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Provisional Peer-Reviewed Toxicity Values for

Benzotrichloride
(CASRN 98-07-7)

Superfund Health Risk Technical Support Center
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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 BENZOTRICHLORIDE (CASRN 98-07-7)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents and appropriate use of this PPRTV assessment should 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).

INTRODUCTION

Benzotrichloride, or α,α,α-trichlorotoluene, is extensively used as an intermediate in the manufacture of benzoyl chloride-substituted benzophenones and in the preparation of dyes and pigments, ultraviolet stabilizers, and other derivatives (IARC, 1982; NTP, 2005). In addition, benzotrichloride is also used in the manufacture of benzotrifluoride, hydroxybenzophenone, antiseptics, and antimicrobial agents (NTP, 2005). Benzotrichloride is an unstable chemical and hydrolyzes rapidly to benzoic acid and hydrochloric acid in the presence of moisture (U.S. EPA, 1982). The empirical formula for benzotrichloride is $C_7H_5Cl_{13}$ (see Figure 1). A table of physicochemical properties is provided below (see Table 1). In this document, unless otherwise noted, "statistical significant" denotes a $p < 0.05$.

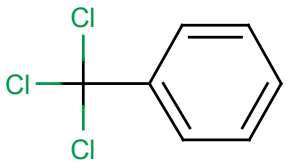


Figure 1. Benzotrichloride

Table 1. Physicochemical Properties Table
Benzotrichloride[a] (CASRN 98-07-7)

Property (unit)	Value
Boiling point (ºC)	220.8
Melting point (ºC)	−5.0
Density (g/cm^3 at 20ºC)	1.3756
Vapor pressure (Pa at 25ºC)	55.15
pH (unitless)	Not available
Solubility in water (mg/L at 5ºC)	53
Relative vapor density (air = 1)	6.77
Molecular weight (g/mol)	195.48
Octanol/water partition coefficient (unitless)	2.92

[a]Values from Hazardous Substances Data Bank (HSDB), 2005.

No chronic oral reference dose (RfD) or chronic reference concentration (RfC) for benzotrichloride is included in the IRIS database (U.S. EPA, 2009b) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2006). The HEAST does not list an RfD or RfC value, but it lists the EPA IRIS as a reference (U.S. EPA, 2009b). CalEPA (2008a,b) has not derived toxicity values for exposure to benzotrichloride; however, CalEPA (1994) reports

two No Significant Risk Levels for benzotrichloride: (1) 5.0×10^{-2} µg/day (oral) based on the cancer potency value calculated by the EPA, and (2) 2.0×10^{-4} µg/day (inhalation) determined in a draft review that is undergoing external review. The CARA list (U.S. EPA, 1994a) includes a Health and Environmental Effects Profile (HEEP) for benzotrichloride (U.S. EPA, 1986). The toxicity of benzotrichloride has not been reviewed by ATSDR (2008) or the World Health Organization (WHO, 2010). An occupational exposure short-term exposure level (STEL) ceiling value of 0.1 ppm with a skin notation has been derived by the American Conference of Governmental Industrial Hygienists (ACGIH, 2009) as reported in the Hazardous Substances Data Bank (HSDB, 2005). The National Institute of Occupational Safety and Health (NIOSH, 2003) has not issued threshold limit values (TLVs), and the Occupational Safety and Health Administration (OSHA, 1998) has not set occupational exposure limits for benzotrichloride.

The HEAST (U.S. EPA, 2009a) does not list cancer slope factors or unit risk values for benzotrichloride but instead cites the IRIS database (U.S. EPA, 2009b), which classifies benzotrichloride as Category B2 (*Probable Human Carcinogen*) based on inadequate human data and sufficient evidence of carcinogenicity in animals, including significantly increased incidence of benign and malignant tumors at multiple sites in one strain of female mice treated orally, dermally, and by inhalation. Additionally, evidence of mutagenicity was observed in several test systems (U.S. EPA, 1986). An oral slope factor (OSF) of 1.3×10^{1} per mg/kg-day and a drinking water unit risk of 3.6×10^{-4} per µg/L were derived in the IRIS cancer assessment using the linearized multistage procedure as the extrapolation method. Benzotrichloride is included in the NTP's *11th Report on Carcinogens* (NTP, 2005) and is categorized as "*Reasonably Anticipated to be a Human Carcinogen.*" The NTP assessment is based on sufficient evidence of animal carcinogenicity, including squamous cell carcinomas of the forestomach, skin, and lungs; adenocarcinomas of the lungs; and upper digestive tract tumors (NTP, 2005). The International Agency for Research on Cancer (IARC, 2000) has classified combined exposures to alpha-chlorinated toluenes (including benzotrichloride) as *Probably Carcinogenic to Humans* (Group 2A). A comprehensive review of toxicological studies of benzotrichloride published through July 2006 was conducted by EPA (2009b), but no new health effects data were identified that would directly affect the revision of the existing carcinogenicity assessment for benzotrichloride.

Literature searches were conducted on sources published from 1900 through October 2010 for studies relevant to the derivation of provisional toxicity values for benzotrichloride, CASRN 98-07-7. Searches were conducted using EPA's Health and Environmental Research Online (HERO) evergreen database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, 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 also searched for information that could support the derivation of provisional risk assessment values: ACGIH, ATSDR, CalEPA, EPA IRIS, EPA HEAST, EPA HEEP, EPA OW, EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides summaries of the potentially relevant toxicity studies. Entries for the principal studies are bolded and identified by the marking "PS."

Table 2. Summary of Potentially Relevant Data for Benzotrichloride (CASRN 98-07-7)

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (Comments)	Notes[a]
Human								
1. Oral (mg/kg-day)[b]								
None								
2. Inhalation (mg/m^3)[b]								
Carcinogenic	163 exposed and 790 unexposed workers (sex not specified); workers were exposed to a mixture of chlorinated toluenes versus benzotrichloride alone, only workers exposed for at least 6 months were considered; exposures occurred between 1923−1945, 1946−1960, and 1961−1970	Exposure not measured	Standardized Mortality Ratios (SMRs) were calculated using mortality rates for the general population as comparison; SMRs were elevated in the exposed group for all causes, all cancers, digestive system cancers, and respiratory system cancers; Using life tables, cancer mortality was significantly increased only in exposed workers who were first employed before 1951.	None identified	Not estimated	None identified	Sorahan et al. (1983)	
Carcinogenic	951 male workers employed between 1977 to 1984; workers were exposed to a mixture of chlorinated toluenes versus benzotrichloride alone; study is a follow up the study performed in 1983; follow-up period was 1977 to 1984	Exposure not measured	The standardized mortality ratios (SMRs) for all causes, all cancers, and all noncancers in workers exposed to mixtures of chlorinated toluenes (including benzotrichloride) were 138, 163, and 129, respectively compared to the general population of England and Wales; significant excess mortality for lung cancer and Hodgkin's disease, with SMRs of 180 and 714; relative risks for deaths from lung cancer were elevated for exposure to benzotrichloride and other chlorinated toluenes, but the association was not statistically significant.	None identified	Not estimated	None identified	Sorahan and Cathcart (1989)	

Table 2. Summary of Potentially Relevant Data for Benzotrichloride (CASRN 98-07-7)								
Category	**Number of Male/Female Species, Study Type, and Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**BMDL/ BMCL[b]**	**LOAEL[b]**	**Reference (Comments)**	**Notes[a]**
Carcinogenic	697 male workers at a chlorination plant (exposed to benzotrichloride, benzylchloride, benzoyl chloride, and other related chemicals); mortality was observed from 1943 to 1982	Exposure not measured	For the cohort as a whole, no statistically significant excess mortality was reported; however, authors state that based on animal data, as well as other epidemiologic studies, together with the internal consistency of analysis by length of employment, there may be an association between the chlorination process of toluene at the plant and an increased risk of respiratory cancer.	None identified	Not estimated	None identified	Wong (1988)	
Animal								
			1. Oral (mg/kg-day)[b]					
Short term	**10M/10F, Sprague-Dawley rat, diet 7 d/wk, 4 wks**	**0, 0.046, 0.46, 4.6, 46**	**Investigators did not observe clinical signs of toxicity and no mortality occurred during the study period; significant changes in SDH levels noted in males treated with benzotrichloride at doses greater than 0.046 mg/kg-day; liver, kidney, and thyroid considered to be target organs, though morphological effects were mild even at high doses. Males more susceptible than females to toxic effects of benzotrichloride.**	**0.046**	**0.048 (based on significant changes in serum SDH levels in males)**	**0.46**	**Chu et al. (1984)**	**PS**

Table 2. Summary of Potentially Relevant Data for Benzotrichloride (CASRN 98-07-7)

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (Comments)	Notes[a]
Carcinogenic	200 Female ICR mouse, gavage, 40 per dose group, 2 d/wk, 25 wks	0, 0.41, 1.62, 6.57, 26.57	Dose-dependent increase in mortality; the primary causes of mortality were lymphosarcoma and stomach cancer. There was a statistically significant positive trend in incidence of tumors of the forestomach, lung, and hematopoietic system.	0.41	Not estimated	1.62	Hooker Chemical Company (1980)	IRIS, U.S. EPA (1990)
Developmental	Female rat, gavage, Gestation Days 6 through 15, 10 days; number of animals not specified	0, 12.5, 25, 50	All dosages reduced mean fetal weight. Reduced number of fetuses per litter at all treated doses; additionally, skeletal anomalies were noted (doses not specified). Histological alterations in the maternal thyroid gland, bone marrow, kidney, and liver were also noted (doses not specified).	None identified	Not estimated	12.5	Ruddick et al. (1982); this study is only available in abstract form; hence, complete study details are unavailable	
Reproductive	None							

Table 2. Summary of Potentially Relevant Data for Benzotrichloride (CASRN 98-07-7)								
Category	**Number of Male/Female Species, Study Type, and Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**BMDL/ BMCL[b]**	**LOAEL[b]**	**Reference (Comments)**	**Notes[a]**
2. Inhalation (mg/m^3)[b]								
Short-term	**10M/10F Sprague-Dawley albino rat, 6 hr/d, 5 d/wk, 4 wks**	**0, 0.91, 8.61, 82.1 (extrarespiratory effects)** **0, 1.77, 16.77, 160 (respiratory effects)**	**All animals in the high exposure group died prior to termination of the study; animals in the mid-dose group exhibited statistically significant reduced body weight compared to the control group; a dose-response trend was observed in absolute and relative organ weights of both males and females; absolute weights of spleen, liver, kidneys, adrenals, and pituitary were significantly reduced in males in the mid-dose group. In females, absolute liver, heart, and lungs and trachea weights were significantly reduced compared to males in the mid-dose group; relative organ-weight analyses indicated statistically significant, dose-related changes in the lungs and trachea, adrenals, thyroid, and brain of both male and female rats; these findings were corroborated by the morphological alterations in the lung, trachea and nasal turbinates.**	**1.77 (based on respiratory effects)**	**1.36 (based on changes in relative brain weight in males)**	**16.77 (based on respiratory effects)**	**Levin (1981)**	**PS**

Table 2. Summary of Potentially Relevant Data for Benzotrichloride (CASRN 98-07-7)

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (Comments)	Notes[a]
Carcinogenic	Male Sprague-Dawley rat, number not specified, 6 hr/d, 5 d/wk, 1−6 mos	3.083	After 6 mos of exposure, squamous metaplasia or hyperplasia of upper respiratory tract, and papillomas in the nasal cavity; later observation also revealed malignant tumors in the skin and the external ear duct (incidence rates not provided in the abstract).	None identified	Not estimated	None identified	Koshi and Fukuda (1986); this study is only available in abstract form; hence, complete study details are unavailable	
Carcinogenic	Female ICR mouse, number of animals not specified, inhalation exposure, 30 mins twice a wk for 5 mos	0.323	Moderate adenoid hyperplasia was recorded in part of the trachea and major bronchi of mice that died at 2 mos after study initiation; paraleukemia and leukemia were noted in animals that died after 5 mos; all exposed animals also exhibited hypertrophy of the thymus, lymph nodes, and spleen which suggested metastasis to other organs; study authors reported pulmonary tumors in all animals; dermal lesions included squamous cell carcinomas and papillomas.	None identified	Not estimated	None identified	Takemoto et al. (1978)	

Table 2. Summary of Potentially Relevant Data for Benzotrichloride (CASRN 98-07-7)

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (Comments)	Notes[a]
Carcinogenic	Female ICR mouse, number of animals not specified, inhalation exposure, 30 mins twice a wk for 12 mos	0.076	Adenomas were seen in mice dying 9 mos after exposure and benign adenomas were seen at 12 mos (per author these animals died during treatment course); leukemoid lesions occurred after 12 mos; cancerous lesions were found in all lungs examined (malignant adenocarcinoma, adenoma, or adenoid proliferation); 90% of those sacrificed at 15 mos had cancerous lesions of the lung.	None identified	Not estimated	None identified	Yoshimura et al. (1979)	
Developmental	None							
Reproductive	None							

[a]IRIS = utilized by IRIS, citation; PS = Principal study.
[b]Dosimetry conversion equations: Oral: $NOAEL_{ADJ}$ = NOAEL × Food Consumption per Day × (1 ÷ Body Weight) × (Days Dosed ÷ Total Days); Inhalation: $NOAEL_{ADJ}$ = NOAEL × (Hours per Day ÷ 4) × (Days Dosed ÷ Total Days); Noncancer oral data are only adjusted for continuous exposure; 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); Equation for HEC conversion: HEC = $NOAEL_{ADJ}$ × RGDR.
[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 exposure to benzotrichloride in humans have been identified. The effects of inhalation exposure of humans to mixtures of chlorinated toluenes including benzotrichloride have been investigated in three epidemiological/occupational studies (Sorahan et al., 1983; Sorahan and Cathcart, 1989; Wong, 1988).

Sorahan et al. (1983) and Sorahan and Cathcart (1989) conducted two studies: the first being a retrospective study of a cohort of 953 people (sex not specified) employed in a chemical factory manufacturing chlorinated toluenes (CT) and the second being a follow-up study to the 1983 cohort. The population in the first study consisted of employees with up to 24 years of exposure with an additional criterion for inclusion in the study being a minimum of 6 months of employment. Employees exposed to chlorinated toluenes from 1923−1945, 1946−1960, and 1961−1970 were included in the study. The study authors compared mortality in 163 exposed employees to 790 employees who were not exposed. The second study included a period of follow-up spanning from 1977 to 1984 for 951 of the original 953 workers.

The study made comparisons using two standard populations in the 1983 study. The first approach used mortality rates in England and Wales as an external standard, while the second approach used regression models in life tables (RMLT) as the internal standard. The study authors used Standardized Mortality Ratio (SMR) and RMLT to analyze the mortality among workers exposed to CT. In the 1989 study, in addition to the SMR data, Sorahan and Cathcart performed a "nested case-control" to gather more detailed information on likely occupational risks. SMR results from the 1983 study indicated a statistically significant ($p < 0.01$) difference in cancer mortality between the group exposed to CT and cancer mortality in the rest of England and Wales. Similarly, for the combined group (with and without CT exposure), mortality from all cancers was significantly elevated ($p < 0.05$) compared to cancer mortality in all of England and Wales. Results from the 1989 study also indicated a statistically significant ($p < 0.05$) difference in lung cancer mortality between the CT-exposed group and the rest of England and Wales. In the 1983 study, RMLT results indicated that the null hypothesis (i.e., CT exposure has no effect on cancer mortality) was rejected at the 5%-level. Though all cancers in the CT-exposed group were of the respiratory and digestive systems, their association with CT exposure failed to reach statistical significance when tumor types were considered individually. The study authors did not find statistically significant relationships between CT exposure and cancer mortality or that of any other cause. The study authors drew these conclusions after controlling for employment entry cohort and age at entry to the study. Using a "nested case control" approach in the 1989 study, the study authors stated that results did not show convincing evidence of occupational involvement, though there was a positive nonsignificant effect for benzotrichloride exposure that was not due to confounding effects of smoking, based on available smoking data. However, based on the incidence of cancers in both studies, the study authors concluded that though the results may be biased, there is evidence of increased cancer mortality, but not from other causes, among the group exposed to CTs. The study authors also stated that based on results of other toxicological studies on benzotrichloride, it is reasonable to assume that benzotrichloride may be a potential human carcinogen. Because these studies involved exposures to a mixture of chlorinated toluenes and the study authors did not report exposure levels to benzotrichloride, a NOAEL or a LOAEL is not identified.

Wong (1988) conducted a "historical prospective" (retrospective) mortality study on 697 males employed at a chlorination plant manufacturing benzotrichloride, benzylchloride, benzoyl chloride, and other related chemicals between 1943 and 1982. Females were not included in the study because the number of females potentially exposed to chlorinated toluenes was low (n = 43). A majority of the study cohort was potentially exposed to benzyl chloride, benzoyl chloride, and other related chemicals. The study reported SMRs computed based on comparisons to age- and gender-specific death rates for the U.S. population. The study authors reported 47 deaths in the entire cohort during the observation period spanning from 1943 to 1982. When compared to the U.S. mortality rates of 46.9, the SMR was 100. Ten of the 47 deaths were attributed to malignant neoplasms, with 8.2 predicted. The study reported that seven deaths were a result of respiratory cancer compared to 2.8 expected. The SMR for respiratory cancer was 246 with a borderline statistical significance (and a lower 95% confidence limit of 99). Seventeen deaths were attributed to diseases of the circulatory system with a SMR of 96, which was not statistically significant. The study authors conducted analyses based on race, job subcohort, chemical-specific analysis, length of employment, and latency, and concluded that there was a statistically significant increase in lung cancer mortality among male employees with 15 or more years of employment (two deaths in workers employed <15 years and five deaths in workers employed >15 years). However, five workers out of the total seven lung cancer deaths were known smokers, and the study authors could not determine whether the observed lung cancer mortality excess was due to exposure to chlorinated toluenes, smoking, or other causes. Based on the study results and toxicity observed in animal data, the study authors concluded that there may be an association between exposure to chlorinated toluenes and an increased risk of respiratory cancer. Because the study involved exposures to a mixture of chlorinated toluenes and exposure doses and did not report data specific to benzotrichloride exposure levels, a NOAEL or a LOAEL is not identified from this study.

ANIMAL STUDIES

Oral Exposure

The effects of oral exposure of animals to benzotrichloride have been evaluated in short-term (Chu et al., 1984), developmental toxicity (Ruddick et al., 1982, presented only as an abstract), and chronic-duration carcinogenicity studies (Published studies investigating the reproductive effects of benzotrichloride in animals have not been identified.

Short-term Study

The study by Chu et al. (1984) is selected as the principal study for deriving the subchronic p-RfD. Chu et al. (1984) conducted a 28-day feeding study in rats. Groups of 10 male and 10 female Sprague-Dawley rats per group were fed diets containing 0, 0.5, 5.0, 50, or 500 ppm (0, 0.046, 0.46, 4.6, and 46 mg/kg-day) of benzotrichloride (purity = 98%) dissolved in corn oil via the diet daily, for 7 days a week, for 4 weeks. The control groups were fed a diet containing 4%-corn oil only. The study authors recorded body weights and food consumption weekly and made clinical observations daily. At study termination, all animals were euthanized, and gross examinations were performed at necropsy. The study authors analyzed hepatic mixed function oxidase activity and serum enzyme levels along with various hematological parameters including hemoglobin concentration (Hgb), packed cell volume, total and differential leukocyte counts, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and mean corpuscular hemoglobin (MCH). At necropsy, the study authors examined the liver, brain, heart, spleen, and kidney for gross lesions. Statistical analyses were carried out using a one-way multiple analyses of variance and Duncan's multiple range tests. No clinical

signs, mortality, or gross changes were observed in any of the treated animals. Significant ($p < 0.05$) increases in serum sorbitol dehydrogenase (SDH) activity were noted in male rats treated with 0.46-, 4.6-, and 46-mg.kg-day benzotrichloride compared to the concurrent control group. The study did not provide SDH levels at the 0.046-mg/kg-day dose level; thus, it raises uncertainty in dose response. Benzotrichloride exposure was also associated with elevated lactate dehydrogenase (LDH) activity at the 46-mg/kg-day dose (control: 1336 ± 309; 500 ppm: 1646 ± 163). Hematological parameters and bone marrow (no information is presented indicating whether this was assessed histopathologically) were not affected as a result of exposure to benzotrichloride. Histopathological changes were noted in the liver, kidney, and the thyroid gland. The study authors stated that the morphological changes in these organs were mild even at the highest administered dose of benzotrichloride and that male rats were more susceptible to these changes than females (incidence data for these morphological changes were not provided in the study report). However, the study authors also reported that the histological changes produced by benzotrichloride became progressively more severe and occurred with greater frequency as dose levels increased. Because the study does not present dose-specific incidence data, a dose-response trend in these histological changes is not estimated. The study summary does not present dose-specific incidence data on morphological changes in various organs. Architectural changes in the liver consisted of mild regular and irregular lobular patterns. Hepatocytes exhibited mild anisokaryosis associated with pyknosis, and occasional necrotic hepatocytes were also noted. In addition, cytoplasmic vacuolation and increased eosinophilia were also seen in the portal areas of the hepatic lobule (dose-dependent data not presented). In the kidney, mild but significant (significance level and dose not reported) changes consisting of accumulation of eosinophilic intracytoplasmic inclusions in the epithelium of proximal tubules that were associated with focal-glomerular adhesions and interstitial scarring due to spontaneous aging process were noted. Histological alternations in the thyroid were mild in nature and consisted of a reduction in follicular size and colloid density. The study authors stated that the significant increase in serum SDH activity in male rats treated with benzotrichloride was consistent with the morphological changes observed in the liver because changes in SDH levels indicate liver injury. Though the study authors state that there were statistically significant increases in SDH activities in animals treated with benzotrichloride, the significance level at the lowest administered dose of 0.5 ppm could not be confirmed because SDH levels for this dose group were not provided in the study summary. Significant SDH changes at doses as low as 5 ppm along with morphological changes observed in the liver constitute liver injury. Based on these results, a LOAEL of 0.46 mg/kg-day is identified for statistically significant ($p < 0.05$) changes in SDH levels along with morphological changes in the liver in male and female Sprague-Dawley rats. A NOAEL of 0.046 mg/kg-day is identified in this study.

Chronic-duration Studies

Studies investigating the chronic-duration noncancer toxicity of benzotrichloride via oral exposure have not been located.

Chronic-duration Carcinogenicity Studies

Fukuda et al. (1993) and Hooker Chemical Company (1980) conducted a 25-week carcinogenicity study in ICR-Specific Pathogen Free (SPF) mice. Groups of 40 female ICR-SPF mice were treated with 0.0315, 0.125, 0.5, or 2 μL (0.41, 1.62, 6.57, and 26.57 mg/kg body

weight-day[1]) of benzotrichloride (purity not provided) dissolved in 0.1-ml sesame oil, twice a week, for 25 weeks via gastric intubation. Though the use of a control group is not specifically mentioned in the study report, the results table provides information regarding tumor incidence in the control animals (n = 40). Eighteen months after study initiation, animals were sacrificed, autopsied, and examined histopathologically. Changes in body weights and clinical observations, if performed, were not reported in the study. Mortality increased with dose and occurred earlier in higher dose groups. The study authors recorded 50% mortality at 16.5 and 6.5 months, respectively, in animals treated with 6.57 and 26.57 mg/kg-day of benzotrichloride twice per week. The study authors stated that tumors developed earlier in animals treated with either 6.57 or 26.57 mg/kg-day of benzotrichloride compared to animals treated with a lower dose of the chemical, strengthening the evidence for a dose-response relationship for the observed tumors (see Appendix B, Table B.1). A tumor type that appeared early was thymoma, which appeared within 6 months in 18% (7/38) and 5% (2/40) of animals treated with 26.57 and 6.57 mg/kg-day of benzotrichloride, respectively. The most frequently seen tumor was squamous cell carcinoma of the forestomach; incidence for squamous cell carcinomas and papillomas of the forestomach was 66% in animals treated with 26.57 mg/kg-day of benzotrichloride at 12 months and 58% in animals treated with 6.57 mg/kg-day of benzotrichloride at 18 months. In contrast, incidences of forestomach cancer in the 1.62 and 0.41 mg/kg-day dose groups, and the controls at 18 months were 5% (2/39), 0% (0/39), and 0% (0/39), respectively. Metastases were also noted but only for lymphogenous or hematogenous tumor types. In contrast to forestomach cancers, no glandular stomach tumors were noted. However, low incidences of atypical hyperplasia and hyperplastic metaplasia of the glandular mucosa were noted. Besides squamous cell carcinomas, the other most-frequently seen tumors were adenocarcinoma and adenomas of the lung. The study authors found lung tumors in over 60 of animals in the three highest dose groups at the end of the study. The authors also reported less-frequently occurring tumors of the exocrine glands such as sweat glands, salivary glands, and lacrimal ducts in 7% (10/150) animals treated with 0.41, 1.62, 6.57, and 26.57 mg/kg of benzotrichloride along with one instance of endothelioma of vessels supplying the liver. Cancers of the hematopoietic system were also common in animals dosed with 6.57 or 26.57 mg/kg-day of benzotrichloride (1/39, 2/39, 1/39, 3/40, and 8/38 in the control and the four treatment groups, respectively). Based on these results, the study authors concluded that benzotrichloride is not only a local carcinogen (causing cancers in the forestomach) but also a systemic carcinogen (causing cancers in the lung, thymus, hematopoietic system, and hepatic vascular system).

Developmental and Reproductive Studies

No studies investigating the reproductive effects of benzotrichloride via oral exposure have been identified. Ruddick et al. (1982; in abstract form only) administered benzotrichloride to pregnant rats (number of animals not specified) on Gestation Days (GDs) 6 through 15 via gavage at doses of 0, 12.5, 25, or 50 mg/kg-day. Maternal-weight gain, changes in organs, hematology, residue analysis (details not provided in the abstract), microscopic examination, and 15 biochemical parameters were used to evaluate maternal toxicity. The study authors measured teratogenicity by examining litter size, fetal weight, deciduoma, skeleton and visceral parameters, residue analysis, and microscopic examination of fetuses. A significant (p < 0.05)

[1]Dose (mg/kg-BW-day) = $\frac{\text{Dose (µl)} \times \text{Density of the chemical (g)} \times 1 \times 1 \times 1000 \text{ mg} \times 2}{\text{Day} \times \text{ml} \times 1000 \text{ µl} \times \text{Animal Body Weight (kg)} \times \text{g} \times 7}$

decrease in maternal-weight gain was noted in dams receiving 25- or 50 mg/kg-day benzotrichloride. The highest dose—50 mg/kg-day—increased the number of resorption sites and reduced the number of fetuses per litter. A decrease in mean fetal weight was noted at all three dose levels of benzotrichloride compared to the control group. The number of skeletal anomalies was most evident in pups exposed to benzotrichloride (dose-specific information not provided). Histological changes were evident in the maternal thyroid gland, bone marrow, kidney, and the liver. Significant (significance level not provided) changes were observed in some clinical and hematological parameters along with changes in organ weights in animals (no data on whether these changes were noted in the dams or pups) treated with 50 mg/kg-day benzotrichloride. These results were available only in abstract form. Based on the results presented here, a LOAEL of 12.5 mg/kg-day is derived for benzotrichloride based on decreased mean fetal weight. A NOAEL cannot be determined from this study.

Inhalation Exposure

The effects of inhalation exposure of animals to benzotrichloride have been evaluated in short-term (Levin, 1981) and chronic-duration carcinogenicity studies (Yoshimura et al., 1979; Takemoto et al., 1978; Koshi and Fukuda, 1986). Published studies investigating reproductive and developmental effects of benzotrichloride in animals via inhalation exposure have not been identified.

Short-term Study

The study by Levin (1981) is selected as the principal study for deriving the subchronic p-RfC. The International Research and Development Corporation (IRDC), Mattawan, Michigan (1981; unpublished study) conducted a 4-week inhalation study on benzotrichloride using rats. Groups of 10 male and 10 female Sprague-Dawley albino rats per group were exposed 6 hours/day, 5 days/week, for 4 weeks to clean filtered air or 5.1, 48.2, or 460 µg/L (mg/m^3) of benzotrichloride (purity = 96.4%) vapor. Body weights were determined prior to study initiation and once every week thereafter until study termination. The study authors noted signs of toxicity once every week and checked animals for mortality twice per day prior to benzotrichloride exposure and again after each exposure until study termination. At study termination, various serum biochemical, hematological, and urine analyses were conducted. In addition, the study authors determined absolute and relative organ weights and conducted histopathological evaluations after animal sacrifice. Animals that died or were sacrificed in extremis prior to study termination were evaluated using the same methods, except body and organ weights were not measured. Marked dyspnea, nasal and ocular discharge, and gasping were noted in animals exposed to 460 mg/m^3 benzotrichloride during Week 1 of the study. In contrast, only mild dyspnea was observed in animals exposed to 48.2 mg/m^3 benzotrichloride. All animals exposed to 460 mg/m^3 of benzotrichloride either died or were sacrificed in extremis by the seventh day of the study. One female treated with 48.2 mg/m^3 of benzotrichloride died prior to final sacrifice. None of the other animals died during the study period. Body weights for both male and female rats treated with 48.2 mg/m^3 benzotrichloride were statistically significantly ($p < 0.05$) lower when compared to the corresponding control group (see Appendix B, Table B.2). In contrast, animals treated with 5.1 mg/m^3 of benzotrichloride exhibited no apparent difference in body weights from the control group. Examination of hematological, biochemical, and urine analyses data indicated no compound-related changes. Absolute organ weight analysis indicated statistically significant ($p < 0.01$) changes in the spleen (males), liver (males and females), kidney (males), and heart (females) of animals dosed with 48.2 mg/m^3 benzotrichloride compared to the control group (see

Appendix B, Table B.3). Relative organ weight analyses indicated statistically significant changes in the lungs and trachea ($p < 0.01$; apparently excised as a unit and weighed together), adrenals ($p < 0.05$), thyroid, and brain ($p < 0.01$) of both male and female rats (see Appendix B, Table B.4). The study authors suggest that the changes in relative brain weights may be related to the effect of benzotrichloride on body weight rather than a direct effect on organs.

Histopathological examination revealed treatment-related morphological alterations in the lung, trachea, and nasal turbinates in male and female rats treated with 48.2- and 460-mg/m^3 benzotrichloride. Lesions in the lung included infiltrates of acute inflammatory cells, ulcerations, and desquamation of the superficial epithelial cells of the main bronchial stem and bronchioles of all sections. The severity of these lesions was reported to be comparable in both the 48.2- and 460-mg/m^3 dose groups. Lesions in the nasal turbinates and the trachea included focal-to-diffuse and slight-to-moderate infiltrations of the acute inflammatory cells along with squamous metaplasia of the superficial epithelial cells that lined the tissues. These lesions were not noted in the low-dose males and females. Hepatocellular necrosis/necrotic foci were noted in the livers of some of the treated animals but not in the control group. The study authors stated that such lesions are common spontaneous findings in rats and were not considered to be treatment related. Based on the results presented above, a LOAEL of 48.2 mg/m^3 is identified for statistically significant ($p < 0.01$) changes in relative adrenal and thyroid weights in males, and relative lungs and trachea weight in male and female rats, which is corroborated by the morphological alterations in the lung, trachea, and nasal turbinates. A NOAEL of 5.1 mg/m^3 is identified in this study.

Chronic-duration Studies

No studies investigating the effects of chronic-duration systemic toxicity of benzotrichloride in animals via inhalation exposure have been identified.

Chronic-duration Carcinogenicity Studies

Koshi and Fukuda (1986) conducted a 6-month carcinogenicity study in rats along with 1- and 3-month studies. Groups (number not specified) of male Sprague-Dawley rats were exposed to benzotrichloride (purity not specified) at 1 ppm in air for 6 hours/day, 5 days/week, for 1, 3, or 6 months. The corresponding average daily concentration was 3.083 mg/m^3. Details of this study are limited as the study is available only as an abstract; therefore the details of the control group are not reported. Neoplastic changes were not noted in the 1- and 3-month exposure groups. However, in the 6-month exposure group with an observation period of 5 months, malignant and benign tumors were observed in the respiratory system as well as in the skin and external ear duct. Additionally, at the end of the 6-month exposure period, squamous metaplasia or hyperplasia of the upper respiratory tract, and papillomas in the nasal cavity were recorded. These results suggest that inhalation exposure to 1 ppm benzotrichloride is carcinogenic to male Sprague-Dawley rats.

Takemoto et al. (1978) conducted a 5-month study in ICR mice. A group of (number of animals not clearly specified) ICR female mice were exposed to average air concentrations of 6.8 ppm benzotrichloride (purity not specified) vapors for 30 minutes, twice weekly, for 5 months. The equivalent average continuous concentration over the study period was 0.323 mg/m^3. The study summary does not discuss the use of a control group. At the end of 5 months of exposure, the animals were observed without exposure for an additional 1 or 5 months and sacrificed and autopsied 6 and 10 months after study initiation. All animals,

including animals that died during the study period, received histopathological examination. Moderate adenoid hyperplasia was recorded in the tracheas and major bronchi of mice that died within 2 months of study initiation. In the majority of animals that died by the end of the 5-month exposure period, epithelial proliferation of the trachea, bronchus, and bronchiole were manifested as mild-to-intermediate adenoid proliferation. In animals that died by the fifth month, 50% (6/12) had paraleukemia and leukemia, whereas only 10% (2/20) of animals that died after 5 months of the study exhibited incidence of leukemia. All animals also exhibited hypertrophy of the thymus, lymph nodes, and spleen, which suggested tumor metastasis to other organs. All animals (n = 8) that survived the 10-month observation period exhibited adenoid proliferation of the trachea and intrapulmonary bronchial epithelia, whereas two animals exhibited papillomas of the intrapulmonary bronchi. Additionally, the study authors reported pulmonary tumors in all eight animals sacrificed at the end of the 10-month observation period. Dermal lesions included squamous cell carcinomas in three animals, and papillomas in four animals. Mild keratocyte proliferation in the stomach was also noted in several animals (number not specified) along with inflammatory damages in the spleen. These results suggest that benzotrichloride is carcinogenic to female ICR mice via the inhalation exposure route.

Yoshimura et al. (1979) conducted a 12-month carcinogenicity study of benzotrichloride in ICR mice. A group of ICR-JCL female mice (number of animals not clearly specified) were exposed to 1.6-ppm benzotrichloride (purity not specified) vapors for 30 minutes, twice weekly, for 12 months at room temperature and at 50°C. The corresponding average continuous concentration was 0.076 mg/m^3 over the course of the study period. The use of a control group is not discussed in the study summary. At the end of 12 months of exposure, the animals were observed without further exposure and sacrificed and autopsied 12 and 15 months after study initiation. All animals, including animals that died during the study period, received histopathological examination. The authors reported incidence of cancerous lesions in mice as early as 9 months after study initiation. Among the animals that died by 12 months, some exhibited mild adenoid proliferation in the bronchial epithelia (3/4), while others exhibited benign adenoma (3/4). In animals exposed to benzotrichloride at 50°C, the incidence of leukemoid lesions was 11% (4/37). All 10 animals sacrificed and autopsied at the end of the 12-month exposure period exhibited epithelial proliferation of the trachea, bronchus, and terminal bronchiole along with localized squamous epithelialization. Cancerous lesions were also noted in all examined lungs. All animals that were sacrificed at 15 months exhibited proliferation of the tracheal and terminal bronchiolar epithelia. When compared to animals sacrificed and observed at the end of 12 months, the 15 month-group exhibited more advanced squamous epithelial proliferation as well as epithelial keratinization. The study authors also reported skin lesions that included papillomas and epidermoid carcinomas. Examination of other organs indicated evidence of keratinization of the gastric mucosa. These results suggest that benzotrichloride is carcinogenic to female ICR-JCL mice via the inhalation exposure route.

Developmental and Reproductive Studies

No studies investigating the developmental and reproductive toxicity of benzotrichloride in animals via inhalation exposure have been identified.

Other Exposures

No studies investigating benzotrichloride toxicity in humans or animals by other exposure pathways have been identified**.**

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Little information is available on the toxicokinetics of benzotrichloride. Available studies (U.S. EPA, 1986; Yu and Nietschmann, 1980) indicate that benzotrichloride is rapidly and extensively absorbed from the gastrointestinal tract of rats and efficiently eliminated in the urine (90%) and feces (10%) 48 hours after a single oral dose of radiolabeled benzotrichloride (data regarding specific carbon labeling is not provided). The elimination half-life of ^{14}C was estimated to be about 22 hours. Total radiocarbon in tissues was 1.5% of the dose after 72 hours with fat, liver, and kidney exhibiting higher residue levels compared to other tissues and muscle exhibiting the lowest residue levels. Excretion of benzotrichloride seemed to follow first-order kinetics with rapid distribution in the body followed by elimination of 90% of the dose in urine with the remaining 10% being eliminated in the feces. Yu and Nietchsmann (1980) reported that benzotrichloride was rapidly metabolized via hydrolysis (data regarding hydrolysis via enzyme interaction are not provided) to form benzoic acid, which was further metabolized to hippuric acid following conjugation with glycine.

The genotoxicity of benzotrichloride has been evaluated in various studies using in vitro and in vivo test systems (Khudoley et al., 1987; Yasuo et al., 1978; Zeiger et al.,1988; You et al., 1986; Koshi and Fukuda, 1986). These test results indicate that benzotrichloride has mutagenic (with metabolic activation) and clastogenic activity.

Table 3 summarizes the results of the toxicokinetics and genotoxicity studies of benzotrichloride.

Table 3. Other Studies for Benzotrichloride (CASRN 98-07-7)

Tests	Materials and Methods	Results	Conclusions	References
Toxicokinetic	Eight groups of 4-wk-old Sprague-Dawley albino rats (2−3 rats/group, M or F) were administered one oral dose (40 mg/kg) of ^{14}C-benzotrichloride in corn oil. Urine and feces samples were collected at 24 (Groups 2 and 3), 48 (Group 4), and 72 (Groups 5, 6, 7, and 8) hrs after dosing. Group 1 samples were collected after 8 hrs, when these animals were sacrificed.	Benzotrichloride was rapidly absorbed by the gastrointestinal tract and eliminated well by the urine (90%) and feces (10%) after 48 hrs. A half-life for absorption was estimated at 3 hrs; the half-life for elimination from blood was 22 hrs and about 14 hrs for elimination from tissues (kidney, liver, muscle, fat, brain, heart, spleen, gonads, uterus, lung, and blood). Radiocarbon residue in tissues was low, with only about 1.5% left in the body after 72 hrs. Distribution data indicated that residue was highest in fat, followed by the liver and kidney. No parent compound was detected in the urine; authors suggested that the benzotrichloride was hydrolyzed to benzoic acid, which then was conjugated with glycine to form hippuric acid, which was the predominate metabolite detected in urine.	Benzotrichloride was rapidly and efficiently absorbed by the gastrointestinal tract. However, based on the data, authors concluded that benzotrichloride should not be accumulative or persistent in mammals.	Yu and Nietschmann (1980); U.S. EPA (1986)
Genotoxicity	Ames mutagenicity assay was used to test mutagenic potential of a number of compounds, including benzotrichloride. *Salmonella typhimurium* strains TA98, TA100, TA1538, TA1530, TA1535, TA1537, TA97, and TA102 were metabolically activated with S-9 from Aroclor-treated rats to test for mutagenicity.	Data showed that the benzotrichloride was mutagenic in strains TA98, TA100, and TA1538 (the frequency of mutations were more than spontaneous background by 2−5 fold), but not in strains TA1530, TA1535, TA1537, TA97, or TA102.	Benzotrichloride was one of 126 compounds assayed; results for the group of compounds including benzotrichloride mirrored other available data. No specific conclusions were drawn by the authors regarding benzotrichloride despite findings of mutagenicity in some strains.	Khudoley et al. (1987)

Table 3. Other Studies for Benzotrichloride (CASRN 98-07-7)

Tests	Materials and Methods	Results	Conclusions	References
Genotoxicity	Ames mutagenicity assay was used to test for mutagenic potential. *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 were used with activation by S-9 fractions of Aroclor 1254-induced, male Sprague-Dawley rat and male Syrian hamster livers.	In the TA100 strain, benzotrichloride was mutagenic without activation, with activation of Aroclor 1254-hamster liver S-9, and with Aroclor 1254-induced rat liver S-9. In the TA98 strain, two tests without activation yielded negative and questionable results, respectively. In two tests (from two different laboratories) TA98 mutagenicity tests with Aroclor 1254-hamster liver S-9 results were positive or questionable. Both tests using TA98 with Aroclor 1254-induced rat liver S-9 were positive.	The authors concluded that benzotrichloride is mutagenic in bacterial test strains.	Zeiger et al. (1988)
Genotoxicity and Mutagenicity	Benzotrichloride and three other compounds were tested for mutagenicity in vitro by rec-assay (for DNA damage) using *Bacillus subtilis,* reversion assays (for gene mutations) using *E. coli* WP2, and Ames *Salmonella* TA strains with and without metabolic activation.	Benzotrichloride was positive in the rec-assay. However, benzotrichloride required metabolic activation in several of the *Salmonella* and *E. coli* strains before showing mutagenic response. Benzotrichloride was highly mutagenic in the reversion assays for WP2 *hcr,* TA100, TA98, and TA1535 when metabolically activated. *E. coli B/r WP2 try* (hcr^+) was not as sensitive to the mutagenicity of benzotrichloride as WP2 *try hcr*.	Benzotrichloride was positive in the rec-assay without S-9; however, it did require metabolic activation to induce mutation. The requirement of activation in only some of these assays may be related to differences in the permeability of cell membranes and/or to the differences in metabolic systems of *B. subtilis, E. coli* or *S. typhimurium*.	Yasuo et al. (1978)
	Benzotrichloride was tested using alkaline elution to measure DNA strand breaks in human bronchial epithelial cells. Cells were labeled by incubation for 3 days in medium containing 0.1 µCi/ml of [^{3}H] thymidine. The cells were treated with BTC or benzo(a)pyrene for 1 hr (0.1−1 µg), washed, suspended, and impinged onto polycarbonate filters for detection of DNA strand breaks.	Benzotrichloride induced DNA strand breaks at all concentrations and was 3−4 times more active than benzo(a)pyrene.	The data indicate that benzotrichloride is a strong inducer of DNA strand breaks in human precursor cells for lung cancer.	You et al. (1986)

Table 3. Other Studies for Benzotrichloride (CASRN 98-07-7)

Tests	Materials and Methods	Results	Conclusions	References
Clastogenicity	Male Sprague-Dawley rats were exposed via inhalation to 1 ppm of benzotrichloride for 6 hrs a day, 5 days a wk, over a period of 1, 3, or 6 mos.	There was a small but significant increase for all exposure periods (1, 3, and 6 mos) in chromosomal aberrations in bone marrow cells, particularly chromatid gaps. There was a significantly higher occurrence of sister-chromatid exchanges in peripheral blood lymphocytes in each exposure group when compared to controls. Chromosomal aberrations in peripheral blood lymphocytes were similar to controls for the 1-mo exposure, but aberrant metaphases were significantly higher for the 6-mo exposure group.	Results suggest clastogenic effects occurred over all exposure periods. However, authors concluded that the individual responses did not always correlate well with these effects.	Koshi and Fukuda (1986) (Abstract)

DERIVATION OF PROVISIONAL VALUES

Table 4 below summarizes the noncancer reference values. Table 5 summarizes the cancer values. The toxicity values have been converted to HED/HEC units. IRIS data are included in the table if available.

Table 4. Summary of Reference Values for Benzotrichloride (CASRN 98-07-7)

Toxicity Type (Units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic p-RfD (mg/kg-day)	Sprague-Dawley rat; M/F	Significantly increased SDH levels beginning at the 0.046 mg/kg-day dose group accompanied by morphological changes in the liver, kidney, and thyroid	5×10^{-5}	BMDL	0.048	1000	Chu et al. (1984)
Chronic p-RfD (mg/kg-day)	None	None	None	None	None	None	None
Screening Subchronic p-RfC (mg/m^3)	Albino Rat (strain not specified); M/F	Significant ($p < 0.01$) changes in relative lungs and trachea weight and morphological alterations in the lung, trachea, and nasal turbinates	5×10^{-3}	BMCL	1.36	300	Levin (1981)
Chronic p-RfC (mg/m^3)	None	None	None	None	None	None	None

Table 5. Summary of Cancer Values for Benzotrichloride (CASRN 98-07-7)

Toxicity Type[a]	Species/Sex	Tumor Type	Cancer Value	Principal Study
OSF (IRIS, 1990)	ICR-JCL Mouse/F	Squamous cell carcinoma in the forestomach; adenocarcinoma and adenoma in the lung; lymphosarcoma of the thymus, lymphatic leukemia in the hematopoietic system	1.3×10^{1} $(mg/kg\text{-}day)^{-1}$	Hooker Chemical Company (1980)
p-IUR	None	None	None	None

[a]All the reference values obtained from IRIS are indicated with the latest review date.

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic p-RfD

The study by Chu et al. (1984) is selected as the principal study for deriving the subchronic p-RfD. This study is a 28 day study and is the only available study for this purpose. Administered dose levels in this study were: control, 0.5, 5.0, 50.0, and 500.0 ppm (0, 0.046, 0.46, 4.6, and 46 mg/kg-day). The critical endpoints reported are changes in liver SDH levels commensurate with morphological changes reported (as occurring but not quantified) in the liver of male and female Sprague-Dawley rats. Changes in SDH levels were reported as statistically significant ($p < 0.05$) beginning at the 5.0 ppm dose level. However, no data was presented for the 0.5 ppm level. This study is in a peer-reviewed journal publication and the study follows standards of study design and performance. Supporting studies are Fukuda et al. (1993) and Ruddick et al. (1982). Fukuda reported increased incidence of tumors in the forestomach as well as lung, thymus, hematopoietic system, and hepatic vascular system at doses of 1.62 mg/kg-day. Ruddick reported that the high dose of 50 mg/kg-day increased the number of resorption sites and reduced number of fetuses per litter and decrease in mean fetal weight at 12.5, 25, or 50 mg/kg-day. Details are provided in the "Review of Potentially Relevant Data" section of this report. These levels are higher than those of effects at low doses in the principal study (Chu et al., 1984).

Since no data for SDH or other effects were reported for the 0.5 ppm level, this point could not be considered in a BMD analysis; i.e., the point was ignored. The remaining points, 0.0, 5.0, 50.0, and 500.0 ppm were subjected to BMD analysis (see Figure C.1). The data (extracted from the paper) are shown in Table 6.

Table 6. Data Extracted from Chu et al. (1984)

Treatment Level (ppm)	Treatment Level (mg/kg-day)	Serum SDH (mIU/ml) & SD
Control	0.0	19 ± 4.8
5.0	0.46	32 ± 8.9*
50	4.6	38 ± 15*
500	46	29 ± 12*

*Significant $p > 0.05$

Modeling failed for all models for the database which included the 500 ppm level. After dropping this level, an exponential model with nonhomogeneous variance is the best fit of the data. A change in one standard deviation from the control mean is the appropriate default approach for the determination of the POD since expected normal ranges are unknown. Since only two dose levels could be modeled, using the non-homogeneous variance causes loss of one degree of freedom. Hence the model failed Test 6a (Degrees of Freedom = 0) as indicated in Appendix C. However, visual inspection of the fitted curve and observation that the scaled residuals were small (<2.0) provides justification for accepting the model, regardless. The BMD and $BMDL_{1SD}$ is 0.12 and 0.048, respectively. See Appendix C for BMD information.

Adjusted doses for Continuous Exposure:

The study authors report that "growth rate and food consumption were not affected by treatment," and "body weight and food consumption were determined weekly…". However, the food consumption values were not reported. The dose conversion from ppm in diet to mg/kg-day; 0.0, 0.5, 5.0, 50, and 500 ppm to 0.0, 0.046, 0.46, 4.6, and 46 mg/kg-day is calculated as follows. The conversion is based on a food consumption of 0.0215 kg/day (males and females). This food consumption value (0.0215 kg food/day) can be compared to the default food factor (subchronic for Sprague-Dawley rats) of 0.023 kg food /day for male and 0.020 for female (U.S. EPA, 1988). The dosimetric conversion is as follows, using 0.5 ppm as an example:

$$\begin{aligned} \text{Dose}_{\text{adj}} &= \text{Dose(ppm)} \times (\text{food consumption/BW}) \times 1 \text{ (dose is continuous)} \\ &\quad 0.5 \text{ ppm (mg/kg food)} \times (0.0215 \text{ kg food/day} \div 0.2355 \text{ kg bw}) \\ &= 0.046 \text{ mg/kg-day} \end{aligned}$$

The adjusted doses were modeled and a $BMDL_{1SD}$ of 0.048 mg/kg-day for increased serum SDH in males was chosen as the POD.

$$\begin{aligned} \textbf{Subchronic p-RfD} &= BMDL_{1SD} \div UF_C \\ &= 0.048 \text{ mg/kg-day} \div 1000 \\ &= \mathbf{5 \times 10^{-5} \text{ mg/kg-day}} \end{aligned}$$

Tables 7 and 8 summarize the associated uncertainty factors and confidence descriptors.

Table 7. Uncertainty Factors for Subchronic p-RfD for Benzotrichloride (CASRN 98-07-7)

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans. There are no data to determine whether humans are more or less sensitive than rats used in Chu et al. (1984) to liver effects of benzotrichloride.
UF_D	10	The only study that is available is the Chu et al. (1984) study. No other studies of longer duration examining a full suite of effects are available. The database includes an abstract of a developmental study via the oral exposure route but no multigeneration reproduction studies. As such, there is a need for developmental and multigeneration reproductive toxicity studies via the oral route. The results of the available developmental study indicate that the lowest administered dose exhibited a decrease in mean fetal body weights. Additionally, skeletal anomalies, resorption sites, and reduced number of fetuses per litter were also reported at higher doses in the studies indicating a compound-related developmental effect. Additional studies are needed for confirming these developmental effects. As such, an UF of 10 is applied.
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of definitive information on the variability of response in humans.
UF_L	1	A UF_L of 1 is applied because the POD has been developed using a BMDL.
UF_S	1	A UF_S of 1 is applied because the principal study (Chu et al., 1984) is a subchronic study.
UF_C ≤3000	1000	

Table 8. Confidence Descriptor for Subchronic p-RfD for Benzotrichloride

Confidence Categories	Designation[a]	Discussion
Confidence in study	L	Confidence in the key study is low. Although appropriate endpoints were evaluated in sufficient number of animals, the exposure duration is short. SDH values in the lowest dose administered (0.046 mg/kg-day) were not reported. Though morphological changes in the liver, kidney, and the thyroid gland were noted, incidences of these occurrences in animals were also not reported. Additionally, though the authors state that there were statistically significant increases in SDH activities in animals treated with benzotrichloride, significance level at the lowest administered dose of 0.046 mg/kg-day could not be confirmed because SDH levels for this dose group were not provided in the study summary.
Confidence in database	L	The database includes one chronic-duration carcinogenicity study in rats (Fukuda et al., 1993). One developmental toxicity study (Ruddick et al., 1982) in the form of an abstract was available. However, a two-generation reproduction study via the oral route was not available.
Confidence in subchronic p-RfC[b]	L	The overall confidence in the subchronic p-RfD for benzotrichloride is low because there are data gaps in the principal study as outlined in the "Review of Potentially Relevant Data" section.

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

Derivation of Chronic p-RfD

No published studies investigating the noncancer effects of chronic-duration oral exposure to benzotrichloride in humans or animals have been identified. A short-duration (28-day) study (Chu et al., 1984) is available. In addition, a developmental toxicity study (Ruddick et al., 1982) is available but was reported in abstract form only. The 28-day study would require additional UF of 10 for duration which could result in a composite UF of 10,000. Therefore, the derivation of a chronic oral toxicity value is precluded. A screening chronic p-RfD was not derived due to the combination of the large composite UF and the short duration (28 days) of the available study (Chu et al., 1984).

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic p-RfC

No subchronic RfC is presented here because the selected study, although well designed and managed, is unpublished. For this reason a screening value is presented in this document that may be useful in certain instances. Please see the attached Appendix A for details.

Derivation of Chronic p-RfC

No published studies investigating the effects of chronic-duration inhalation exposure to benzotrichloride in humans or animals have been identified. Lack of data precludes the derivation of a chronic inhalation toxicity value.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

IRIS (U.S. EPA, 1990) provides a WOE Descriptor of B2; probable human carcinogen.

DERIVATION OF PROVISIONAL CANCER VALUES

Derivation of a p-OSF

IRIS (U.S. EPA, 1990) provides an OSF of 1.3×10^{1} per mg/kg-day.

Derivation of a p-IUR

IRIS (U.S. EPA, 1990) did not develop an IUR. The available inhalation studies were evaluated and are all of less than chronic duration. Accordingly, lack of quantitative information from chronic-duration inhalation studies precludes derivation of a p-IUR.

APPENDIX A. DERIVATION OF A SCREENING SUBCHRONIC p-RfC

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for benzotrichloride. However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix 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 Levin (1981, unpublished) is selected as the principal study for the derivation of a screening subchronic p-RfC value. The critical endpoints are statistically significant ($p < 0.01$) changes in relative lungs and trachea weights that are corroborated with morphological alterations in the lung, trachea, and nasal turbinates in males and females and significant ($p < 0.01$) changes in relative adrenal and thyroid weights in males and females. This study was submitted to the EPA, Office of Pesticides and Toxic Substances (as stated in the cover letter of the study) by Velsicol Chemical Corporation, follows GLP guidelines, and seems to follow the standards of study design and performance with the number of animals, examination of potential toxicity endpoints, and presentation of results. Details are provided in the "Review of Potentially Relevant Data" section.

Justification

Available information regarding the effects of chlorinated toluenes including benzotrichloride by inhalation in humans is limited to three occupational exposure studies (Sorahan and Cathcart, 1989; Sorahan et al., 1983; Wong,1988). Besides cancer mortality, none of these studies provide information regarding systemic toxicity effects. Subchronic- and chronic-duration studies investigating systemic toxicity of benzotrichloride in animals via inhalation have not been identified. The only short-term study that is identified pertaining to the toxicity of inhaled benzotrichloride is the Levin (1981) study. This study is well conducted, and the authors state that GLP protocols were followed. Additionally, the study authors also examined several other endpoints, including hematological, biochemical, and urine analysis. Also, the study authors observed animals for mortality, appearance, and behavior after every exposure and once a week, respectively. Because no other short-term, subchronic-duration, or chronic-duration systemic toxicity inhalation studies have been identified, the 4-week inhalation study in Sprague-Dawley rats by Levin (1981) is selected as the principal study for the derivation of a subchronic p-RfC.

Derivation of Screening Subchronic p-RfC

Because both respiratory and extrarespiratory effects were noted in treated animals, dosimetric adjustments using equations for extrarespiratory and respiratory effects are presented below.

Extrarespiratory Effects

To determine the POD for the derivation of the subchronic p-RfC for relative changes in brain and adrenals weight, exposure concentrations were converted to Human Equivalent Concentration (HEC) using dosimetric adjustments for inhalation for extrarespiratory effects as specified in the RfC guidelines (U.S. EPA, 1994b).

$$\begin{aligned} NOAEL_{HEC,\ ExResp} &= (\text{Dose in mg/m}^3) \times (\text{continuous adjustment}) \times \\ &\quad (\text{blood} \div \text{gas partition coefficient}) \\ &= 5.1\ \text{mg/m}^3 \times (6 \div 24) \times (5 \div 7) \times (1)2 = 5.1 \times 0.860 \\ &= 0.91\ \text{mg/m}^3 \end{aligned}$$

Respiratory Effects

To determine the POD for the derivation of subchronic p-RfC for relative changes in lungs and trachea weight that were corroborated with morphological alterations in the lung, trachea, and nasal turbinates in males and females, exposure concentrations were converted to HECs (changes in relative lungs and trachea weight as well as morphological alterations in the lung, trachea, and nasal turbinates) using the dosimetric adjustments for inhalation for respiratory effects as specified in the RfC guidelines (U.S. EPA, 1994b).

$$\begin{aligned} NOAEL_{HEC,\ Resp} &= (\text{Dose in mg/m}^3) \times (\text{continuous adjustment}) \times RGDR^* \\ &= 5.1\ \text{mg/m}^3 \times (6 \div 24) \times (5 \div 7) \times 1.9 \\ &= 1.77\ \text{mg/m}^3 \end{aligned}$$

$$\begin{aligned} {}^*RGDR &= [(V_E/SA^*)_A \div (V_E/SA^*)_H] \\ {}^*SA &= \text{Total surface area} \\ RGDR &= [(0.2464591\ \text{m}^3/\text{day}/0.34375\ \text{m}^2) \div (20\ \text{m}^3/\text{day}/54.34\ \text{m}^2)] \\ RGDR &= 1.9480126 \end{aligned}$$

Default values for V_E human and animal and SA human and animal obtained from U.S. EPA (1994b).

HECs for extrarespiratory effects are lower than respiratory. Therefore, only extrarespiratory effects were modeled.

All of the $BMCL_{1SD}$ predicted values in Table A.1 are greater than the study NOAEL of 0.91 mg/m^3. Since the study NOAEL is correlated to study design and only identifies a lower point for no effects while the BMCL utilizes additional data from the study to predict a NOAEL, the lowest $BMCL_{1SD}$ is used as a POD. The relative brain weight in male rats, being the lowest, is selected for use in the derivation of the p-RfC.

$$\begin{aligned} POD &= (BMCL_{1SD}, \text{extrarespiratory}) \times 1 \text{ (modeling was done with duration adjusted inputs)} \times (\text{blood partition coefficient}) \\ &= 1.36\ \text{mg/m}^3 \times 1 \\ POD\ (BMCL_{\text{Adjusted, HEC}}) &= 1.36\ \text{mg/m}^3 \end{aligned}$$

A screening subchronic p-RfC is developed as follows:

Screening Subchronic p-RfC = $BMCL_{Adjusted, HEC} \div UF_C$
= $1.36\ mg/m^3 \div 300$
= $\mathbf{5 \times 10^{-3}\ mg/m^3}$

Tables A.2 and A.3, respectively, summarize the UFs and the confidence descriptor for the screening subchronic p-RfC.

Table A.1. BMC Modeling Summary

Effect[a]	$BMCL_{1SD}$
Relative weight changes in adrenals in female rats (Table C.1)	3.37
Relative weight changes in adrenals in male rats (Table C.2)	2.27
Relative weight changes in brain in female rats (Table C.3)	4.92
Relative weight changes in brain in male rats (Table C.4)	1.36
Relative weight changes in thyroid in female rats (Table C.5)	5.89
Relative weight changes in thyroid in male rats (Table C.6)	3.60

[a]See tables indicated.

Table A.2. Uncertainty Factors for Screening Subchronic p-RfC for Benzotrichloride

UF	Value	Justification
UF_A	3	A UF_A of 3 is applied for animal-to-human extrapolation to account for the toxicodynamic portion of the UF_A because the toxicokinetic portion ($10^{0.5}$) has been addressed in dosimetric conversions.
UF_D	10	Other than the principal study, there are no other inhalation studies available. There is an the oral developmental study available in abstract format only indicating that the lowest administered dose exhibited a decrease in mean fetal body weights. Additionally, the study authors reported skeletal anomalies, resorption sites, and reduced number of fetuses per litter at higher doses in the study, indicating a compound related developmental effect.
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of definitive information on the variability of response in humans.
UF_L	1	A UF_L of 1 is applied because the POD has been developed using a BMCL.
UF_S	1	A UF_S of 1 is applied because the principal study (Levin, 1981) is of subchronic duration.
UF_C $\leq$3000	300	

Table A.3. Confidence Descriptor for Screening Subchronic p-RfC for Benzotrichloride

Confidence Categories	Designation[a]	Discussion
Confidence in Study	L	Confidence in the key study is low. Although the study evaluated appropriate endpoints in an adequate number of animals, the exposure duration is short.
Confidence in Database	L	The database includes three chronic-duration carcinogenicity studies in rats and mice (Koshi and Fukuda, 1986; Takemoto et al., 1978; Yoshimura et al., 1979). No developmental toxicity studies and no two-generation reproduction studies are available via the inhalation route.
Confidence in Screening Subchronic p-RfC[b]	L	The overall confidence in the subchronic p-RfC for benzotrichloride is low.

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

APPENDIX B. DATA TABLES

Table B.1. Cancer Incidence in Mice Exposed to Benzotrichloride via Gastric Intubation for 25 Weeks[a]

Dose Group (µl/day)	No. of Mice With Tumors/ No. of Effective Mice (%)	No. of Mice With Tumors							
		Forestomach			Lung			Hematopoietic System (%)	Others (%)
		SCC	PA	(%)	ADC	AD	(%)		
0	4/39 (10)	0	0	0	1	1	5	1 (3)	1[b]
0.0315	10/39 (26)	0	0	0	1	6	18	2 (5)	2[c]
0.125	30/39 (77)*	2	0	5	9	17	67*	1 (3)	3[d]
0.5	39/40 (98)*	21	2	58*	16	19	88*	3 (8)	5[e]
2.0	36/38 (95)*	24	1	66*	10	14	63*	8 (21)*	4[f]

[a]Values obtained from Fukuda et al. (1993)
[b]Fibrosarcoma of the uterus
[c]One hemangioendothelioma of the liver and one adenoma of the Harderian gland
[d]One adenocarcinoma of the salivary gland, and one adenocarcinoma and adenoma of the mammary gland
[e]One squamous cell carcinoma of the esophagus, one carcinosarcoma and one adenocarcinoma of the salivary gland, and one adenocarcinoma and adenoma of the mammary gland
[f]One adenoma of the salivary gland, one adenosquamous carcinoma, one adenocarcinoma, and one adenoma of the mammary gland

*Statistically significantly different from the control ($p < 0.01$) (Fisher's exact probability test)

SCC = Squamous cell carcinoma; PA = Papilloma; ADC = Adenocarcinoma; AD = Adenoma

Table B.2. Group Mean Body Weight in Rats Treated with Benzotrichloride via Inhalation Exposure[a]

Dose Group (ppm)	PreExposure Body Weight (g)	Body Weight (g)							
		Week 1		Week 2		Week 3		Week 4	
		Body Weight (% Change Compared to Control)	% Change Compared to Preexposure	Body Weight (% Change Compared to Control)	% Change Compared to Preexposure	Body Weight (% Change Compared to Control)	% Change Compared to Preexposure	Body Weight (% Change Compared to Control)	% Change Compared to Preexposure
Males									
0	212 ± 5.6	272 ± 11.3	28%	315 ± 17.3	49%	350 ± 18.9	65%	379 ± 20.3	79%
5.1	212 ± 4.9	270 ± 15.2 (−0.7%)	27%	317 ± 19.7 (0.63%)	50%	352 ± 25.5 (0.57%)	66%	379 ± 32.5 (0%)	79%
48.2	211 ± 4.2	241 ± 4.8* (−11%)	14%	255 ± 14.6* (−19%)	21%	272 ± 12.8* (−22%)	29%	286 ± 17.9* (−25%)	36%
460.0[b]	213 ± 8.3	150 (−45%)	−30%	NA	NA	NA	NA	NA	NA
Females									
0	161 ± 8.9	193 ± 13.5	15%	210 ± 11.2	35%	225 ± 15.7	40%	238 ± 15.4	48%
5.1	162 ± 8.2	193 ± 9.8 (0%)	15%	215 ± 13.1 (2.4%)	33%	229 ± 17.8 (1.7%)	41%	243 ± 19.3 (2.1%)	50%
48.2	163 ± 5.9	179 ± 8.0* (−7%)	10%	189 ± 10.7** (−10%)	16%	198 ± 14.7** (−12%)	21%	203 ± 19.7** (−14.7%)	25%
460.0[b]	160 ± 5.6	105 ± 3.5** (−46%)	−34%	NA	NA	NA	NA	NA	NA

[a]Values obtained from Levin (1981) and presented as mean body weight in grams ± standard deviation
[b]All animals in this dose group either died or were killed in extremis by the seventh day of the study

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

NA = Not applicable

Table B.3. Results of Absolute Organ Weights in Rats Exposed to Benzotrichloride via Inhalation for 4 Weeks[a]

Dose Group (µg/L)	No. of Animals	Absolute Organ Weight (% Change Compared to Control)						
		Spleen (g)	Liver (g)	Kidney (g)	Heart (g)	Lungs/Trachea (g)	Adrenals (mg)	Pituitary (g)
Males								
0	10	0.69 ± 0.094	9.88 ± 1.162	2.57 ± 0.169	1.34 ± 0.174	1.40 ± 0.149	57 ± 5.7	12 ± 1.1
5.1	10	0.74 ± 0.164 (7)	9.72 ± 1.001 (−1.6)	2.51 ± 0.308 (−2.3)	1.37 ± 0.284 (2.2)	1.43 ± 0.172 (2.1)	53 ± 5.4 (−7)	11 ± 2.3 (−8.3)
48.2	10	0.48 ± 0.082** (−30)	7.37 ± 0.561** (−25)	2.00 ± 0.137** (−22)	1.03 ± 0.096 (−23)	1.53 ± 0.137 (9.3)	50 ± 7.0* (−12.3)	9 ± 1.3** (−25)
Females								
0	10	0.49 ± 0.128	6.47 ± 0.456	1.64 ± 0.137	0.86 ± 0.080	1.10 ± 0.130	62 ± 4.8	12 ± 1.2
5.1	10	0.53 ± 0.092 (8.2)	6.58 ± 0.626 (1.7)	1.67 ± 0.208 (1.8)	0.89 ± 0.144 (3.5)	1.22 ± 0.228 (11)	66 ± 6.0 (6.5)	13 ± 2.1 (8.3)
48.2	9	0.43 ± 0.074 (−12)	5.49 ± 0.401** (−15)	1.48 ± 0.098 (−9.8)	0.74 ± 0.100** (−14)	1.36 ± 0.183** (24)	64 ± 5.3 (3.2)	11 ± 2.0 (−8.33)

[a]Values obtained from Levin (1981) and presented as mean ± standard deviation

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

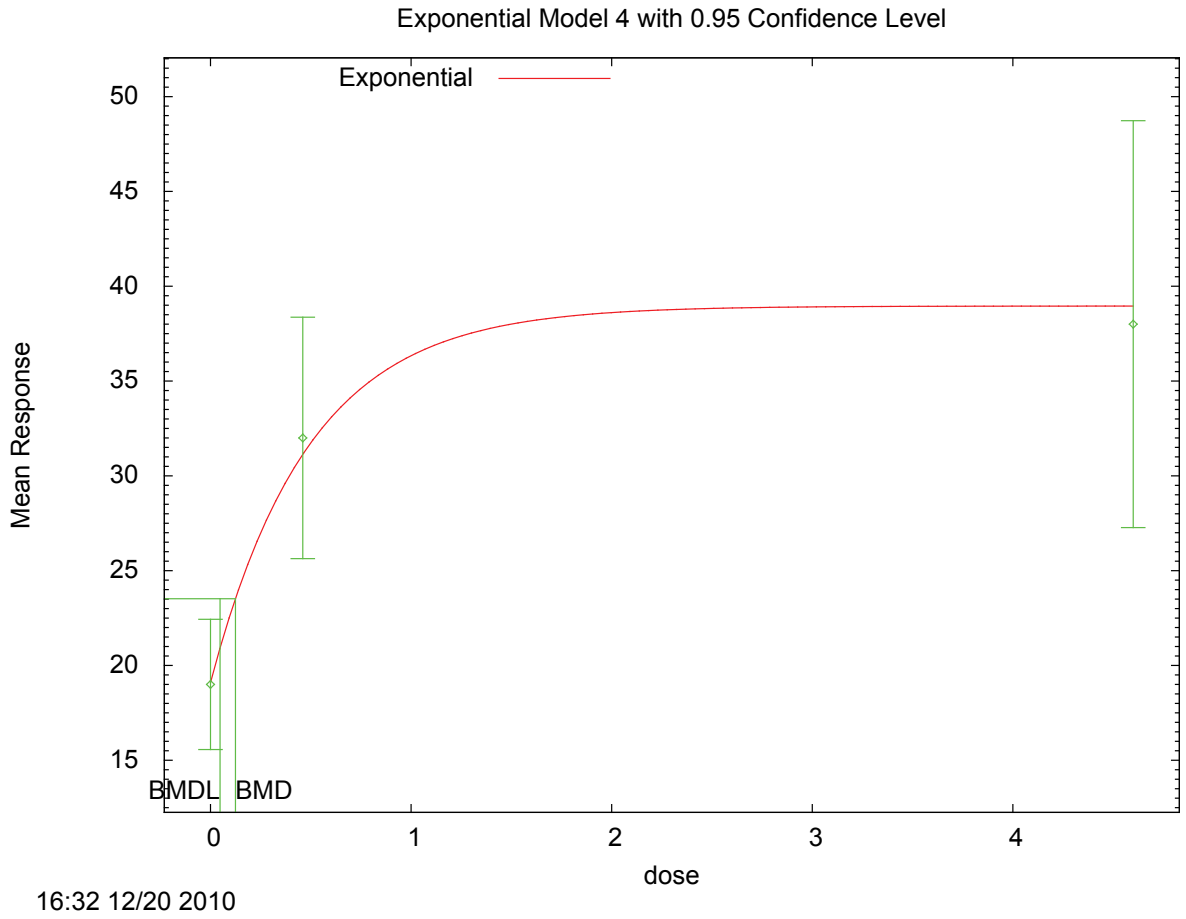
Table B.4. Results of Relative Organ Weights in Rats Exposed to Benzotrichloride via Inhalation for 4 Weeks[a]

Dose Group (µg/L)	No. of Animals	Relative Organ Weight (g) (% Change Compared to Control)			
		Lungs/Trachea	Brain	Adrenals	Thyroid
Males					
0	10	0.40 ± 0.04	0.57 ± 0.04	0.016 ± 0.001	0.0060 ± 0.0010
5.1	10	0.42 ± 0.03 (5)	0.57 ± 0.03 (0)	0.016 ± 0.002 (0)	0.0059 ± 0.0006 (−1.7)
48.2	9	0.60 ± 0.08** (50)	0.75 ± 0.06** (32)	0.019 ± 0.003* (19)	0.0074 ± 0.0012** (23.3)
Females					
0	10	0.51 ± 0.034	0.88 ± 0.078	0.029 ± 0.0035	0.0076 ± 0.0017
5.1	10	0.56 ± 0.091 (9.8)	0.84 ± 0.043 (−4.5)	0.030 ± 0.0031 (3.4)	0.0072 ± 0.0016 (−5.3)
48.2	9	0.75 ± 0.067** (39.2)	1.00 ± 0.066** (13.6)	0.035 ± 0.0039** (20.7)	0.0086 ± 0.0018 (13.2)

[a]Values obtained from Levin (1981) are presented as percentage of body weight ± standard deviation; study authors do not provide information on whether preexposure body weights, or body weights after 4 weeks of exposure were used to determine the relative organ weights

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

APPENDIX C. BMC MODELING OUTPUTS FOR BENZOTRICHLORIDE



Chu et al., 1984: Output for selected model; Exponential (SDH)

```
========================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\USEPA\BMDS21\Data\Trichlorotoluene\exp_Trichlorotoluene-
lastdose_chlorotoluene-exponcv-1.(d)
        Gnuplot Plotting File:
                                            Mon Dec 20 16:32:53 2010
 ========================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.
```

Model 2 is nested within Models 3 and 4.
Model 3 is nested within Model 5.
Model 4 is nested within Model 5.

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 3
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

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	-5.98576
rho	3.07359
a	18.05
b	0.547585
c	2.21053
d	1

Parameter Estimates

Variable	Model 4
lnalpha	-6.20098
rho	3.11033
a	19.0972
b	2.02513
c	2.03987
d	1

NC = No Convergence

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	19	4.8
0.46	10	32	8.9
4.6	10	38	15

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	19.1	4.422	-0.06952
0.46	31.13	9.455	0.29
4.6	38.95	13.4	-0.2252

Other models for which likelihoods are 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 + log(mean(i)) * rho)

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

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-83.80127	4	175.6025
A2	-78.04677	6	168.0935
A3	-78.28222	5	166.5644
R	-91.22702	2	186.454
4	-78.28222	5	166.5644

Additive constant for all log-likelihoods = -27.57. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	26.36	4	< 0.0001
Test 2	11.51	2	0.003168
Test 3	0.4709	1	0.4926
Test 6a	5.684e-014	0	N/A

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.

Degrees of freedom for Test 6a are less than or equal to 0. The Chi-Square test for fit is not valid.

```
  Benchmark Dose Computations:

    Specified Effect = 1.000000

           Risk Type = Estimated standard deviations from control

    Confidence Level = 0.950000

                 BMD =     0.124376

                BMDL =    0.0477324
```

Levin, 1981: Relative Weight Changes in Adrenals in Female Rats

Table C.1. Model Predictions for Relative Weight Changes in Adrenals in Female Rats[a]

Model	Homogeneity Variance *p*-Value	Goodness-of-Fit *p*-Value[b]	AIC for Fitted Model	BMC_{1SD} (mg/m^3)	$BMCL_{1SD}$ (mg/m^3)	Conclusions
Linear (constant variance)	0.790	0.796	−296.10	4.89	3.37	Lowest AIC Lowest BMCL
Polynomial (constant variance)	0.790	0.796	−296.10	4.89	3.37	Lowest AIC Lowest BMCL Maximum order beta = 0 β2 = 0
Power (constant variance)	0.790	0.796	−296.10	4.89	3.37	Lowest AIC Lowest BMCL hit bound (power = 1)

[a]Levin, 1981
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria

AIC = Akaike's Information Criteria; BMC = benchmark concentration; BMCL lower confidence limit (95%) on the benchmark concentration

Output for selected model: Linear

Levin, 1981: Relative Weight Changes in Adrenals in Female Rats

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\Levin_1981_Adrenals_F_Linear_2.(d)
         Gnuplot Plotting File:  C:\1\Levin_1981_Adrenals_F_Linear_2.plt
                                                Mon May 03 22:13:09 2010
 ================================================================

 [add notes here]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 3
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 = 1.22469e-005
rho = 0 Specified
beta_0 = 0.0291803
beta_1 = 0.000678636

Asymptotic Correlation Matrix of Parameter Estimates

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

	alpha	beta_0	beta_1
alpha	1	1.3e-009	2.6e-010
beta_0	1.3e-009	1	-0.62
beta_1	2.6e-010	-0.62	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	1.10054e-005	2.89015e-006	5.34078e-006	1.667e-005
beta_0	0.0291802	0.000784162	0.0276433	0.0307171
beta_1	0.000678924	0.000162535	0.000360361	0.000997487

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	0.029	0.0292	0.0035	0.00332	-0.172
0.9107	10	0.03	0.0298	0.0031	0.00332	0.192
8.607	9	0.035	0.035	0.0039	0.00332	-0.0214

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	151.081809	4	-294.163619
A2	151.318092	6	-290.636184
A3	151.081809	4	-294.163619
fitted	151.048341	3	-296.096682
R	144.218266	2	-284.436532

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	14.1997	4	0.006684
Test 2	0.472566	2	0.7896
Test 3	0.472566	2	0.7896
Test 4	0.0669367	1	0.7959

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

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

Benchmark Dose Computation

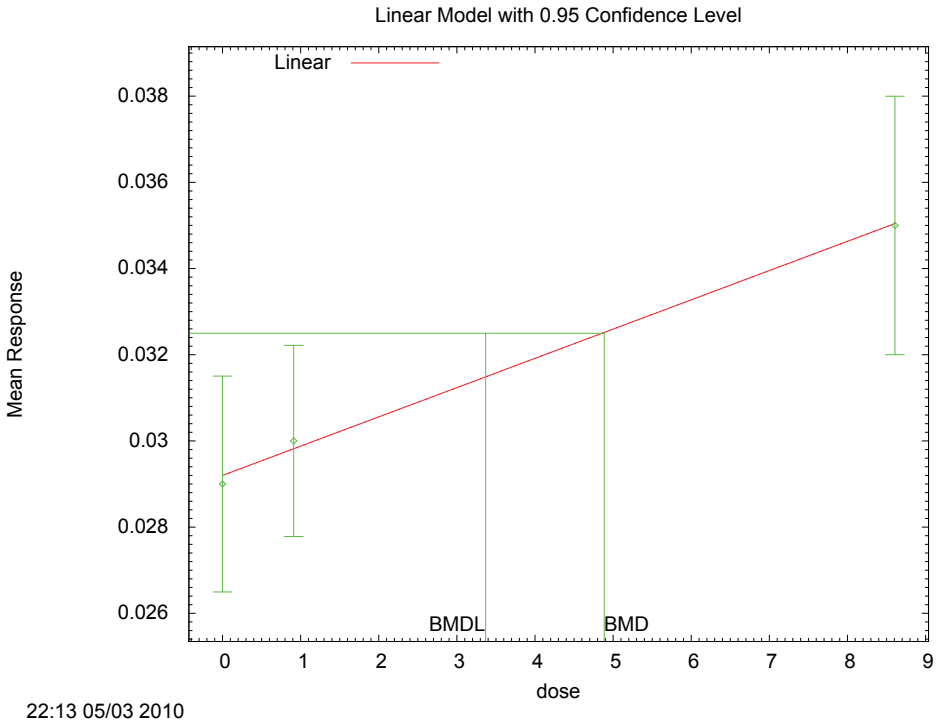
Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMC = 4.88631

BMCL = 3.36777


Linear Model with 0.95 Confidence Level
Linear
Mean Response
0.038
0.036
0.034
0.032
0.03
0.028
0.026
BMDL
BMD
0
1
2
3
4
5
6
7
8
9
dose
22:13 05/03 2010

Levin, 1981: Relative Weight Changes in Adrenals in Female Rats

Levin, 1981: Relative Weight Changes in Adrenals in Male Rats

Table C.2. Model Predictions for Relative Weight Changes in Adrenals in Male Rats[a]

Model	Homogeneity Variance *p*-Value	Goodness-of-Fit *p*-Value[b]	AIC for Fitted Model	BMC_{1SD} (mg/m^3)	$BMCL_{1SD}$ (mg/m^3)	Conclusions
Power (nonconstant variance)	0.006	NA	125388.30	−999.00	−999.00	Invalid BMC Invalid BMCL *p*-score 4 < 0.1 Poor variance model
Linear (nonconstant variance)	**0.006**	**0.615**	**−340.03**	**3.88**	**2.27**	**Lowest AIC Lowest BMCL Poor variance model**
Polynomial (nonconstant variance)	**0.006**	**0.615**	**−340.03**	**3.88**	**2.27**	**Lowest AIC Lowest BMCL Poor variance model Maximum order beta = 0 β2 = 0**

[a]Levin, 1981
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria

AIC = Akaike's Information Criteria; BMC = benchmark concentration; BMCL lower confidence limit (95%) on the benchmark concentration

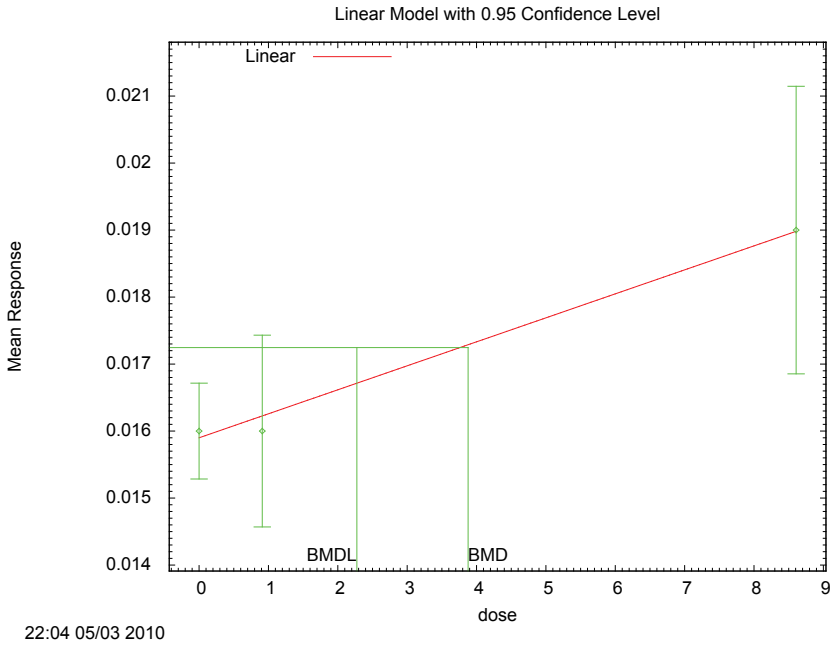
Output for selected model: Linear

Levin, 1981: Relative Weight Changes in Adrenals in Male Rats

```
 ======================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\Levin_1981_Adrenals_M_Linear_1.(d)
         Gnuplot Plotting File:  C:\1\Levin_1981_Adrenals_M_Linear_1.plt
                                              Mon May 03 22:04:40 2010
 ======================================================================

 [add notes here]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 3
   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 =     -12.2751
                            rho =            0
                         beta_0 =    0.0158432
                         beta_1 =  0.000364611


           Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho       beta_0       beta_1

    lalpha             1            1        0.062        -0.12

       rho             1            1        0.062        -0.12

    beta_0         0.062        0.062            1        -0.44

    beta_1         -0.12        -0.12        -0.44            1


                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha          22.0711          14.1123           -5.58851            49.7308
            rho          8.50195          3.45995            1.72057            15.2833
         beta_0        0.0158586      0.000339921          0.0151924          0.0165248
         beta_1      0.000357602      0.000116287         0.000129684         0.000585521


     Table of Data and Estimated Values of Interest

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

    0    10      0.016       0.0159        0.001      0.00139          0.322
```

```
0.9107    10      0.016       0.0162        0.002      0.00151         -0.385
8.607     10      0.019       0.0189        0.003      0.00295         0.0681


 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          170.706390           4    -333.412781
              A2          175.895471           6    -339.790943
              A3          174.141539           5    -338.283079
          fitted          174.014936           4    -340.029872
               R          164.864419           2    -325.728838


                   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              22.0621          4       0.0001948
   Test 2              10.3782          2        0.005577
   Test 3              3.50786          1         0.06108
   Test 4             0.253206          1          0.6148

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
```

```
BMC =         3.87848

BMCL =        2.27453
```



Levin, 1981: Relative Weight Changes in Adrenals in Male Rats

Levin, 1981: Relative Weight Changes in Brain in Female Rats

Table C.3. Model Predictions for Relative Weight Changes in Brain in Female Rats[a]

Model	Homogeneity Variance *p*-Value	Goodness-of-Fit *p*-Value[b]	AIC for Fitted Model	BMC_{1SD} (mg/m^3)	$BMCL_{1SD}$ (mg/m^3)	Conclusions
Linear (constant variance)	0.185	0.048	−123.76	3.91	2.82	*p*-score 4 < 0.1
Power (constant variance)	0.185	NA	−123.56	7.88	3.20	*p*-score 4 < 0.1
Polynomial (constant variance)	**0.185**	**0.132**	**−125.40**	**5.76**	**4.92**	**Lowest AIC Lowest BMCL**

[a]Levin, 1981
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria

AIC = Akaike's Information Criteria; BMC = benchmark concentration; BMCL lower confidence limit (95%) on the benchmark concentration

Output for selected model: Polynomial

Levin, 1981: Relative Weight Changes in Brain in Female Rats

```
 ========================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\Levin_1981_Brain_F_Poly_2.(d)
         Gnuplot Plotting File:  C:\1\Levin_1981_Brain_F_Poly_2.plt
                                                Mon May 03 22:14:34 2010
 ========================================================================

 [add notes here]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 3
   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 =   0.00408635
                            rho =            0   Specified
                         beta_0 =         0.88
                         beta_1 =            0
                         beta_2 =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho    -beta_1
                 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_2

     alpha             1    -4.5e-009    -1.9e-010

    beta_0    -4.5e-009            1        -0.56

    beta_2    -1.9e-010        -0.56            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha       0.00396162       0.00104037          0.00192253          0.00600071
         beta_0         0.859331        0.0141536             0.83159            0.887072
         beta_1     3.87762e-024               NA
         beta_2       0.00189536      0.000342935          0.00122322           0.0025675

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	10	0.88	0.859	0.078	0.0629	1.04
0.9107	10	0.84	0.861	0.043	0.0629	-1.05
8.607	9	1	1	0.066	0.0629	0.0124

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	66.834899	4	-125.669797
A2	68.522550	6	-125.045100
A3	66.834899	4	-125.669797
fitted	65.700977	3	-125.401955
R	55.268815	2	-106.537629

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	26.5075	4	<.0001
Test 2	3.3753	2	0.185
Test 3	3.3753	2	0.185
Test 4	2.26784	1	0.1321

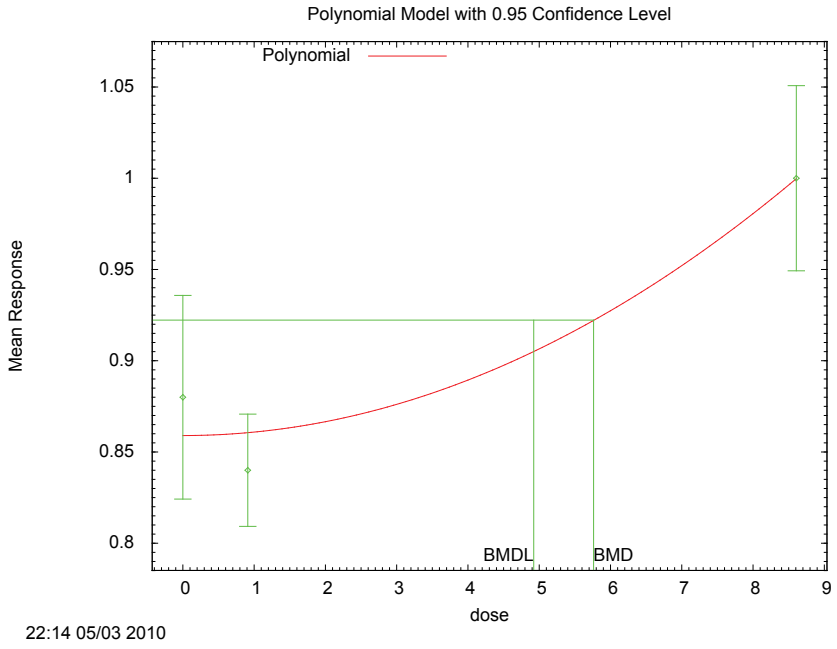
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

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

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

             BMC =       5.76266

            BMCL =       4.92272
```



Levin, 1981: Relative Weight Changes in Brain in Female Rats

Levin, 1981: Relative Weight Changes in Brain in Male Rats

Table C.4. Model Predictions for Relative Weight Changes in Brain in Male Rats[a]

Model	Homogeneity Variance *p*-Value	Goodness-of-Fit *p*-Value[b]	AIC for Fitted Model	BMC_{1SD} (mg/m^3)	$BMCL_{1SD}$ (mg/m^3)	Conclusions
Linear (nonconstant variance)	0.089	0.154	−153.11	1.60	1.19	Lowest BMCL
Polynomial (nonconstant variance)	**0.089**	**0.782**	**−155.06**	**3.70**	**1.36**	**Lowest AIC β1 = 0**
Power (nonconstant variance)	0.089	NA	−153.12	7.13	1.37	*p*-score 4 < 0.1 BMC/BMCL ratio > 3

[a]Levin, 1981
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria

AIC = Akaike's Information Criteria; BMC = benchmark concentration; BMCL lower confidence limit (95%) on the benchmark concentration

Output for selected model: Polynomial

Levin, 1981: Relative Weight Changes in Brain in Male Rats

```
 ========================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\Levin_1981_Brain_M_Poly_1.(d)
         Gnuplot Plotting File:  C:\1\Levin_1981_Brain_M_Poly_1.plt
                                                Mon May 03 22:02:33 2010
 ========================================================================

 [add notes here]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

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


   Dependent variable = Mean
   Independent variable = Dose
   The polynomial coefficients are restricted to be positive
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 3
   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 =     -6.19808
                            rho =            0
                         beta_0 =         0.57
                         beta_1 =            0
                         beta_2 =   0.00271731


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -beta_1
                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_2

    lalpha           1         0.96       1e-005     -0.00024

       rho        0.96            1    -8.7e-006     -0.00021

    beta_0       1e-005    -8.7e-006            1         -0.4

    beta_2     -0.00024     -0.00021         -0.4            1



                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha         -4.63533         0.971828           -6.54008            -2.73059
            rho          3.82488          1.99069          -0.076796             7.72656
         beta_0         0.569001       0.00756025           0.554183            0.583818
         beta_1                0               NA
         beta_2       0.00244278      0.000264367          0.00192463          0.00296093

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	10	0.57	0.569	0.04	0.0335	0.0943
0.9107	10	0.57	0.571	0.03	0.0337	-0.0962
8.607	10	0.75	0.75	0.06	0.0568	0.00206

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	79.551590	4	-151.103179
A2	81.968852	6	-151.937704
A3	81.570537	5	-153.141074
fitted	81.532234	4	-155.064468
R	55.608044	2	-107.216087

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	52.7216	4	<.0001
Test 2	4.83452	2	0.08917
Test 3	0.79663	1	0.3721
Test 4	0.0766067	1	0.7819

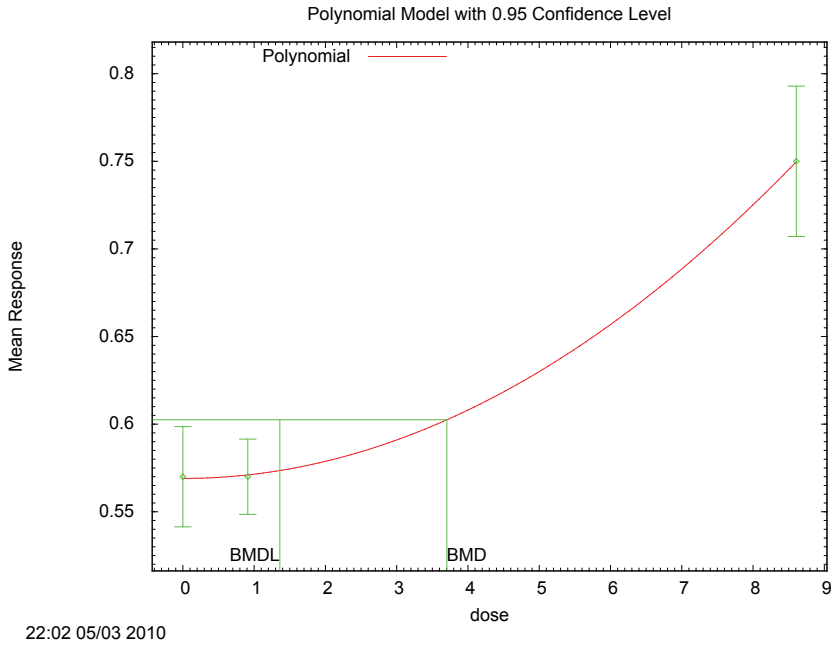
The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

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

             BMC =       3.70353


            BMCL =       1.36067
```



Levin, 1981: Relative Weight Changes in Brain in Male Rats

Levin, 1981: Relative Weight Changes in Thyroid in Female Rats

Table C.5. Model Predictions for Relative Weight Changes in Thyroid in Female Rats[a]

Model	Homogeneity Variance *p*-Value	Goodness-of-Fit *p*-Value[b]	AIC for Fitted Model	BMC_{1SD} (mg/m^3)	$BMCL_{1SD}$ (mg/m^3)	Conclusions
Linear (constant variance)	0.943	0.462	−337.56	11.48	5.89	Lowest BMCL
Power (constant variance)	0.943	NA	−335.80	8.90	6.02	*p*-score 4 < 0.1
Polynomial (constant variance)	**0.943**	**0.566**	**−337.78**	**9.98**	**7.20**	**Lowest AIC**

[a]Levin, 1981
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria

AIC = Akaike's Information Criteria; BMC = benchmark concentration; BMCL lower confidence limit (95%) on the benchmark concentration

Output for selected model: Polynomial

Levin, 1981: Relative Weight Changes in Thyroid in Female Rats

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\Levin_1981_Thyroids_F_Poly_2.(d)
         Gnuplot Plotting File:  C:\1\Levin_1981_Thyroids_F_Poly_2.plt
                                              Mon May 03 22:12:00 2010
 ================================================================

 [add notes here]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 3
   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 = 2.88346e-006
                            rho =            0   Specified
                         beta_0 =       0.0076
                         beta_1 =            0
                         beta_2 =            0


           Asymptotic Correlation Matrix of Parameter Estimates
```

(*** The model parameter(s) -rho -beta_1
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_2
alpha	1	5e-010	-9.5e-012
beta_0	5e-010	1	-0.56
beta_2	-9.5e-012	-0.56	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	2.61465e-006	6.86641e-007	1.26886e-006	3.96044e-006
beta_0	0.00739443	0.000363612	0.00668176	0.0081071
beta_1	2.03355e-025	NA		
beta_2	1.62389e-005	8.81012e-006	-1.02863e-006	3.35064e-005

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	10	0.0076	0.00739	0.0017	0.00162	0.402
0.9107	10	0.0072	0.00741	0.0016	0.00162	-0.407
8.607	9	0.0086	0.0086	0.0018	0.00162	0.0048

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

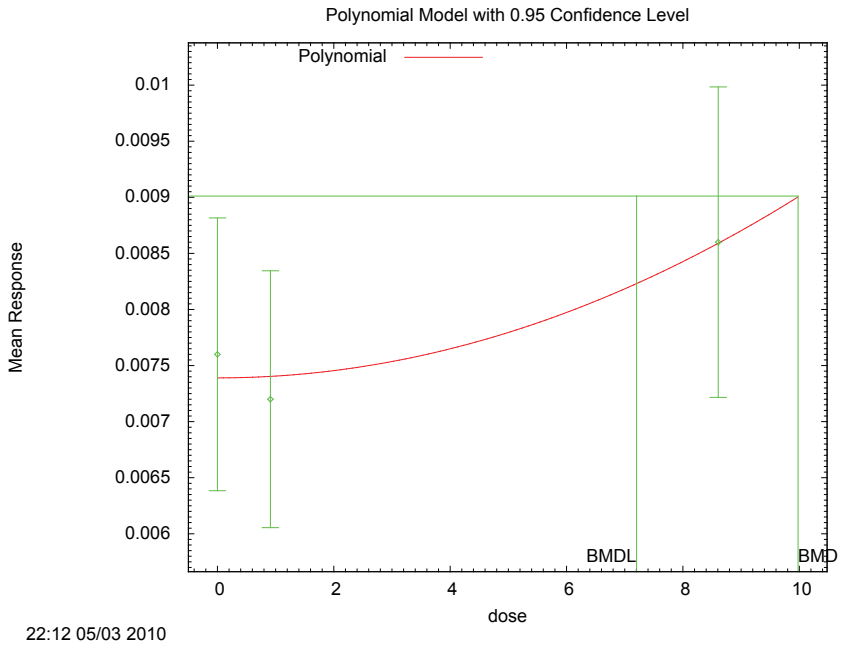
Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	172.052916	4	-336.105832
A2	172.112133	6	-332.224266
A3	172.052916	4	-336.105832
fitted	171.888511	3	-337.777023
R	170.282159	2	-336.564317

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              3.65995          4           0.454
   Test 2             0.118434          2          0.9425
   Test 3             0.118434          2          0.9425
   Test 4              0.32881          1          0.5664

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

             BMC =        9.97873


            BMCL =        7.20419
```



Levin, 1981: Relative Weight Changes in Thyroid in Female Rats

Levin, 1981: Relative Weight Changes in Thyroid in Male Rats

Table C.6. Model Predictions for Relative Weight Changes in Thyroid in Male Rats[a]

Model	Homogeneity Variance *p*-Value	Goodness-of-Fit *p*-Value[b]	AIC for Fitted Model	BMC_{1SD} (mg/m^3)	$BMCL_{1SD}$ (mg/m^3)	Conclusions
Linear (constant variance)	**0.105**	**0.818**	**−385.29**	**5.27**	**3.60**	**Lowest AIC Lowest BMCL**
Power (constant variance)	0.105	NA	−381.64	8.16	3.68	*p*-score 4 < 0.1
Polynomial (constant variance)	0.105	0.777	−383.62	6.83	5.66	

[a]Levin, 1981
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria

AIC = Akaike's Information Criteria; BMC = benchmark concentration; BMCL lower confidence limit (95%) on the benchmark concentration

Output for selected model: Linear

Levin, 1981: Relative Weight Changes in Thyroid in Male Rats

```
 ======================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\Levin_1981_Thyroids_M_Linear_2.(d)
         Gnuplot Plotting File:  C:\1\Levin_1981_Thyroids_M_Linear_2.plt
                                                Mon May 03 22:10:52 2010
 ======================================================================

 [add notes here]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 3
   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 = 9.33333e-007
                            rho =           0   Specified
                         beta_0 =   0.00587747
                         beta_1 =   0.00017521


!!! Warning:  optimum may not have been found. !!!
!!! You may want to try choosing different initial values.  !!!
```

Asymptotic Correlation Matrix of Parameter Estimates

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

	beta_0	beta_1
beta_0	1	-0.63
beta_1	-0.63	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	8.51334e-007	NA		
beta_0	0.00587747	0.00021804	0.00545012	0.00630482
beta_1	0.00017521	4.36342e-005	8.96887e-005	0.000260732

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	10	0.006	0.00588	0.001	0.000923	0.42
0.9107	10	0.0059	0.00604	0.0006	0.000923	-0.47
8.607	10	0.0074	0.00739	0.0012	0.000923	0.0497

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

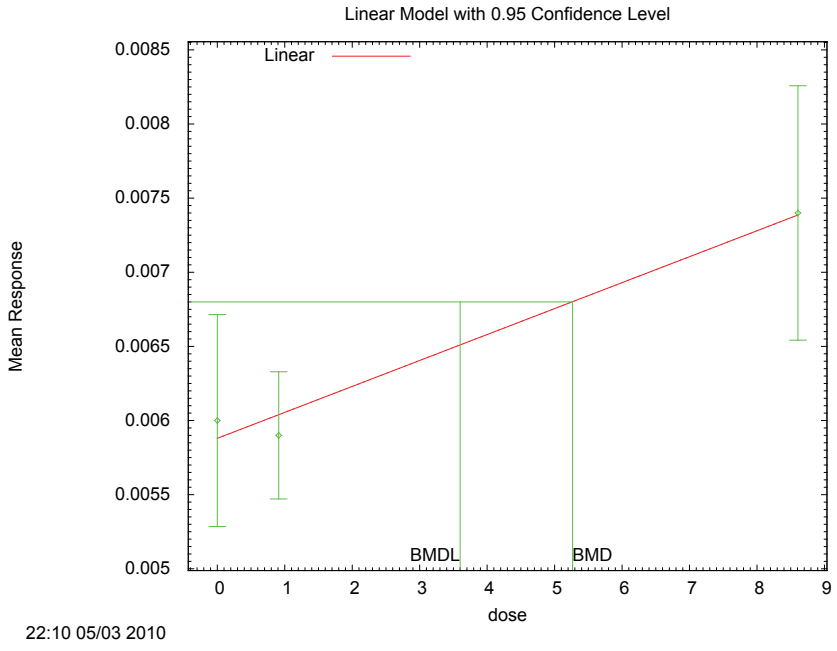
Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	194.847959	4	-381.695918
A2	197.098107	6	-382.196214
A3	194.847959	4	-381.695918
fitted	194.646919	2	-385.293839
R	188.194979	2	-372.389959

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              17.8063          4        0.001346
   Test 2               4.5003          2          0.1054
   Test 3               4.5003          2          0.1054
   Test 4             0.402079          2          0.8179

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

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

             BMC =        5.26612


            BMCL =        3.59958
```



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APPENDIX D. REFERENCES

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