value[b]	AIC for Fitted Model	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)	Conclusions
	Mouse	F		Data were not modeled because the values for all doses were the same						
Total Leukocytes (WBC)	Mouse	F	C.7.1	Linear (nonconstant variance)	0.003	0.113	90.52	311.05	204.12	Lowest AIC Lowest BMDL
			C.7.2	Polynomial (nonconstant variance)	0.003	0.113	90.52	311.05	204.12	Lowest AIC Lowest BMDL Maximum order beta = 0 β2 = 0 β3 = 0
			C.7.3	Power (nonconstant variance)	0.003	0.113	90.52	311.05	204.12	Lowest AIC Lowest BMDL hit bound (power = 1)
Total Leukocytes (WBC)	Mouse	M	C.8	Hill (constant variance)	0.632	NA	49.27	7.56	0.00	Lowest AIC Lowest BMDL p-score 4 < 0.1 BMD/BMDL ratio > 3
Total Leukocytes (WBC)—includes high dose	Mouse	F	C.9.1	Linear (nonconstant variance)	0.000	0.002	109.52	1020.34	713.21	Lowest AIC p-score 4 < 0.1
			C.9.2	Polynomial (nonconstant variance)	0.000	0.002	109.52	1020.34	713.21	Lowest AIC p-score 4 < 0.1 β3 = 0
			C.9.3	Power (nonconstant variance)	0.000	0.002	109.52	1020.34	713.21	Lowest AIC p-score 4 < 0.1 hit bound (power = 1)

Table C.1. BMD Modeling Output Summary for BCMEE[a]

Endpoint	Species	Sex	Figure	Model	Homogeneity Variance *p*-Value	Goodness-of-Fit *p*-Value[b]	AIC for Fitted Model	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)	Conclusions
Total Leukocytes (WBC)— includes high dose	Mouse	M	C.10	Hill (constant variance)	0.068	0.014	58.99	5.11	1.71	Lowest BMDL p-score 4 < 0.1 Poor variance model Wrong variance model hit bound (n = 1)

[a]All endpoints modeled from data in Mitsumori et al. (1979).
[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; 1SD = 1 standard deviation; M = Male; F = Female.

Models Considered for the Derivation of a Subchronic p-RfD for Bis(2-chloro-1-methylethyl)ether

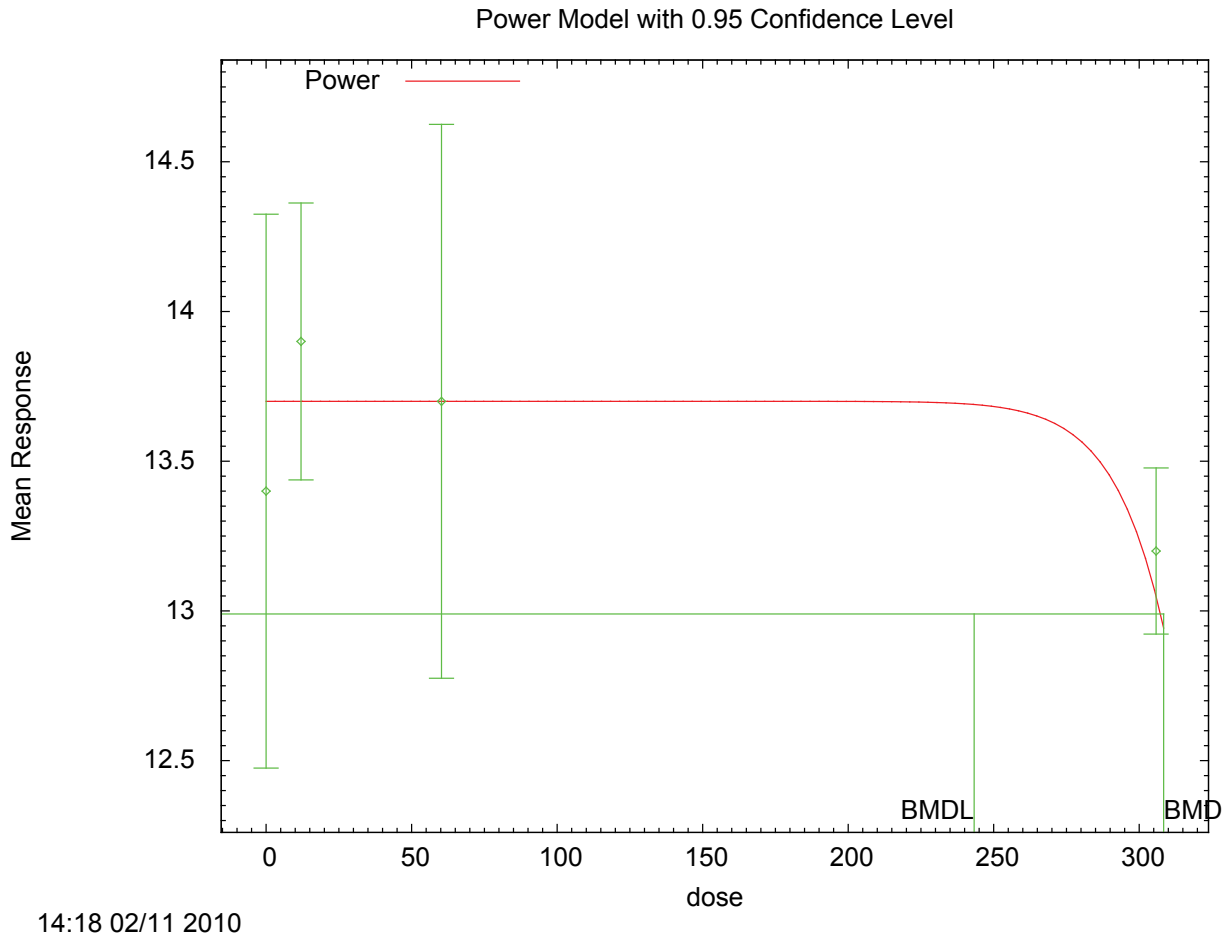

Figure C.1. Power Nonconstant Variance BMD Model for Female Hemoglobin Data (Mitsumori et al., 1979)

Text Output for Power Nonconstant Variance BMD Model for Female Hemoglobin Data (Mitsumori et al., 1979)

```
 ================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\BCMEE\Mitsumori_1979_13wk_Hb_female_Power_1.(d)
        Gnuplot Plotting File:
C:\BCMEE\Mitsumori_1979_13wk_Hb_female_Power_1.plt
                                          Thu Feb 11 14:18:24 2010
 ================================================================

 Table3_13wks_Hb_females
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =    -0.536143
                            rho =            0
                        control =         13.2
                          slope =      1.17467
                          power =    -0.208394


          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 )

                lalpha      control        slope

    lalpha           1        -0.52         0.22

   control       -0.52            1        -0.66

     slope        0.22        -0.66            1


                                Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha         -47.7331         0.320638            -48.3616
-47.1047
            rho               18               NA
        control          13.7454         0.164149             13.4237
14.0672
          slope    -1.18724e-045     3.95895e-046       -1.96318e-045       -
4.11304e-046
          power               18               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	7	13.4	13.7	1	0.756	-1.21
11.99	7	13.9	13.7	0.5	0.756	0.541
60.26	7	13.7	13.7	1	0.756	-0.159
305.8	7	13.2	13.1	0.3	0.489	0.562

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	-4.335882	5	18.671765
A2	1.437949	8	13.124101
A3	-2.994674	6	17.989348
fitted	-3.106005	3	12.212010
R	-6.226495	2	16.452991

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	15.3289	6	0.01785
Test 2	11.5477	3	0.009105
Test 3	8.86525	2	0.01188
Test 4	0.222662	3	0.9739

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 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 = 308.389

BMDL = 243.285

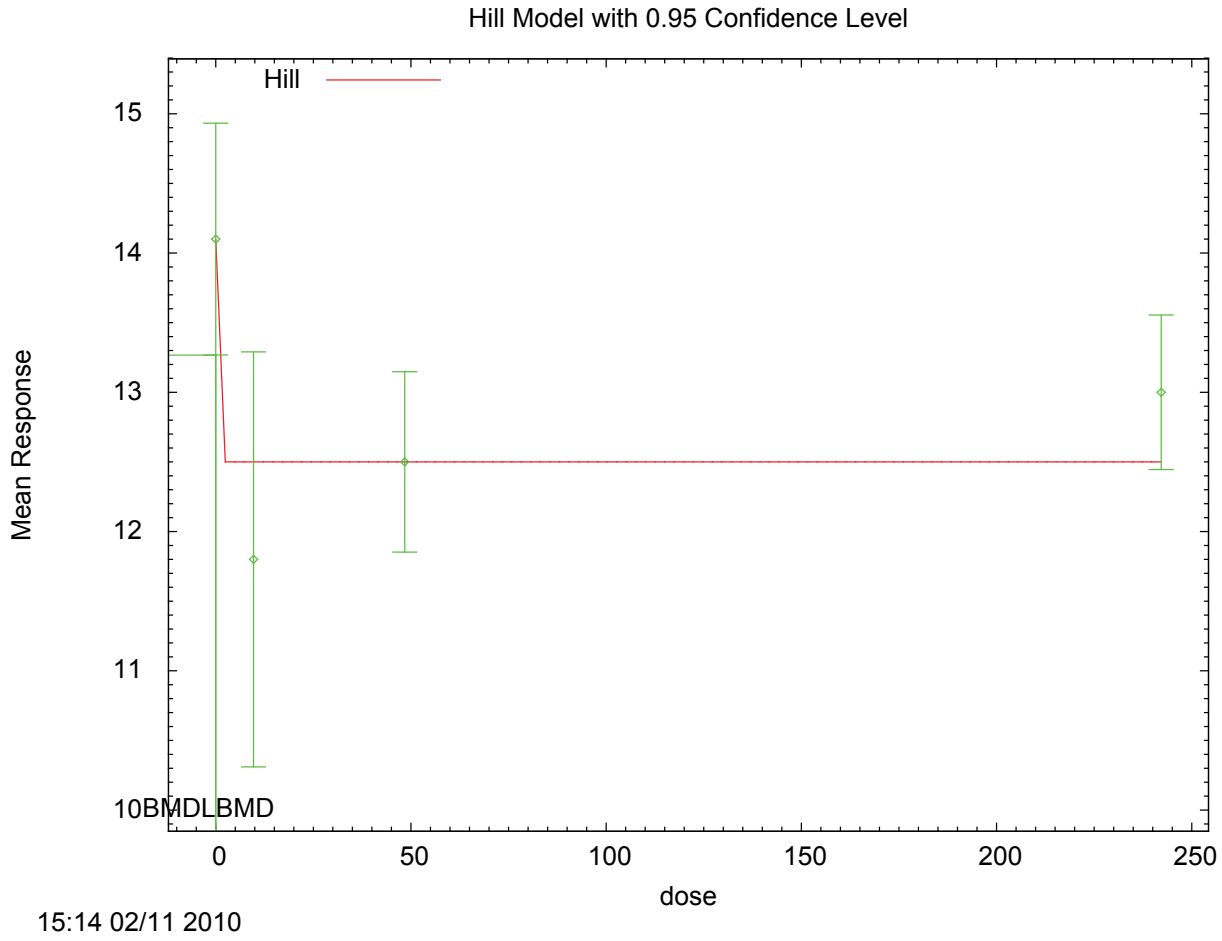

Figure C.2. Hill Nonconstant Variance BMD Model for Male Hemoglobin Data (Mitsumori et al., 1979)

Text Output for Hill Nonconstant Variance BMD Model for Male Hemoglobin Data (Mitsumori et al., 1979)

```
 ================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\BCMEE\Mitsumori_1979_13wk_Hb_male_Hill_1.(d)
        Gnuplot Plotting File:
C:\BCMEE\Mitsumori_1979_13wk_Hb_male_Hill_1.plt
                                          Thu Feb 11 15:14:59 2010
 ================================================================

 Table3_13wks_Hb_males
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =    -0.336109
                            rho =            0
                      intercept =         14.1
                              v =         -2.3
                              n =     0.179559
                              k =        4.845


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -n    -k
                 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

    lalpha            1           -1       -0.039        0.049

       rho           -1            1        0.039       -0.049

 intercept       -0.039        0.039            1        -0.84

         v        0.049       -0.049        -0.84            1


                                Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha          2.54557          13.2991            -23.5202
28.6113
            rho         -1.09987          5.19753            -11.2868
9.0871
      intercept             14.1         0.314934             13.4827
14.7173
              v             -1.6         0.375368            -2.33571
-0.864292
              n                1              NA
              k      2.4218e-013              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	7	14.1	14.1	0.9	0.833	1.87e-008
9.69	5	11.8	12.5	1.2	0.89	-1.76
48.42	7	12.5	12.5	0.7	0.89	-2.78e-008
242.2	7	13	12.5	0.6	0.89	1.49

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	-6.458884	5	22.917768
A2	-4.925139	8	25.850278
A3	-6.321516	6	24.643032
fitted	-9.515180	4	27.030360
R	-16.105402	2	36.210805

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	22.3605	6	0.001042
Test 2	3.06749	3	0.3813
Test 3	2.79275	2	0.2475
Test 4	6.38733	2	0.04102

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 greater than .1. Consider running a homogeneous model

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

Benchmark Dose Computation

Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 2.63176e-013

BMDL = 2.63176e-013

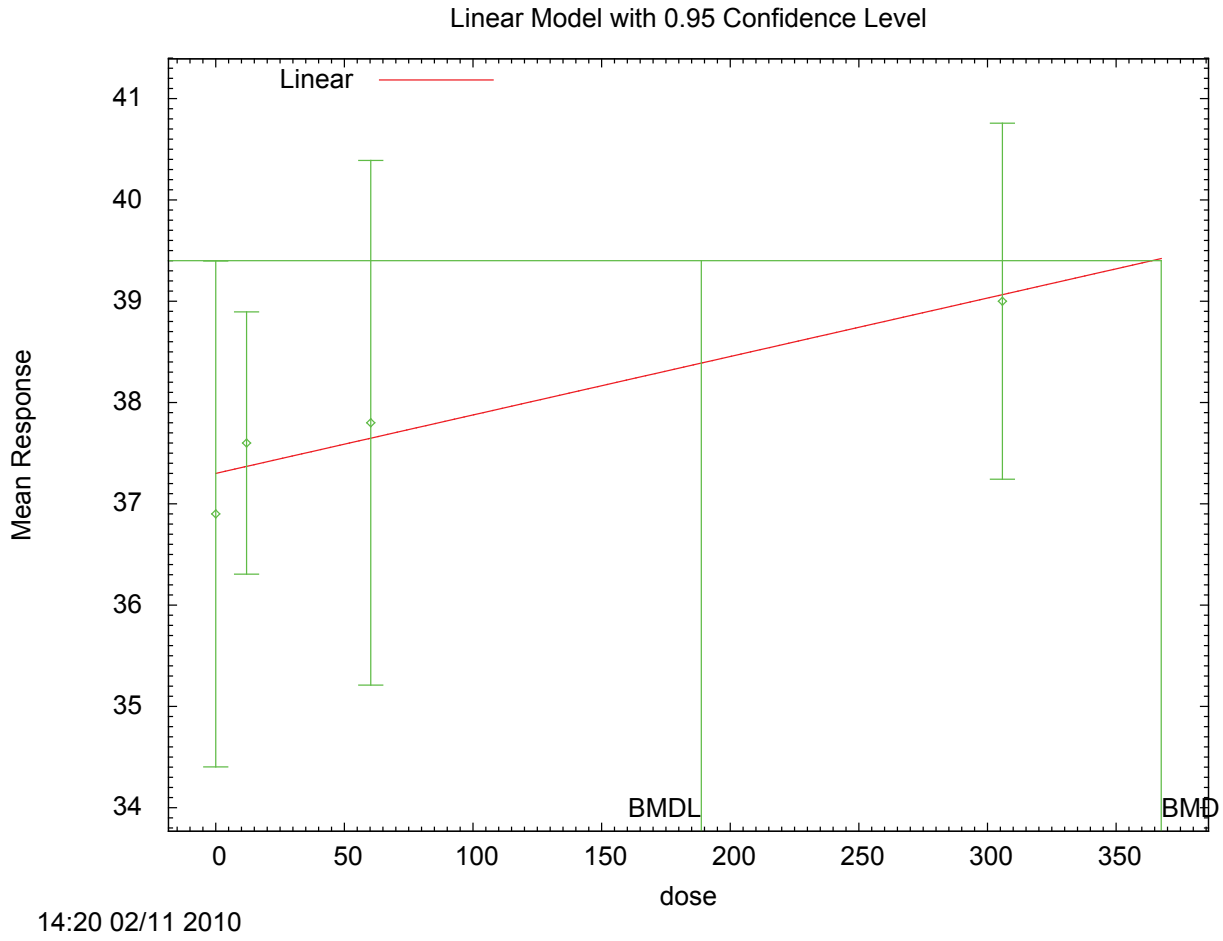

Figure C.3.1. Linear Constant Variance BMD Model for Female Hematocrit Data (Mitsumori et al., 1979)

Text Output for Linear Constant Variance BMD Model for Female Hematocrit Data (Mitsumori et al., 1979)

```
 ================================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File:
C:\BCMEE\Mitsumori_1979_13wk_Ht_female_LinearCV_1.(d)
        Gnuplot Plotting File:
C:\BCMEE\Mitsumori_1979_13wk_Ht_female_LinearCV_1.plt
                                          Thu Feb 11 14:20:08 2010
 ================================================================================

 Table3_13wks_Ht_females
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 5.175
rho = 0 Specified
beta_0 = 37.2798
beta_1 = 0.0057687

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	8.1e-010	4.1e-013
beta_0	8.1e-010	1	-0.61
beta_1	4.1e-013	-0.61	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	4.49546	1.20146	2.14064	6.85028
beta_0	37.2798	0.503728	36.2925	38.2671
beta_1	0.0057687	0.00322994	-0.000561875	0.0120993

Table of Data and Estimated Values of Interest

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

0	7	36.9	37.3	2.7	2.12	-0.474
11.99	7	37.6	37.3	1.4	2.12	0.313
60.26	7	37.8	37.6	2.8	2.12	0.215
305.8	7	39	39	1.9	2.12	-0.0547

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	-34.855641	5	79.711282
A2	-32.850272	8	81.700543
A3	-34.855641	5	79.711282
fitted	-35.042945	3	76.085889
R	-36.553365	2	77.106729

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	7.40619	6	0.2849
Test 2	4.01074	3	0.2603
Test 3	4.01074	3	0.2603
Test 4	0.374607	2	0.8292

The p-value for Test 1 is greater than .05. There may not be a diffence between responses and/or variances among the dose levels

```
Modelling the data with a dose/response curve may not be appropriate

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


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 =        367.544


            BMDL =        188.749
```

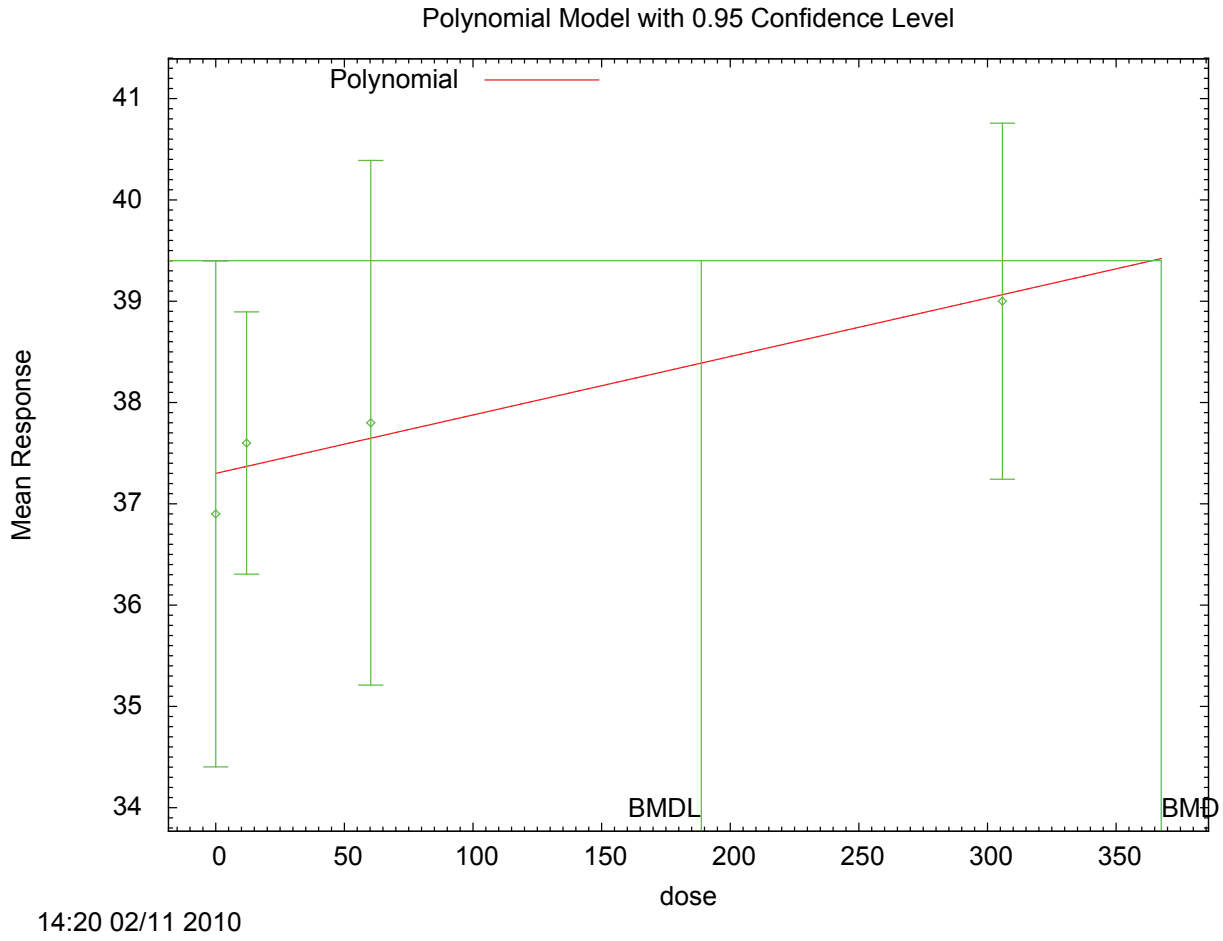

Figure C.3.2. Polynomial Constant Variance BMD Model for Female Hematocrit Data (Mitsumori et al., 1979)

Text Output for Polynomial Constant Variance BMD Model for Female Hematocrit Data (Mitsumori et al., 1979)

```
 ================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\BCMEE\Mitsumori_1979_13wk_Ht_female_PolyCV_1.(d)
        Gnuplot Plotting File:
C:\BCMEE\Mitsumori_1979_13wk_Ht_female_PolyCV_1.plt
                                        Thu Feb 11 14:20:08 2010
 ================================================================

 Table3_13wks_Ht_females
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =        5.175
                          rho =            0   Specified
                       beta_0 =         36.9
                       beta_1 =    0.0713065
                       beta_2 =            0
                       beta_3 = 2.95163e-006


          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    -4.1e-008     2.1e-008

    beta_0    -4.1e-008            1        -0.61

    beta_1     2.1e-008        -0.61            1


                              Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          4.49546          1.20146             2.14064
6.85028
         beta_0          37.2798         0.503728             36.2925
38.2671
         beta_1        0.0057687       0.00322994        -0.000561875
0.0120993
         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	7	36.9	37.3	2.7	2.12	-0.474
11.99	7	37.6	37.3	1.4	2.12	0.313
60.26	7	37.8	37.6	2.8	2.12	0.215
305.8	7	39	39	1.9	2.12	-0.0547

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	-34.855641	5	79.711282
A2	-32.850272	8	81.700543
A3	-34.855641	5	79.711282
fitted	-35.042945	3	76.085889
R	-36.553365	2	77.106729

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	7.40619	6	0.2849
Test 2	4.01074	3	0.2603
Test 3	4.01074	3	0.2603
Test 4	0.374607	2	0.8292

The p-value for Test 1 is greater than .05. There may not be a
diffence between responses and/or variances among the dose levels
Modelling the data with a dose/response curve may not be appropriate

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

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 = 367.544

BMDL = 188.749

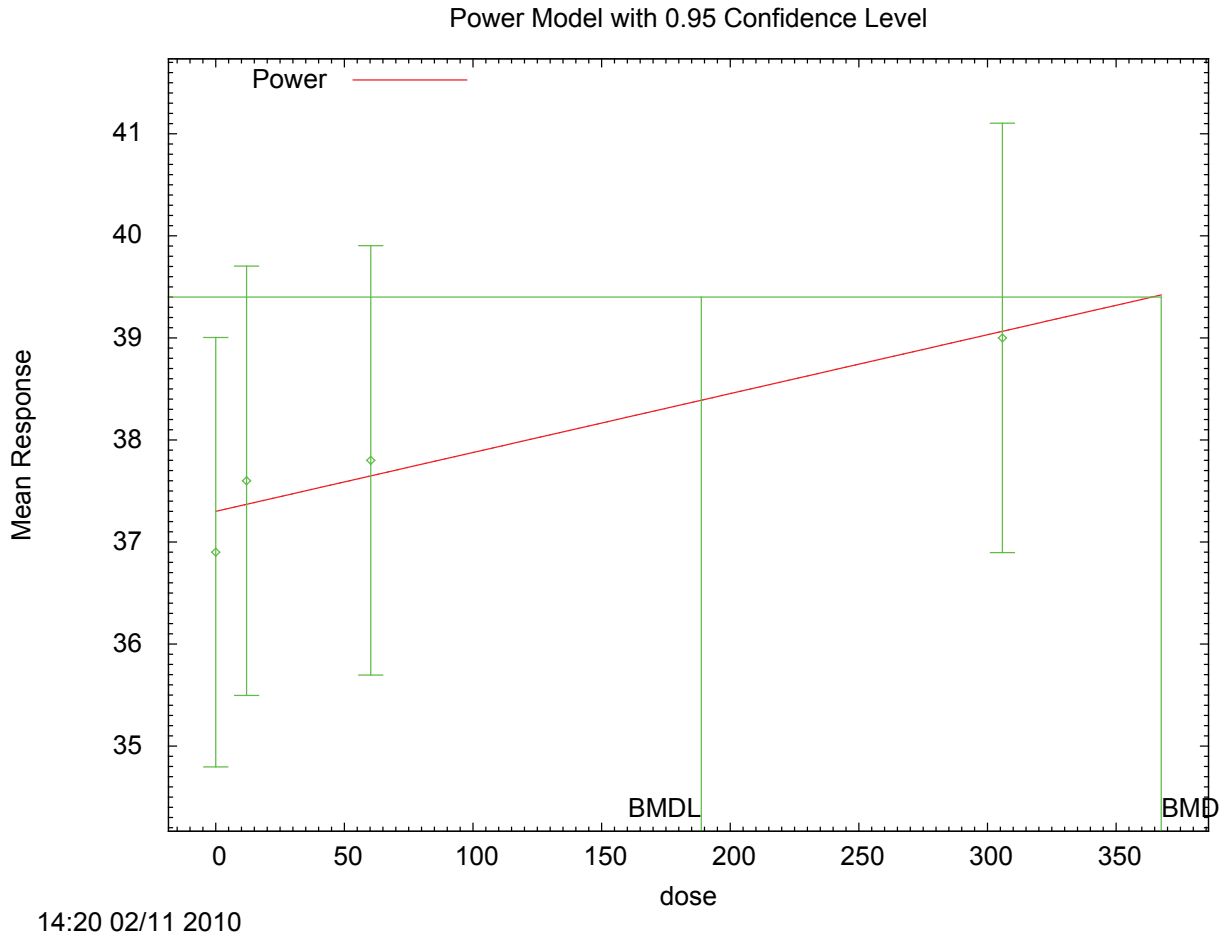

Figure C.3.3. Power Constant Variance Model for Female Hematocrit Data (Mitsumori et al., 1979)

Text Output for Power Constant Variance Model for Female Hematocrit Data (Mitsumori et al., 1979)

```
 ================================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\BCMEE\Mitsumori_1979_13wk_Ht_female_PowerCV_1.(d)
        Gnuplot Plotting File:
C:\BCMEE\Mitsumori_1979_13wk_Ht_female_PowerCV_1.plt
                                          Thu Feb 11 14:20:08 2010
 ================================================================================

 Table3_13wks_Ht_females
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =        5.175
                            rho =            0   Specified
                        control =         36.9
                          slope =     0.301101
                          power =     0.339379


           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     8.4e-010    -3.3e-009

   control     8.4e-010            1        -0.61

     slope    -3.3e-009        -0.61            1


                                Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          4.49546          1.20146             2.14064
6.85028
        control          37.2798         0.503728             36.2925
38.2671
          slope        0.0057687       0.00322994        -0.000561875
0.0120993
          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	7	36.9	37.3	2.7	2.12	-0.474
11.99	7	37.6	37.3	1.4	2.12	0.313
60.26	7	37.8	37.6	2.8	2.12	0.215
305.8	7	39	39	1.9	2.12	-0.0547

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	-34.855641	5	79.711282
A2	-32.850272	8	81.700543
A3	-34.855641	5	79.711282
fitted	-35.042945	3	76.085889
R	-36.553365	2	77.106729

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	7.40619	6	0.2849
Test 2	4.01074	3	0.2603
Test 3	4.01074	3	0.2603

```
   Test 4             0.374607          2          0.8292

The p-value for Test 1 is greater than .05.  There may not be a
diffence between responses and/or variances among the dose levels
Modelling the data with a dose/response curve may not be appropriate

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


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 = 367.544


            BMDL = 188.749
```

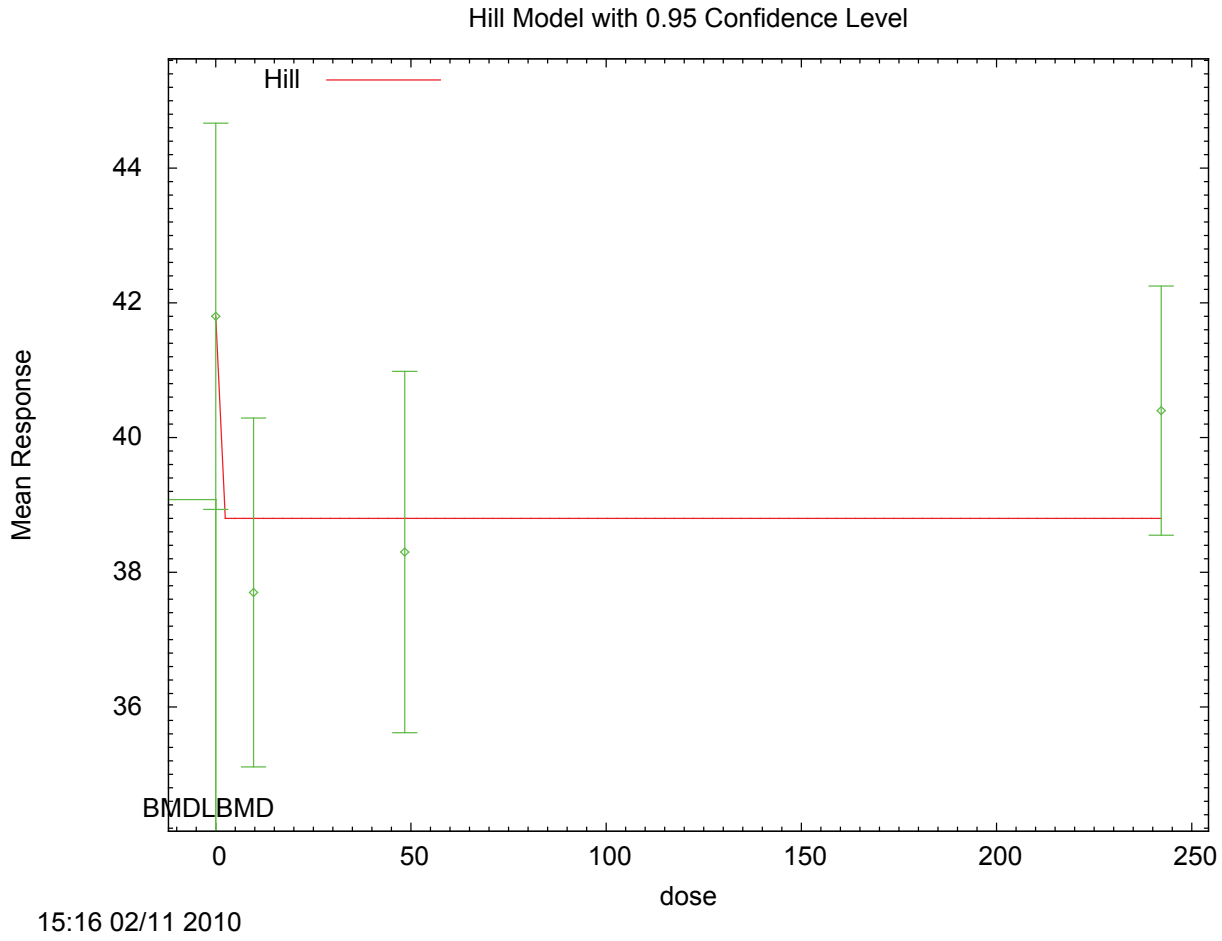

Figure C.4. Hill Constant Variance BMD Model for Male Hematocrit Data (Mitsumori et al., 1979)

Text Output for Hill Constant Variance BMD Model for Male Hematocrit Data (Mitsumori et al., 1979)

```
 ================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\BCMEE\Mitsumori_1979_13wk_Ht_male_HillCV_1.(d)
        Gnuplot Plotting File:
C:\BCMEE\Mitsumori_1979_13wk_Ht_male_HillCV_1.plt
                                        Thu Feb 11 15:16:07 2010
 ================================================================

 Table3_13wks_Ht_males
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =        7.465
                           rho =            0   Specified
                     intercept =         41.8
                             v =            0
                             n =            1
                             k =            0


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho    -k
                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            n

     alpha            1    -1.2e-008     2.7e-009    -6.2e-007

 intercept    -1.2e-008            1        -0.87       8e-007

         v     2.7e-009        -0.87            1    -2.3e-007

         n    -6.2e-007       8e-007    -2.3e-007            1


                                Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          7.40357          1.97869             3.52541
11.2817
      intercept             41.8          1.02842             39.7843
43.8157
              v               -3          1.18752             -5.3275
-0.672503
              n          1.31004            20690            -40550.4
40553
              k     2.4218e-013               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	7	41.8	41.8	3.1	2.72	4.39e-008
9.69	7	37.7	38.8	2.8	2.72	-1.07
48.42	7	38.3	38.8	2.9	2.72	-0.486
242.2	7	40.4	38.8	2	2.72	1.56

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	-39.985047	5	89.970093
A2	-39.274047	8	94.548093
A3	-39.985047	5	89.970093
fitted	-42.027475	4	92.054950
R	-44.902099	2	93.804198

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	11.2561	6	0.08078
Test 2	1.422	3	0.7004
Test 3	1.422	3	0.7004
Test 4	4.08486	1	0.04327

The p-value for Test 1 is greater than .05. There may not be a
diffence between responses and/or variances among the dose levels
Modelling the data with a dose/response curve may not be appropriate

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

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

Benchmark Dose Computation

Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 1.37755e-012

BMDL = 1.37755e-012

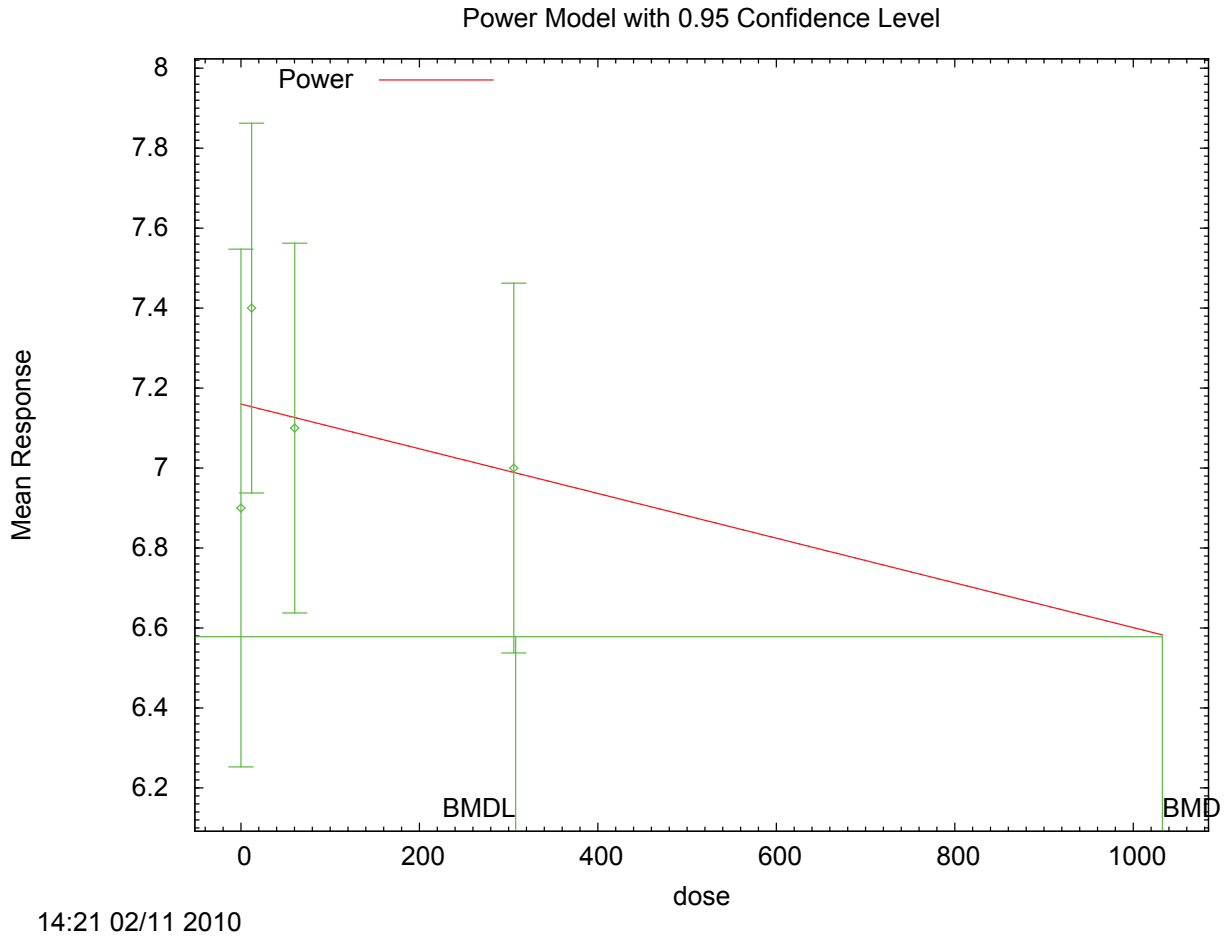

Figure C.5. Power Nonconstant Variance BMD Model for Female Erythrocyte Data (Mitsumori et al., 1979)

Text Output for Power Nonconstant Variance BMD Model for Female Erythrocyte Data (Mitsumori et al., 1979)

```
 ================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\BCMEE\Mitsumori_1979_13wk_RBC_female_Power_1.(d)
        Gnuplot Plotting File:
C:\BCMEE\Mitsumori_1979_13wk_RBC_female_Power_1.plt
                                        Thu Feb 11 14:21:49 2010
 ================================================================

 Table3_13wks_RBC_females
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =	-1.17118
rho =	0
control =	6.9
slope =	1.65359
power =	-0.496845

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)

	lalpha	control	slope
lalpha	1	-0.63	0.11
control	-0.63	1	-0.56
slope	0.11	-0.56	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-36.5206	0.372436	-37.2506	-35.7907
rho	18	NA		
control	7.15536	0.122337	6.91558	7.39513
slope	-0.000558929	0.000554705	-0.00164613	0.000528273
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	7	6.9	7.16	0.7	0.577	-1.17
11.99	7	7.4	7.15	0.5	0.572	1.16
60.26	7	7.1	7.12	0.5	0.553	-0.104
305.8	7	7	6.98	0.5	0.464	0.0887

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	4.554671	5	0.890657
A2	5.210925	8	5.578150
A3	4.903201	6	2.193599
fitted	3.266896	3	-0.533793
R	2.822326	2	-1.644651

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	4.7772	6	0.5727
Test 2	1.31251	3	0.7262

```
   Test 3             0.615449          2          0.7351
   Test 4              3.27261          3          0.3515

The p-value for Test 1 is greater than .05.  There may not be a
diffence between responses and/or variances among the dose levels
Modelling the data with a dose/response curve may not be appropriate

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

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 = 1032.7


            BMDL = 307.908
```

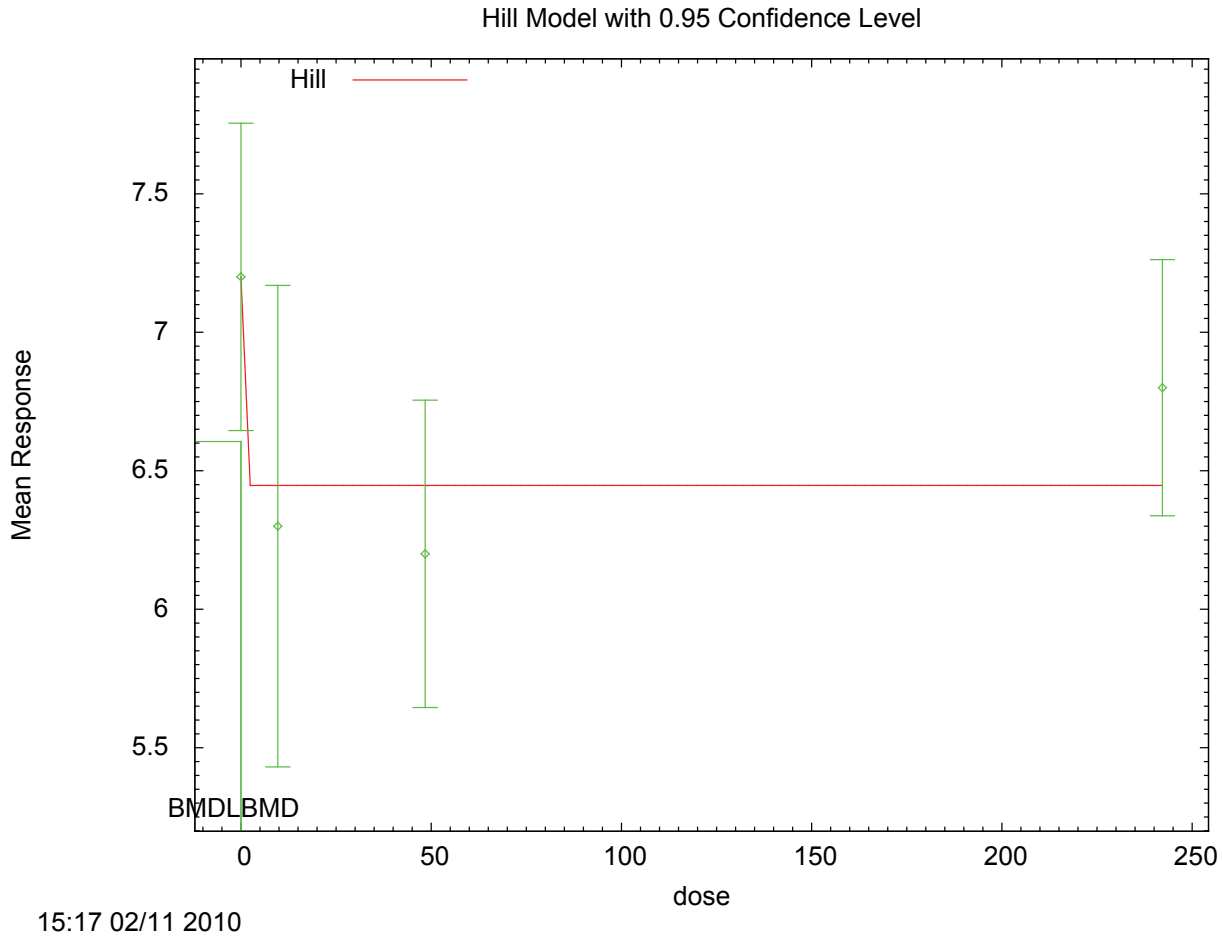

Figure C.6. Hill Constant Variance BMD Model for Male Erythrocyte Data (Mitsumori et al., 1979)

Text Output for Hill Constant Variance BMD Model for Male Erythrocyte Data (Mitsumori et al., 1979)

```
 ================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\BCMEE\Mitsumori_1979_13wk_RBC_male_HillCV_1.(d)
        Gnuplot Plotting File:
C:\BCMEE\Mitsumori_1979_13wk_RBC_male_HillCV_1.plt
                                        Thu Feb 11 15:17:29 2010
 ================================================================

 Table3_13wks_RBC_males
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =     0.353636
                          rho =            0   Specified
                    intercept =          7.2
                            v =            0
                            n =            1
                            k =            0


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho    -k
                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            n

     alpha            1    -2.2e-009     1.5e-009    -4.2e-009

 intercept    -2.2e-009            1        -0.85     4.5e-009

         v     1.5e-009        -0.85            1     1.7e-009

         n    -4.2e-009     4.5e-009     1.7e-009            1


                              Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          0.35336        0.0980045            0.161275
0.545446
      intercept              7.2         0.224678             6.75964
7.64036
              v        -0.752632         0.262827            -1.26776
-0.2375
              n          1.76817     3.17576e+006       -6.22437e+006
6.22437e+006
              k      2.4218e-013               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	7	7.2	7.2	0.6	0.594	7.91e-009
9.69	5	6.3	6.45	0.7	0.594	-0.554
48.42	7	6.2	6.45	0.6	0.594	-1.1
242.2	7	6.8	6.45	0.5	0.594	1.57

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	2.685023	5	4.629955
A2	2.963405	8	10.073191
A3	2.685023	5	4.629955
fitted	0.523471	4	6.953058
R	-3.040290	2	10.080580

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	12.0074	6	0.0618
Test 2	0.556764	3	0.9063
Test 3	0.556764	3	0.9063
Test 4	4.3231	1	0.0376

The p-value for Test 1 is greater than .05. There may not be a
diffence between responses and/or variances among the dose levels
Modelling the data with a dose/response curve may not be appropriate

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

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

Benchmark Dose Computation

Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 5.12028e-013

BMDL = 5.12028e-013

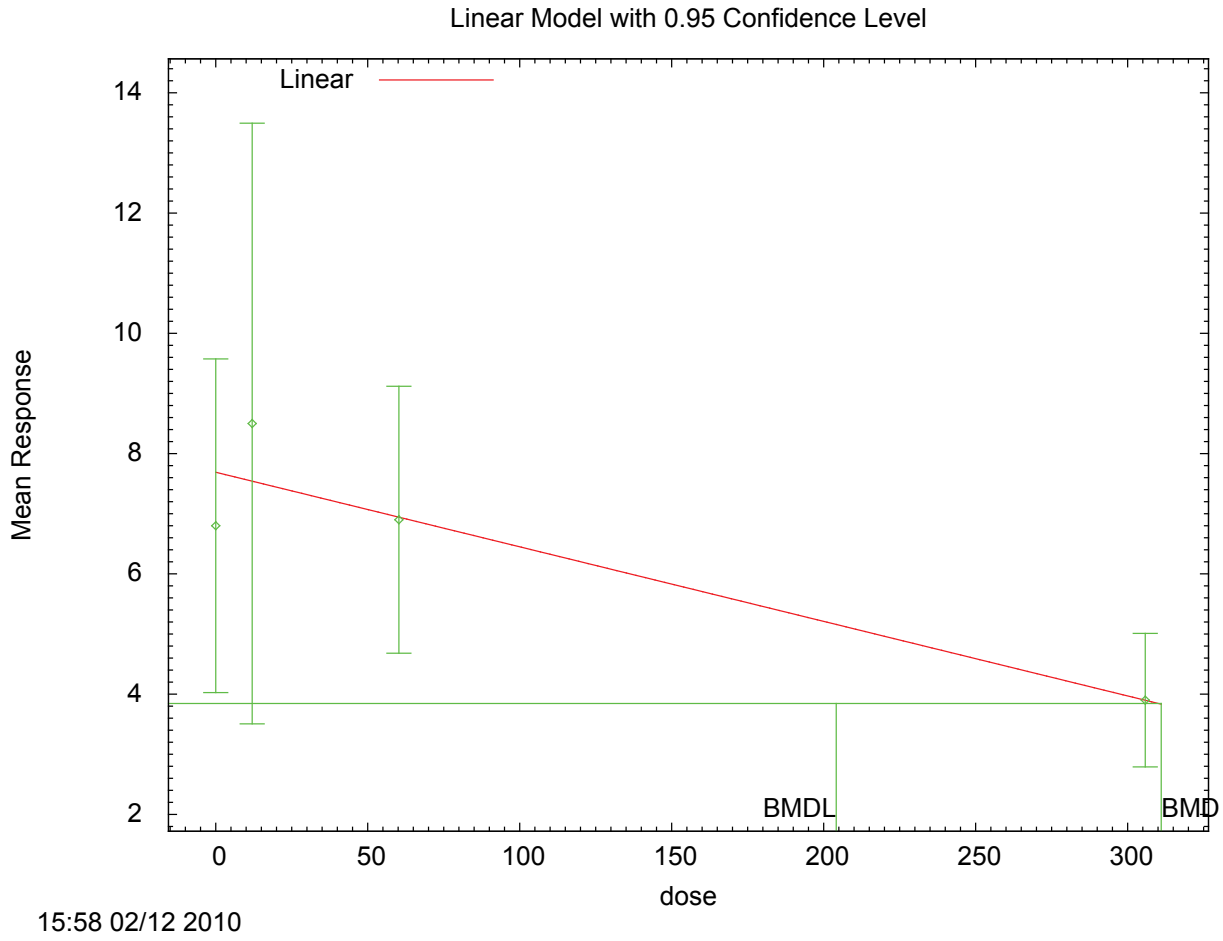

Figure C.7.1. Linear Nonconstant Variance BMD Model for Female Leukocyte Data (Mitsumori et al., 1979)

Text Output for Linear Nonconstant Variance BMD Model for Female Leukocyte Data (Mitsumori et al., 1979)

```
 ================================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\BCMEE\Mitsumori_1979_13wk_WBC_female_Linear_1.(d)
        Gnuplot Plotting File:
C:\BCMEE\Mitsumori_1979_13wk_WBC_female_Linear_1.plt
                                          Fri Feb 12 15:58:18 2010
 ================================================================================

 Table3_13wks_WBC_females
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =	2.42834
rho =	0
beta_0 =	7.6864
beta_1 =	-0.0122883

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	-0.037	0.052
rho	-0.99	1	0.036	-0.05
beta_0	-0.037	0.036	1	-0.91
beta_1	0.052	-0.05	-0.91	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-4.94521	1.74128	-8.35806	-1.53236
rho	3.74478	0.934776	1.91266	5.57691
beta_0	7.69041	0.854003	6.0166	9.36423
beta_1	-0.0123644	0.00317559	-0.0185885	-0.00614039

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	7	6.8	7.69	3	3.85	-0.613

11.99	7	8.5	7.54	5.4	3.71	0.683
60.26	7	6.9	6.95	2.4	3.18	-0.0377
305.8	7	3.9	3.91	1.2	1.08	-0.0229

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	-45.838599	5	101.677197
A2	-38.741501	8	93.483002
A3	-39.074696	6	90.149391
fitted	-41.257910	4	90.515820
R	-49.328666	2	102.657331

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	21.1743	6	0.001707
Test 2	14.1942	3	0.002652
Test 3	0.666389	2	0.7166
Test 4	4.36643	2	0.1127

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 =         311.05


             BMDL =        204.122
```

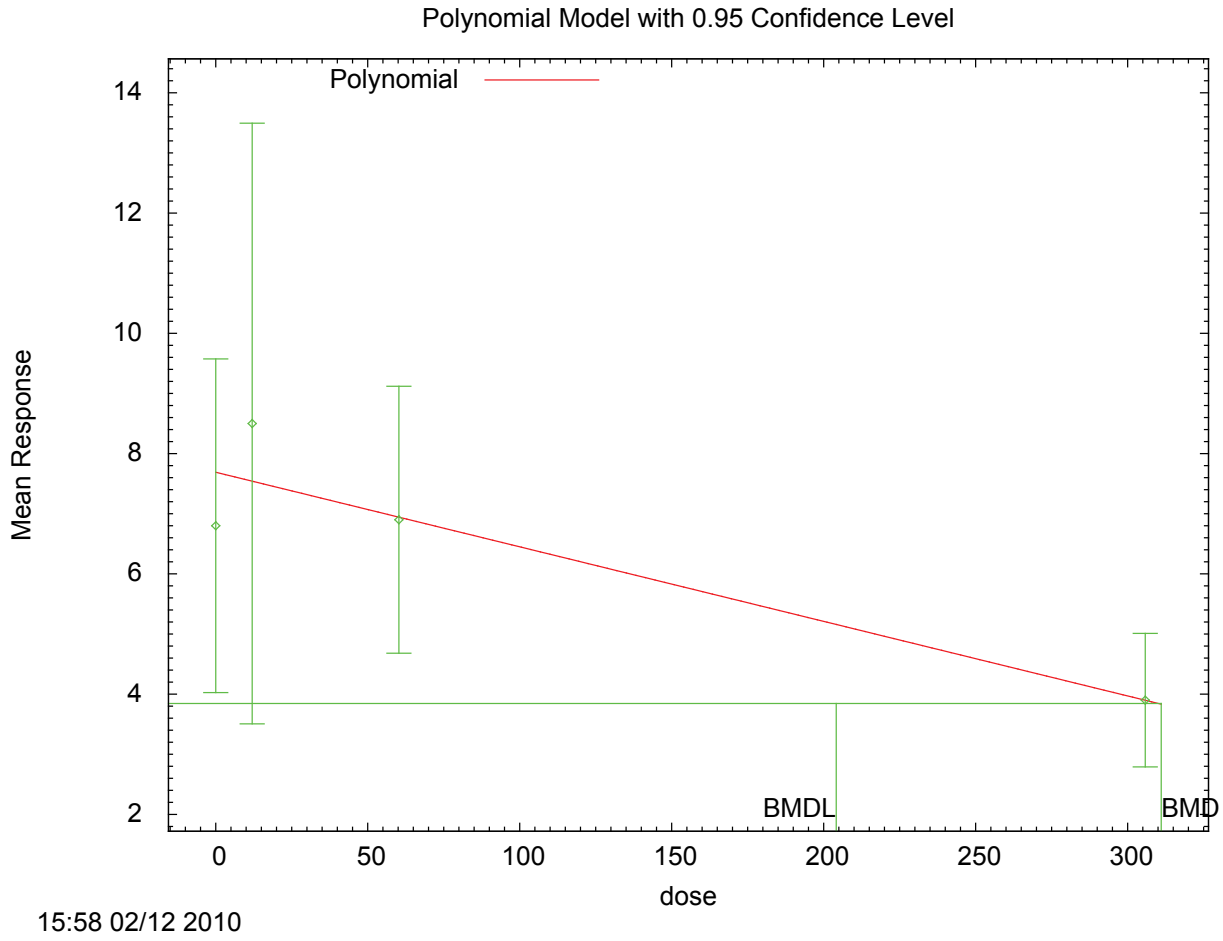

Figure C.7.2. Polynomial Nonconstant Variance BMD Model for Female Leukocyte Data (Mitsumori et al., 1979)

Text Output for Polynomial Nonconstant Variance BMD Model for Female Leukocyte Data (Mitsumori et al., 1979)

```
 ================================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\BCMEE\Mitsumori_1979_13wk_WBC_female_Poly_1.(d)
        Gnuplot Plotting File:
C:\BCMEE\Mitsumori_1979_13wk_WBC_female_Poly_1.plt
                                          Fri Feb 12 15:58:19 2010
 ================================================================================

 Table3_13wks_WBC_females
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 negative
   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 =      2.42834
                            rho =            0
                         beta_0 =          6.8
                         beta_1 =            0
                         beta_2 =  -0.00360565
                         beta_3 =            0


           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       -0.037        0.052

       rho        -0.99            1        0.036        -0.05

    beta_0       -0.037        0.036            1        -0.91

    beta_1        0.052        -0.05        -0.91            1


                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha         -4.94521          1.74128            -8.35806
-1.53236
            rho          3.74478         0.934776             1.91266
5.57691
         beta_0          7.69041         0.854003              6.0166
9.36423
         beta_1       -0.0123644       0.00317559          -0.0185885
-0.00614039
         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	7	6.8	7.69	3	3.85	-0.613
11.99	7	8.5	7.54	5.4	3.71	0.683
60.26	7	6.9	6.95	2.4	3.18	-0.0377
305.8	7	3.9	3.91	1.2	1.08	-0.0229

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	-45.838599	5	101.677197
A2	-38.741501	8	93.483002
A3	-39.074696	6	90.149391
fitted	-41.257910	4	90.515820
R	-49.328666	2	102.657331

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	21.1743	6	0.001707
Test 2	14.1942	3	0.002652
Test 3	0.666389	2	0.7166
Test 4	4.36643	2	0.1127

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 = 311.05

BMDL = 204.122

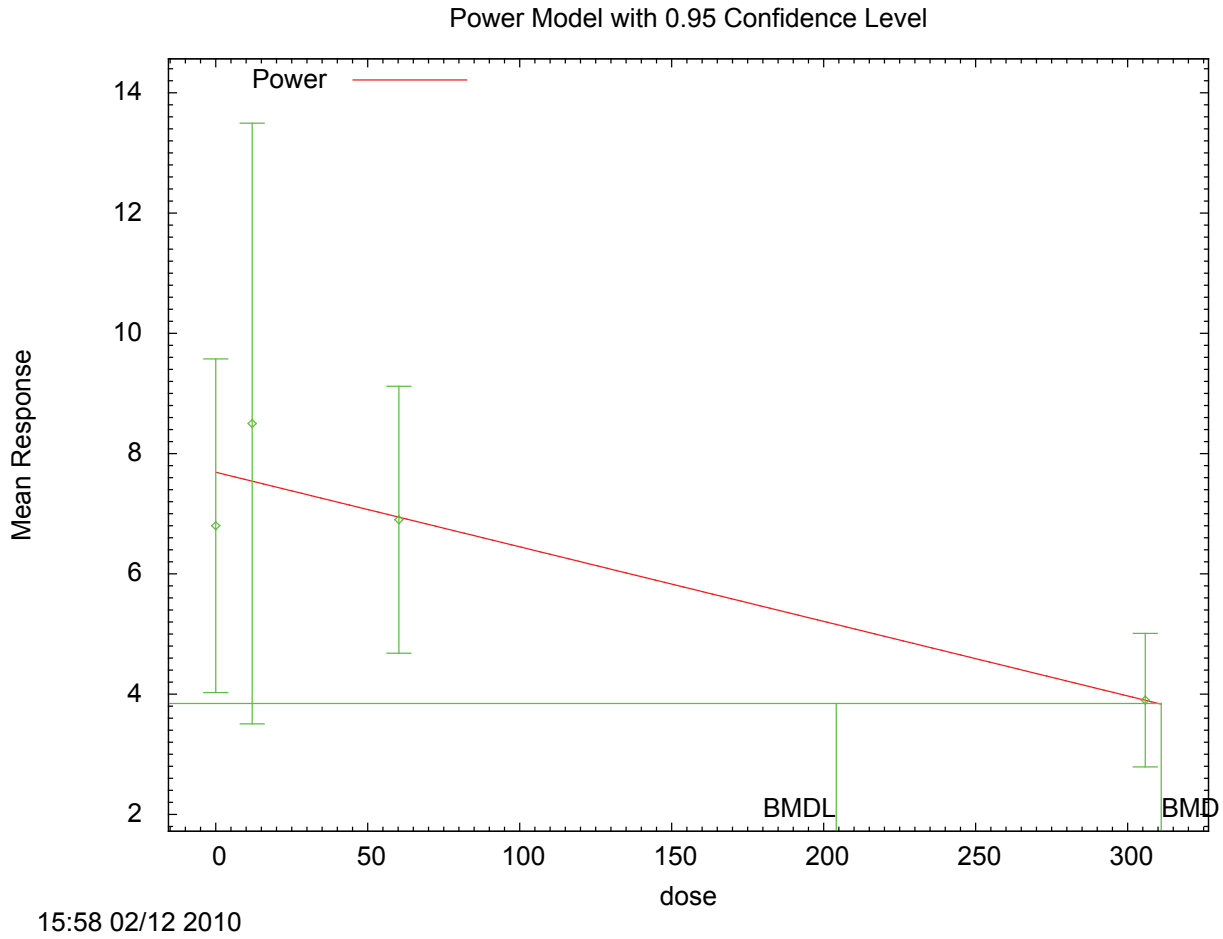

Figure C.7.3. Power Nonconstant Variance BMD Model for Female Leukocyte Data (Mitsumori et al., 1979)

Text Output for Power Nonconstant Variance BMD Model for Female Leukocyte Data (Mitsumori et al., 1979)

```
 ================================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\BCMEE\Mitsumori_1979_13wk_WBC_female_Power_1.(d)
        Gnuplot Plotting File:
C:\BCMEE\Mitsumori_1979_13wk_WBC_female_Power_1.plt
                                          Fri Feb 12 15:58:19 2010
 ================================================================================

 Table3_13wks_WBC_females
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =      2.42834
                            rho =            0
                        control =          3.9
                          slope =      8.87895
                          power =    -0.264738


          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        -0.98         0.39        -0.57

       rho        -0.98            1        -0.51         0.65

   control         0.39        -0.51            1         -0.9

     slope        -0.57         0.65         -0.9            1


                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha         -4.94521          2.28079           -9.41547
-0.474956
            rho          3.74478          1.27322            1.24931
6.24025
        control          7.69041           0.8493            6.02582
9.35501
          slope       -0.0123644       0.00313495         -0.0185088
-0.00622005
          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	7	6.8	7.69	3	3.85	-0.613
11.99	7	8.5	7.54	5.4	3.71	0.683
60.26	7	6.9	6.95	2.4	3.18	-0.0377
305.8	7	3.9	3.91	1.2	1.08	-0.0229

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	-45.838599	5	101.677197
A2	-38.741501	8	93.483002
A3	-39.074696	6	90.149391
fitted	-41.257910	4	90.515820
R	-49.328666	2	102.657331

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	21.1743	6	0.001707
Test 2	14.1942	3	0.002652
Test 3	0.666389	2	0.7166
Test 4	4.36643	2	0.1127

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 = 311.05

BMDL = 204.122

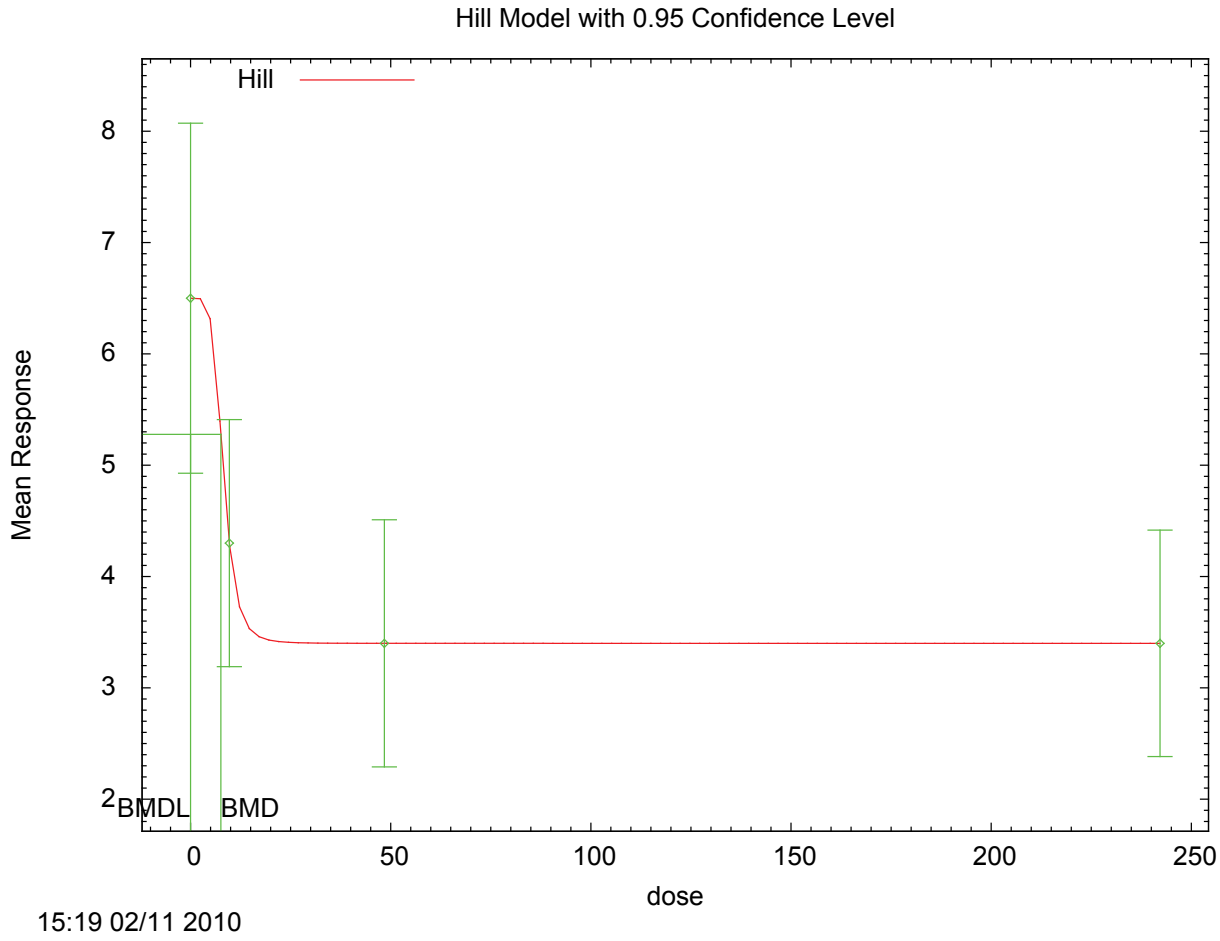

Figure C.8. Hill Constant Variance BMD Model for Male Leukocyte Data (Mitsumori et al., 1979)

Text Output for Hill Constant Variance BMD Model for Male Leukocyte Data (Mitsumori et al., 1979)

```
 ================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\BCMEE\Mitsumori_1979_13wk_WBC_male_HillCV_1.(d)
        Gnuplot Plotting File:
C:\BCMEE\Mitsumori_1979_13wk_WBC_male_HillCV_1.plt
                                          Thu Feb 11 15:19:43 2010
 ================================================================

 Table3_13wks_WBC_males
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =        1.745
                            rho =            0   Specified
                      intercept =          6.5
                              v =         -3.1
                              n =      2.55229
                              k =      6.82705


           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    intercept            v            n            k

     alpha             1     3.5e-008    -2.7e-005    -6.9e-005    -6.9e-005

 intercept     3.5e-008            1        -0.75    -4.7e-005      -0.0011

         v    -2.7e-005        -0.75            1         0.38         0.38

         n    -6.9e-005    -4.7e-005         0.38            1            1

         k    -6.9e-005      -0.0011         0.38            1            1


                              Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          1.49571         0.399746            0.712226
2.2792
      intercept              6.5         0.462248             5.59401
7.40599
              v         -3.10012         0.613029            -4.30163
-1.8986
              n           5.3383          1236.86            -2418.86
2429.53
```

```
             k          8.19631          317.522            -614.136
630.528


     Table of Data and Estimated Values of Interest

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

    0     7        6.5          6.5          1.7         1.22     -1.26e-007
 9.69     7        4.3          4.3          1.2         1.22      3.73e-007
48.42     7        3.4          3.4          1.2         1.22      -0.000256
242.2     7        3.4          3.4          1.1         1.22       0.000255

Degrees of freedom for Test A3 vs fitted <= 0


 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          -19.636454           5      49.272909
            A2          -18.775961           8      53.551923
            A3          -19.636454           5      49.272909
         fitted         -19.636454           5      49.272909
             R          -29.842855           2      63.685710


                 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	22.1338	6	0.001145
Test 2	1.72099	3	0.6323
Test 3	1.72099	3	0.6323
Test 4	1.30476e-007	0	NA

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 greater than .1. A homogeneous variance model appears to be appropriate here

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

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-Square
test for fit is not valid

Benchmark Dose Computation

Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 7.5642

BMDL = 7.43034e-006

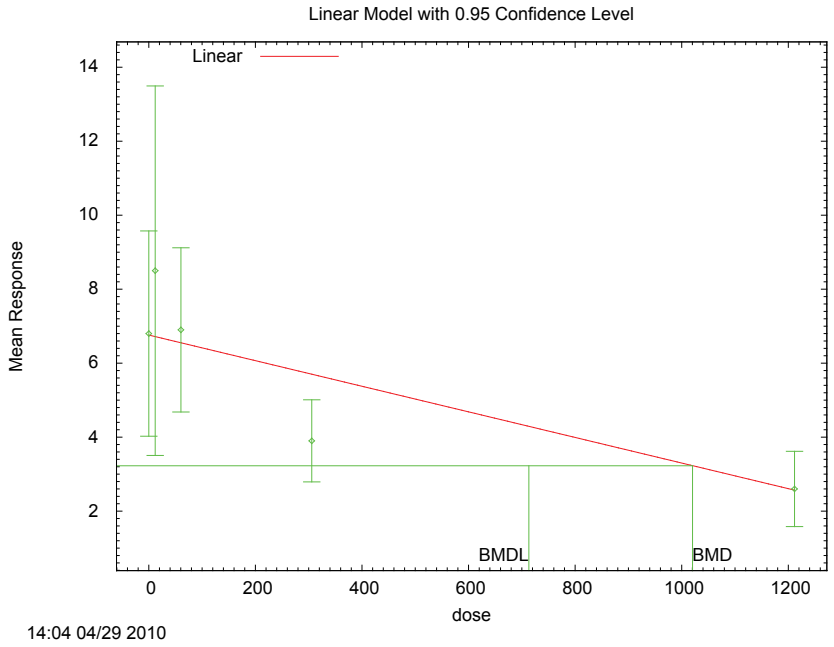

Figure C.9.1. Linear Nonconstant Variance Model for Female Mouse Total Leukocyte Data (includes high dose) (Mitsumori et al., 1979)

Text Output for Linear Nonconstant Variance Model for Female Mouse Total Leukocyte Data (includes high dose) (Mitsumori et al., 1979)

```
 ===============================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File:
C:\BCMEE\Mitsumori_1979_13wk_WBC_f_hidose_Linear_1.(d)
        Gnuplot Plotting File:
C:\BCMEE\Mitsumori_1979_13wk_WBC_f_hidose_Linear_1.plt
                                          Thu Apr 29 14:04:39 2010
 ===============================================================================

 Table3_13wks_WBC_females_including_high_dose
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 5
   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 = 2.23152
rho = 0
beta_0 = 7.01907
beta_1 = -0.00402286

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.97	0.047	-0.041
rho	-0.97	1	-0.051	0.047
beta_0	0.047	-0.051	1	-0.88
beta_1	-0.041	0.047	-0.88	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-2.54051	1.05508	-4.60843	-0.472588
rho	2.65055	0.613422	1.44827	3.85284
beta_0	6.76048	0.683554	5.42074	8.10022
beta_1	-0.0034637	0.000659636	-0.00475656	-0.00217083

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	7	6.8	6.76	3	3.53	0.0296
11.99	7	8.5	6.72	5.4	3.51	1.34
60.26	7	6.9	6.55	2.4	3.39	0.272
305.8	7	3.9	5.7	1.2	2.82	-1.69
1212	7	2.6	2.56	1.1	0.978	0.0987

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	-53.853939	6	119.707879
A2	-42.369145	10	104.738290
A3	-43.457904	7	100.915808
fitted	-50.761704	4	109.523407
R	-61.908764	2	127.817528

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	39.0792	8	<.0001
Test 2	22.9696	4	0.0001284
Test 3	2.17752	3	0.5364
Test 4	14.6076	3	0.002185

```
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
```

```
            Benchmark Dose Computation

Specified effect =            1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =       1020.34


            BMDL =         713.21
```

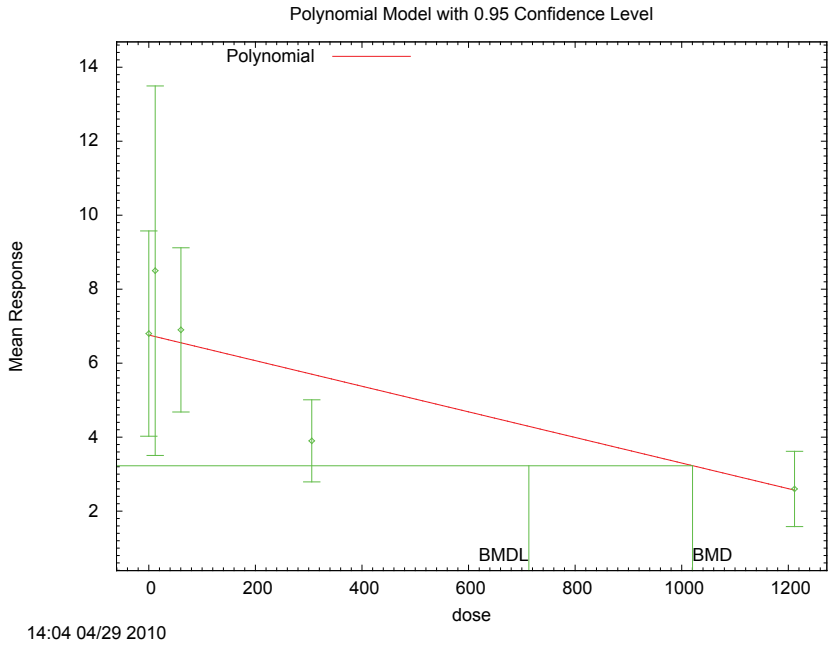

Figure C.9.2. Polynomial Nonconstant Variance Model for Female Mouse Total Leukocyte Data (includes high dose) (Mitsumori et al., 1979)

Text Output for Polynomial Nonconstant Variance Model for Female Mouse Total Leukocyte Data (includes high dose) (Mitsumori et al., 1979)

```
================================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\BCMEE\Mitsumori_1979_13wk_WBC_f_hidose_Poly_1.(d)
        Gnuplot Plotting File:
C:\BCMEE\Mitsumori_1979_13wk_WBC_f_hidose_Poly_1.plt
                                          Thu Apr 29 14:04:39 2010
 ================================================================================

 Table3_13wks_WBC_females_including_high_dose
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

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

   Total number of dose groups = 5
   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 =	2.23152
rho =	0
beta_0 =	6.8
beta_1 =	0
beta_2 =	-0.00378976
beta_3 =	0
beta_4 =	-8.06922e-009

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -beta_2 -beta_3 -beta_4
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	-0.97	0.047	-0.041
rho	-0.97	1	-0.051	0.047
beta_0	0.047	-0.051	1	-0.88
beta_1	-0.041	0.047	-0.88	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-2.54051	1.05508	-4.60843	-0.472586
rho	2.65055	0.613422	1.44827	3.85284
beta_0	6.76048	0.683554	5.42074	8.10022
beta_1	-0.0034637	0.000659636	-0.00475656	-0.00217084
beta_2	-7.67647e-138	NA		
beta_3	0	NA		
beta_4	-5.22843e-144	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	7	6.8	6.76	3	3.53	0.0296
11.99	7	8.5	6.72	5.4	3.51	1.34
60.26	7	6.9	6.55	2.4	3.39	0.272
305.8	7	3.9	5.7	1.2	2.82	-1.69
1212	7	2.6	2.56	1.1	0.978	0.0987

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	-53.853939	6	119.707879
A2	-42.369145	10	104.738290
A3	-43.457904	7	100.915808
fitted	-50.761704	4	109.523407
R	-61.908764	2	127.817528

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	39.0792	8	<.0001
Test 2	22.9696	4	0.0001284
Test 3	2.17752	3	0.5364
Test 4	14.6076	3	0.002185

```
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


             Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        1020.34


            BMDL =         713.21
```

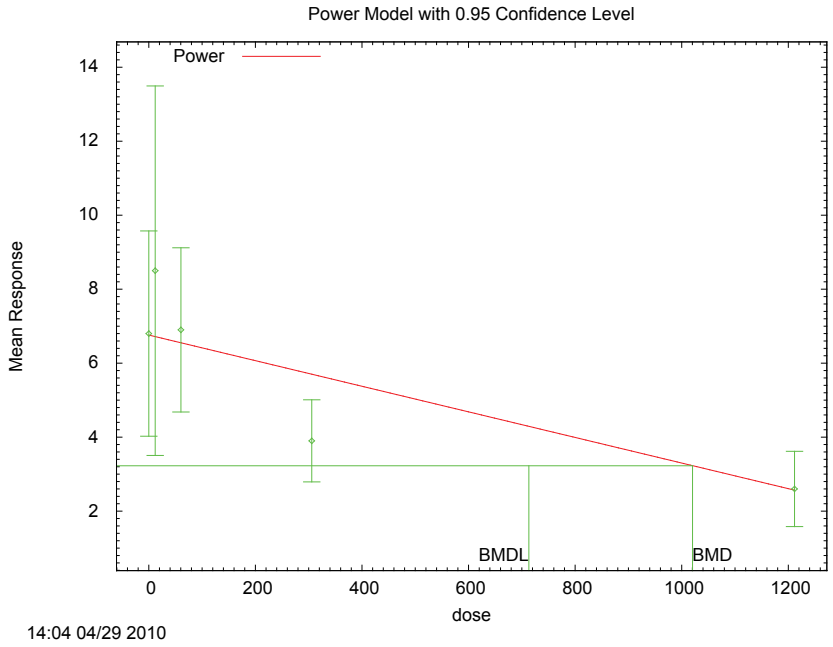

Figure C.9.3. Power Nonconstant Variance Model for Female Mouse Total Leukocyte Data (includes high dose) (Mitsumori et al., 1979)

Text Output for Power Nonconstant Variance Model for Female Mouse Total Leukocyte Data (includes high dose) (Mitsumori et al., 1979)

```
 ================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File:
C:\BCMEE\Mitsumori_1979_13wk_WBC_f_hidose_Power_1.(d)
        Gnuplot Plotting File:
C:\BCMEE\Mitsumori_1979_13wk_WBC_f_hidose_Power_1.plt
                                        Thu Apr 29 14:04:40 2010
 ================================================================

 Table3_13wks_WBC_females_including_high_dose
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 5
   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 = 2.23152
rho = 0
control = 2.6
slope = 21.803
power = -0.467282

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	-0.97	0.3	-0.53
rho	-0.97	1	-0.44	0.63
control	0.3	-0.44	1	-0.89
slope	-0.53	0.63	-0.89	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-2.54051	1.39065	-5.26614	0.18512
rho	2.65055	0.834998	1.01399	4.28712
control	6.76048	0.695291	5.39773	8.12322
slope	-0.0034637	0.000668727	-0.00477438	-0.00215302
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	7	6.8	6.76	3	3.53	0.0296
11.99	7	8.5	6.72	5.4	3.51	1.34
60.26	7	6.9	6.55	2.4	3.39	0.272
305.8	7	3.9	5.7	1.2	2.82	-1.69
1212	7	2.6	2.56	1.1	0.978	0.0987

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	-53.853939	6	119.707879
A2	-42.369145	10	104.738290
A3	-43.457904	7	100.915808
fitted	-50.761704	4	109.523407
R	-61.908764	2	127.817528

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	39.0792	8	<.0001
Test 2	22.9696	4	0.0001284
Test 3	2.17752	3	0.5364
Test 4	14.6076	3	0.002185

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


               Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 1020.34


            BMDL = 713.21
```

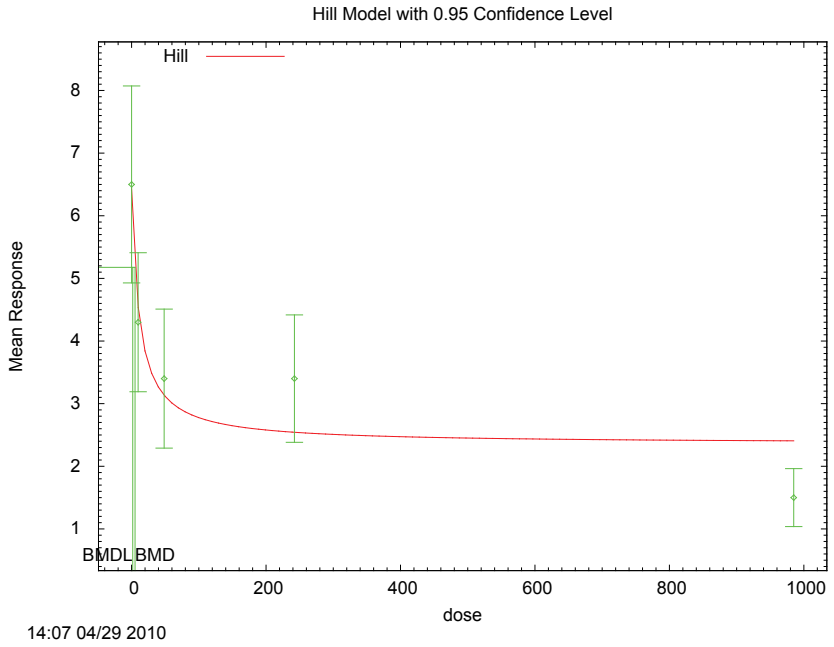

Figure C.10. Hill Constant Variance Model for Male Mouse Total Leukocyte Data (includes high dose) (Mitsumori et al., 1979)

Text Output for Hill Constant Variance Model for Male Mouse Total Leukocyte Data (includes high dose) (Mitsumori et al., 1979)

```
================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File:
C:\BCMEE\Mitsumori_1979_13wk_WBC_m_hidose_HillCV_1.(d)
        Gnuplot Plotting File:
C:\BCMEE\Mitsumori_1979_13wk_WBC_m_hidose_HillCV_1.plt
                                        Thu Apr 29 14:07:28 2010
 ================================================================

 Table3_13wks_WBC_males_with_high_dose
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 5
   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 =	1.446	
rho =	0	Specified
intercept =	6.5	
v =	-5	
n =	0.377889	
k =	22.6	

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	1.8e-007	4.6e-007	-6e-007
intercept	1.8e-007	1	-0.76	-0.5
v	4.6e-007	-0.76	1	0.016
k	-6e-007	-0.5	0.016	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	1.57915	0.37749	0.839287	2.31902
intercept	6.43276	0.490376	5.47164	7.39388
v	-4.06868	0.571192	-5.18819	-2.94916
n	1	NA		
k	11.4417	7.40277	-3.06747	25.9509

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	7	6.5	6.43	1.7	1.26	0.142
9.69	7	4.3	4.57	1.2	1.26	-0.562
48.42	7	3.4	3.14	1.2	1.26	0.544
242.2	7	3.4	2.55	1.1	1.26	1.79
984.9	7	1.5	2.41	0.5	1.26	-1.92

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	-21.256383	6	54.512766
A2	-16.884404	10	53.768807
A3	-21.256383	6	54.512766
fitted	-25.495563	4	58.991126
R	-41.177561	2	86.355121

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	48.5863	8	<.0001
Test 2	8.74396	4	0.06783
Test 3	8.74396	4	0.06783
Test 4	8.47836	2	0.01442

```
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 =        5.11308

            BMDL =       1.71103
```

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