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Provisional Peer-Reviewed Toxicity Values for

p-α,α,α-Tetrachlorotoluene
(CASRN 5216-25-1)



U.S. EPA Office of Research and Development
Center for Public Health and Environmental Assessment

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Center for Public Health and Environmental Assessment
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Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA Office of Research and Development's Center for Public Health and Environmental Assessment.

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COMMONLY USED ABBREVIATIONS AND ACRONYMS[1]

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service registry number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPHEA	Center for Public Health and Environmental Assessment
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
ER	estrogen receptor
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	*N*-acetyl-β-D-glucosaminidase
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_C	composite uncertainty factor
UF_D	database uncertainty factor
UF_H	intraspecies uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
U.S.	United States of America
WBC	white blood cell

[1]Abbreviations and acronyms not listed on this page are defined upon first use in the PPRTV document.

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR *p*-α,α,α-TETRACHLOROTOLUENE (CASRN 5216-25-1)

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 at least two Center for Public Health and Environment Assessment (CPHEA) scientists and an independent external peer review by at least 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.

Currently available PPRTV assessments can be accessed on the U.S. Environmental Protection Agency's (EPA's) PPRTV website at https://www.epa.gov/pprtv. PPRTV assessments are eligible to be updated on a 5-year cycle to incorporate new data or methodologies that might impact the toxicity values or characterization of potential for adverse human-health effects and are revised as appropriate. Questions regarding nomination of chemicals for update can be sent to the appropriate U.S. EPA Superfund and Technology Liaison (https://www.epa.gov/research/fact-sheets-regional-science).

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. 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.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

QUESTIONS REGARDING PPRTVS

Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA Office of Research and Development's (ORD's) CPHEA.

INTRODUCTION

p-α,α,α-Tetrachlorotoluene (4-chlorobenzotrichloride), CASRN 5216-25-1, belongs to the class of compounds known as ring-chlorinated chlorotoluenes. It is used as an intermediate for pigments, pesticides, and pharmaceutical manufacture (Lipper et al., 2017; MAK-Commission, 2012). *p*-α,α,α-Tetrachlorotoluene is listed on the U.S. EPA Toxic Substances Control Act's public inventory (U.S. EPA, 2017) and is registered with Europe's Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) program (ECHA, 2018).

The empirical formula for *p*-α,α,α-tetrachlorotoluene is $C_7H_4C1_4$ (see Figure 1). Table 1 summarizes the physicochemical properties for *p*-α,α,α-tetrachlorotoluene. Under aqueous conditions, *p*-α,α,α-tetrachlorotoluene is expected to hydrolyze rapidly to form *p*-chlorobenzoic acid and hydrochloric acid, based on several nonguideline studies demonstrating that this reaction occurs within minutes (MAK-Commission, 2012; ECB, 2007). Because of the chemical's high rate of reactivity, only estimated values are available for physicochemical properties of *p*-α,α,α-tetrachlorotoluene that would be measured in water, including water solubility, octanol-water partition coefficient (log K_{ow}), Henry's law constant, and soil adsorption coefficient (K_{oc}). Other environmental fate pathways, such as biodegradation, are not expected to be important removal pathways for *p*-α,α,α-tetrachlorotoluene. *p*-α,α,α-Tetrachlorotoluene is a liquid at room temperature (ECHA, 2018). In the atmosphere, *p*-α,α,α-tetrachlorotoluene is expected to react with water vapor. Indirect photochemical degradation is expected to be slow, with an estimated half-life of 43 days for the reaction with hydroxyl radicals.

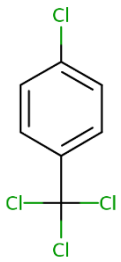


Figure 1. *p*-α,α,α-Tetrachlorotoluene Structure

Table 1. Physicochemical Properties of *p*-α,α,α-Tetrachlorotoluene (CASRN 5216-25-1)

Property (Unit)	Value
Physical state	Liquid[a]
Boiling point (°C)	245[b]
Melting point (°C)	5.82[a]
Density (g/cm^3 at 20°C)	1.4463[b]
Vapor pressure (mm Hg at 20°C)	0.03[a] (converted from 0.04 millibar)
pH (unitless)	NV
pKa (unitless)	NV
Solubility in water (mg/L at 25°C)	4 (estimated)[c]
Octanol-water partition constant (log K_{ow})	4.5 (estimated)[c]
Henry's law constant (atm-m^3/mol at 20°C)	1.9×10^{-4} (estimated)[c]
Soil adsorption coefficient (K_{oc}) (L/kg)	1,600 (estimated)[c]
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	2.5×10^{-13} (estimated)[c]
Atmospheric half-life (d)	43 (estimated)[c]
Relative vapor density (air = 1)	NV
Molecular weight (g/mol)	229.92[a]
Flash point (°C)	110−131[a]

[a]ECHA (2018).
[b]Haynes et al. (2013).
[c]U.S. EPA (2012c) (with user-entered input for boiling point = 245°C).

NV = not available.

A summary of available toxicity values for *p*-α,α,α-tetrachlorotoluene from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for *p*-α,α,α-Tetrachlorotoluene (CASRN 5216-25-1)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2018a)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
ATSDR	NV	NA	ATSDR (2018)
IPCS	NV	NA	IPCS (2018)
CalEPA	NV	NA	CalEPA (2016); CalEPA (2018a); CalEPA (2018b)
OSHA	NV	NA	OSHA (2017a); OSHA (2017b)
NIOSH	NV	NA	NIOSH (2016)
ACGIH	NV	NA	ACGIH (2018)
Cancer			
IRIS	NV	NA	U.S. EPA (2018a)
HEAST/HEED (OSF)	20 $(mg/kg\text{-}d)^{-1}$	Based on adenocarcinoma in the lung, in a study with oral exposure for 17.5 wk in mice	U.S. EPA (1987); U.S. EPA (2011a)
HEED (WOE)	B2: probably carcinogenic to humans	Based on sufficient evidence from animal studies, and no data from epidemiologic studies	U.S. EPA (1987)
CalEPA	Listed as causing cancer under Proposition 65	NA	CalEPA (2011); CalEPA (2018a); CalEPA (2018b)
DWSHA	NV	NA	U.S. EPA (2012a)
NTP	NV	NA	NTP (2016)
IARC	NV	NA	IARC (2018)
ACGIH	NV	NA	ACGIH (2018)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; HEED = Health and Environmental Effects Document; IARC = International Agency for Research on Cancer; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration.
[b]Parameters: OSF = oral slope factor; WOE = weight of evidence.

NA = not applicable; NV = not available.

Non-date-limited literature searches were conducted in October 2017 and updated in December 2018 for studies relevant to the derivation of provisional toxicity values for *p*-α,α,α-tetrachlorotoluene (CASRN 5216-25-1). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, TOXLINE (including TSCATS1), and Web of Science. The following databases were searched outside of HERO for health-related values: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (CalEPA), Defense Technical Information Center (DTIC), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), European Chemicals Agency (ECHA), U.S. EPA Chemical Data Access Tool (CDAT), U.S. EPA ChemView, U.S. EPA Health Effects Assessment Summary Tables (HEAST), U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Office of Water (OW), International Agency for Research on Cancer (IARC), Japan Existing Chemical Data Base (JECDB), National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), Organisation for Economic Co-operation and Development (OECD) Existing Chemicals Database, OECD Screening Information Data Set (SIDS) High Production Volume Chemicals (HPV) via International Programme on Chemical Safety (IPCS) INCHEM, Occupational Safety and Health Administration (OSHA), and World Health Organization (WHO).

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide overviews of the relevant noncancer and cancer databases, respectively, for *p*-α,α,α-tetrachlorotoluene, and include all potentially relevant repeated short-term-, subchronic-, and chronic-duration studies, as well as reproductive and developmental toxicity studies. Principal studies are identified in bold. The phrase "statistical significance," used throughout the document, indicates a *p*-value of < 0.05 unless otherwise specified. The use of the terms "significant" or "significantly" by themselves denotes statistical significance, unless otherwise qualified.

Table 3A. Summary of Potentially Relevant Noncancer Data for *p*-α,α,α-Tetrachlorotoluene (CASRN 5216-25-1)							
Category[a]	**Number of Male/Female, Strain Species, Study Type, Study Duration, Reported Doses**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[c]**
Human							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
ND							
Animal							
1. Oral (mg/kg-d)							
Short-term	6 M/6 F, S-D, rat, gavage, daily for 14 d Reported doses: 0, 1.25, 12.5, 25.0, 75.0, 150, 300 mg/kg-d	0, 1.25, 12.5, 25.0, 75.0, 150, 300	Significantly decreased absolute liver weight in M. At higher doses in both M and F, body weights and food intake were significantly reduced, and clinical signs of toxicity were observed; 100% of animals treated with 300 mg/kg-d died, with indications of gastrointestinal toxicity.	NDr	25.0	Liao (1989b, 1989c) (Lowest 2 doses were tested in a separate experiment and not considered for NOAEL/LOAEL determinations due to lack of a concurrent control).	NPR
Subchronic	**10 M/10 F, S-D, rat, gavage, daily for 90 d** **Reported doses: 0, 1.25, 12.5, 25.0 mg/kg-d**	**0, 1.25, 12.5, 25.0**	**Significant increase in the incidence of tubular atrophy and aspermatogenesis in the testes, decreased absolute and relative testis weights, reduced lymphocyte and leukocyte counts, and decreased body weights in male rats (at the high dose, the changes in males were more pronounced).**	**1.25**	**12.5**	**Liao (1989a, 1989c)**	**NPR, PS**

Table 3A. Summary of Potentially Relevant Noncancer Data for *p*-α,α,α-Tetrachlorotoluene (CASRN 5216-25-1)							
Category[a]	**Number of Male/Female, Strain Species, Study Type, Study Duration, Reported Doses**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[c]**
2. Inhalation (mg/m^3)							
Short-term	**10 M/10 F, albino (CR:WI BR), rat, whole body, 6 hr/d, 5 d/wk, 30 d** **Reported analytical concentrations: 0, 3.98, 18.9, 94.5 mg/m^3**	**HEC$_{ET}$: 0, 0.142, 0.675, 2.53 (M); 0, 0.107, 0.506, 2.03 (F)** **HEC$_{TB}$: 0, 1.49, 6.75, 23.6 (M); 0, 0.995, 4.73, 20.3 (F)** **HEC$_{ER}$: 0, 0.711, 3.38, 16.9**	**Significant increase in incidence of upper respiratory lesions in F; other lesions increased at the same analytical concentration, but with higher HECs, were upper respiratory lesions in M and lower respiratory lesions in both sexes. At the high analytical concentration in both sexes, respiratory lesions were severe and other effects were seen, including mortality; clinical signs; decreases in food and water intake, body and organ weights, and lymphocyte counts; and increases in incidence of degenerative lesions in the testes, spleen, and thymus.**	**0.107**	**0.506**	**Rose et al. (1984)**	**NPR, PS**

Table 3A. Summary of Potentially Relevant Noncancer Data for *p*-α,α,α-Tetrachlorotoluene (CASRN 5216-25-1)

Category[a]	Number of Male/Female, Strain Species, Study Type, Study Duration, Reported Doses	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Reproductive/ Developmental	25 F, CD (SD) BR, rat, whole body, 6 hr/d, GDs 6–19 Reported analytical concentrations: 0, 4.1, 10.4, 25.2 mg/m^3	HEC_{ER}: 0, 1.0, 2.60, 6.30	Maternal: No significant effects were observed. Fetal: Significant decrease in mean fetal weight and increase in fetal incidence per litter of unossified sternebrae.	Maternal: 6.30 Fetal: 2.60	Maternal: NDr Fetal: 6.30	Edwards et al. (1985)	NPR

[a]Duration categories are defined as follows: Acute = exposure for ≤24 hours; short term = repeated exposure for 24 hours to ≤30 days; long term (subchronic) = repeated exposure for >30 days ≤10% lifespan for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% lifespan for humans (>~90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002).
[b]Dosimetry: Doses are presented as ADDs (mg/kg-day) for oral noncancer effects and as HECs (mg/m^3) for inhalation noncancer effects. HECs are calculated differently for systemic (ER), TB, and ET respiratory effects. The HEC for ER effects is calculated by treating *p*-α,α,α-tetrachlorotoluene as a Category 3 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ER} = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human). Because blood-gas coefficients for this chemical are unknown, a default ratio of 1 was used. HEC values for ET and TB regions are calculated by treating *p*-α,α,α-tetrachlorotoluene as a Category 1 gas and using the following equation from U.S. EPA (1994): HEC = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × RGDR, where RGDR is the regional gas dose ratio (animal:human). RGDR (ET) and RGDR (TB) are calculated as per U.S. EPA (1994) using default human V_E and human and animal respiratory tissue surface area values and animal V_E values calculated using study (if available) or U.S. EPA (1988) reference body-weight values.
[c]Notes: NPR = not peer reviewed; PS = principal study.

ADD = adjusted daily dose; BMCL = benchmark concentration lower confidence limit; BMDL = benchmark dose lower confidence limit; ER = extrarespiratory; ET = extrathoracic; F = female(s); GD = gestation day; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; RGDR = regional gas dose ratio; S-D = Sprague-Dawley; TB = tracheobronchial; V_E = minute volume.

Table 3B. Summary of Potentially Relevant Cancer Data for *p*-α,α,α-Tetrachlorotoluene (CASRN 5216-25-1)					
Category	**Number of Male/Female, Strain, Species, Study Type, Study Duration, Reported Doses**	**Dosimetry[a]**	**Critical Effects**	**Reference (comments)**	**Notes[b]**
Human					
1. Oral (mg/kg-d)					
ND					
2. Inhalation (mg/m^3)					
ND					
Animal					
1. Oral (mg/kg-d)					
Carcinogenicity	**30 F, ICR-SLC, mouse, gavage, 2 times/wk for 17.5 wk** **Reported doses: 0, 0.05, 0.13, 0.32, 0.8, 2 µL/d; equivalent to nominal doses of 0, 3.2, 8.4, 21, 51, 130 mg/kg administered twice per wk, ADDs of 0, 0.21, 0.54, 1.3, 3.3, or 8.2 mg/kg-d, and HEDs of 0, 0.028, 0.072, 0.18, 0.44, and 1.1 mg/kg-d averaged over the 18-m study duration (see study description and footnotes on p. 15)**	**0, 0.028, 072, 0.18, 0.44, 1.1**	**Significant increase in the incidence of lung adenocarcinomas at ≥0.32 mg/kg-d (HED). At higher doses, significant increases in the incidences of multiple adenomas in the lung; squamous cell carcinomas, carcinomas in situ, and multiple papillomas in the forestomach; malignant lymphomas; thymomas; and skin squamous cell carcinomas.**	**Fukuda et al. (1980); Fukuda et al. (1979)**	**NPR, PS; published in Japanese but available in an English translation.**

Table 3B. Summary of Potentially Relevant Cancer Data for *p*-α,α,α-Tetrachlorotoluene (CASRN 5216-25-1)					
Category	**Number of Male/Female, Strain, Species, Study Type, Study Duration, Reported Doses**	**Dosimetry[a]**	**Critical Effects**	**Reference (comments)**	**Notes[b]**
2. Inhalation (mg/m^3)					
ND					

[a]Dosimetry: Doses are presented as HEDs (mg/kg-day) for oral cancer effects. The HEDs are calculated using DAFs, as recommended by U.S. EPA (2011b): HED = ADD (mg/kg-day) × DAF. The DAF is calculated as follows: DAF = $(BW_a \div BW_h)^{1/4}$, where DAF = dosimetric adjustment factor, BW_a = animal body weight, and BW_h = human body weight, using study (if available) or U.S. EPA (1988) reference body-weight values for BW_a and the reference value of 70 kg for BW_h.
[b]Notes: NPR = non-peer reviewed; PS = principal study.

ADD = adjusted daily dose; BW = body weight; DAF = dosimetric adjustment factor; F = female(s); HED = human equivalent dose; ND = no data.

HUMAN STUDIES

No adequate human studies that assessed associations between exposure to *p*-α,α,α-tetrachlorotoluene and subsequent health effects have been identified.

ANIMAL STUDIES

Oral Exposures

Short-Term-Duration Studies

Liao (1989b, 1989c)

In an unpublished, non-peer-reviewed, 2-week range-finding study, Liao (1989b) and Liao (1989c) investigated the potential effects of *p*-α,α,α-tetrachlorotoluene in Sprague-Dawley (S-D) rats (six males and six females/group). Rats were administered single daily doses of *p*-α,α,α-tetrachlorotoluene (purity not specified) at 0, 25.0, 75.0, 150, or 300 mg/kg-day by gavage in corn oil for 14 consecutive days (Experiment 1). Two additional dose levels (1.25 and 12.5 mg/kg-day; Experiment 2) were tested for 2 weeks upon completion of Experiment 1, without a concurrent control. All animals were observed for clinical signs at least once daily, and mortality checks were done twice daily. Body weights were measured on Days 1, 8, and 15. Food consumption was measured weekly beginning on Day 1. Necropsies were performed on all animals (i.e., those found dead, as well as those sacrificed at the end of the study). Organ weights were measured for the adrenals, kidneys, liver, testes, and ovaries. Cecum, colon, duodenum, ear, ileum, jejunum, stomach, and gross lesion tissues were fixed in case microscopic examination was desired. No statistical analysis was included in the study. Fisher's exact test and unpaired *t*-tests for comparison of two means were performed for this review.

All animals in the 300-mg/kg-day group died or were sacrificed moribund by Days 3–5; 3/3 moribund males and 4/6 females had tremors. One male and one female in the 150-mg/kg-day group died on Days 7 and 8, respectively. The causes of death were not reported. No mortalities were noted in the other dose groups. An increase in postdosing salivation was observed in males and females at doses ≥75.0 mg/kg-day. At doses ≥150 mg/kg-day, both males and females exhibited statistically significant decreases in activity, increased incidences of urine and fecal stains, dark material around the nose and mouth, dehydration, rough coat, and unkempt appearances.

Following 2 weeks of exposure, statistically significant decreases in mean body weights (−11 to −38%) were observed at ≥75.0 mg/kg-day in both males and females, compared with controls (see Table B-1). Body-weight gains were significantly reduced at doses ≥25.0 mg/kg-day in males after 1 and 2 weeks of exposure, and ≥75.0 mg/kg-day in females after 1 week. Food intake was significantly reduced in a dose-related manner in males (23–46%) in the 75.0- and 150-mg/kg-day dose groups after 1 and 2 weeks of exposure, and in females at ≥75 mg/kg-day after 1 week and at 150 mg/kg-day after 2 weeks (see Table B-2). This may have contributed to the reduced body weights observed in these groups.

There were apparent increases in body weight, body-weight gain, and food consumption in the Experiment 2 dose groups (1.25- and 12.5-mg/kg-day groups). Because no concurrent controls were included, statistical analysis was done using Experiment 1 controls. Although the study authors indicated that control group animals in Experiment 1 were sufficient for comparison, the reliability of these analyses is uncertain, as the animals for Experiment 2 were from a different batch than those in Experiment 1, delivered 1 month later.

After 2 weeks, the study authors reported a dose-related statistically significant reduction in absolute liver weight (–11 to −23%) at ≥25 mg/kg-day in male rats (see Table B-3). At higher doses tested, statistically significant changes were observed in males for absolute testes and kidney weight and relative kidney weight. Directional changes in absolute and relative weights of several organs, however, were inconsistent, and the study authors noted that organ weights were likely impacted by changes in body weight (see Table B-3). For example, in 150-mg/kg-day males, there was a significant decrease in absolute liver weight of 23% (compared with controls), but also a significant increase in relative liver weight of 25%. Body weight was decreased 38% in that group. Only absolute and relative adrenal weights in both males and females were consistently significantly increased, compared with controls, at 150 mg/kg-day. The study authors indicated uncertainty as to whether these changes were related to treatment.

For animals that died during the study, gross necropsy revealed red foci in the stomachs of 5/6 and 4/5 high-dose males and females, respectively, and in both animals that died at the 150-mg/kg-day dose. A smaller number of animals in the high-dose group exhibited pale discoloration of the duodenum, ileum, and jejunum. The study authors suggested that these findings indicate possible gastrointestinal toxicity. Hemorrhagic meningeal vessels in the brains of 4/6 high-dose males and 5/5 high-dose females were also observed but thought by the investigators to be due to death struggle, rather than a direct effect of the treatment. Other findings in the moribund animals included urine stains on the coat of 100% of dead males and females, and lower incidences of soft adrenal glands, dark red discoloration of the lungs, and wet matting around the nose and mouth. The only notable gross necropsy findings in animals that survived until the scheduled sacrifice were small testes in 3/5 males and urine stains on the coat of 3/5 males and 3/5 females in the 150-mg/kg-day group. No microscopic or histological examinations were done.

The data from the 1.25- and 12.5-mg/kg-day dose groups were dropped from consideration in determining no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values due to the lack of a concurrent control for comparison. A short-term oral LOAEL of 25.0 mg/kg-day is identified for statistically and biologically (≥10%) significant reductions in absolute liver weight in male S-D rats exposed by daily gavage to *p*-α,α,α-tetrachlorotoluene for 14 days. At higher doses, body weights and food intake were significantly reduced, and clinical signs of toxicity were observed, in both sexes; 100% of animals treated with 300 mg/kg-day died, with indications of gastrointestinal toxicity. The lowest dose evaluated with a concurrent control was the LOAEL of 25.0 mg/kg-day; therefore, no NOAEL is identified.

Subchronic-Duration Studies

Liao (1989a, 1989c)

In an unpublished, non-peer-reviewed study, Liao (1989a) and Liao (1989c) investigated the potential toxicity of *p*-α,α,α-tetrachlorotoluene in S-D rats (10/sex/group) administered single daily doses of *p*-α,α,α-tetrachlorotoluene (purity not specified) at 0, 1.25, 12.5, or 25.0 mg/kg-day by gavage in corn oil for 90 consecutive days. Doses were selected based on the results of the oral range-finding study described in Liao (1989b) and Liao (1989c) and discussed above. Animals were observed at least once daily for clinical signs of toxicity. Initial body weights were recorded on Day 1, then weekly, and at sacrifice. Food consumption was determined weekly. Ophthalmological examinations were done on all animals prior to study

initiation and near the conclusion of the study. Blood samples were collected from five rats/sex/treatment group for hematological, and biochemical analyses 5 days prior to initiation of the study and again at sacrifice. Necropsies were performed on all animals: five males and five females per group on both study Days 91 and 92. Organ weights were obtained for the adrenals, liver, kidneys, brain, testes, and ovaries, and >30 tissues were prepped for microscopic examination. Histopathological analysis was done on all tissues collected from control and high-dose group animals; the lungs, liver, kidneys, testes, and gross lesions were the only organs analyzed in the mid- and low-dose groups. Statistical analysis was performed by the study authors and used two-tailed tests with a minimum significance level of 5%. Continuous data were analyzed by analysis of variance (ANOVA) and Dunnett's test.

No mortalities were reported. Clinical signs were limited to significant increases in salivation and urine stain on the coat, postdosing, in both males and females at 25.0 mg/kg-day. Body weight was statistically significantly reduced in males starting on Week 7 of the study in the 25.0-mg/kg-day group, and Week 10 of the study at 12.5 mg/kg-day (see Table B-4). Relative to controls, terminal body weights were significantly reduced by 11% at 12.5 mg/kg-day and 15% at 25.0 mg/kg-day. In females, there were sporadic statistically significant decreases in body weights relative to controls for a few weeks in the middle of the study in the 12.5- and 25.0-mg/kg-day groups, but the differences reached to 10% in the 12.5-mg/kg-day groups at the end of experiment. Unlike the range-finding study, no significant food consumption differences were noted in either sex, suggesting that the reductions in body weight in males were not due to decreased appetite.

Hematological analysis identified statistically significant reductions in leukocytes in males at 12.5 and 25.0 mg/kg-day and in females at 25.0 mg/kg-day (see Table B-5). Blood leukocyte profiles indicated that reduced lymphocyte cell counts were likely the primary source of leukocyte reductions. Compared to controls, lymphocyte cell counts were significantly reduced by 37 and 46% at 12.5 and 25.0 mg/kg-day, respectively, in males and by 49% at 25.0 mg/kg-day in females. Erythrocyte counts and hematocrit (Hct) (%) were slightly lower than controls in high-dose males, but hemoglobin (Hb) levels were comparable to controls, and no consistent changes were observed in females. Some statistically significant changes in clinical chemistry were measured; these included increased total protein and sodium levels in low-dose males; increased chloride levels in low- and mid-dose males; increased total protein, albumin, calcium, and phosphorus levels in mid-dose females; and increased sodium and chloride in low- and mid-dose females. The study authors did not consider any of these to be meaningful changes. Ophthalmological examination revealed no treatment-related changes.

At necropsy, the testes were reported to be smaller and softer in males dosed with 12.5 mg/kg-day (7/10) and 25.0 mg/kg-day (9/10), compared with controls (0/10). There were significant dose-related decreases in both absolute and relative testes weights at doses ≥12.5 mg/kg-day; relative testes weights decreased by 28 and 56% in mid- and high-dose males, respectively (see Table B-6). Other statistically significant organ-weight changes in males were increases in relative brain weight (+18%), liver weight (+17%), and kidney weight (+25%) in the high-dose group and increased relative kidney weight (+15%) in the mid-dose group (see Table B-6). Absolute organ weights for brain, liver and kidney were not affected by treatment (see Table B-6). Given the 15% reduction in male body weights at time of necropsy and lack of change in absolute organ weights, the increases in relative organ weights for brain, liver, and kidney are not considered to be biologically significant. In contrast to the 14-day

range-finding study (Liao, 1989b, c), no significant increases in adrenal weights were observed. There were no significant organ-weight changes in females in any treatment group.

Histological analysis showed seminiferous tubular atrophy and aspermatogenesis of the testes, with partial or complete loss of germ cells, and only few Sertoli cells remaining in 70% of males at 12.5 mg/kg-day and in 100% of males at 25.0 mg/kg-day (see Table B-7). Most of these incidences were of marked severity. Aspermia of the epididymis was considered by the investigators to be secondary to the testicular aspermatogenesis. In females, microscopic findings were limited to scattered foci of cellular alteration (4/10 compared with 0/10 in controls) in the livers of high-dose animals; no other significant histological findings were observed.

A NOAEL of 1.25 mg/kg-day and a LOAEL of 12.5 mg/kg-day are identified for decreased body weights, decreased leukocyte and lymphocyte counts, increased incidence of testicular atrophy and aspermatogenesis, and decreased absolute and relative testis weights in males orally exposed to *p*-α,α,α-tetrachlorotoluene for 90 days.

Chronic-Duration/Carcinogenicity Studies

Fukuda et al. (1980); Fukuda et al. (1979)

In an oral cancer study originally published in Japanese, but available in an English translation, Fukuda et al. (1980) and Fukuda et al. (1979)[2] investigated the potential carcinogenicity of *p*-α,α,α-tetrachlorotoluene (purity not reported) in female ICR-SLC mice (30/group) treated with 0, 0.05, 0.13, 0.32, 0.8, or 2 µL (nominal doses of 0, 3.2, 8.4, 21, 51, or 130 mg/kg)[3] in 0.1 mL of sesame oil by gavage, twice per week for 17.5 weeks. The adjusted daily doses (ADDs) are calculated to be 0, 0.21, 0.54, 1.3, 3.3, or 8.2 mg/kg-day by averaging the nominal doses over the entire study duration of 18 months (the animals were observed for up to 18 months following the initiation of the experiment).[4] The study was published as a conference proceedings report and does not appear to have undergone a formal peer-review process. All dead, moribund, and remaining animals that survived to 18 months were necropsied and examined for tumors. Details of the nature of histological analyses were not provided. The timing of 50% mortalities in some dose groups were noted. The study did not include other observations or measurements (e.g., clinical signs, body weights, organ weights, etc.); however, the average age in months of animals that became affected after the treatment, as well as cumulative incidences of select tumors by months, was recorded. No statistical analysis of the data was provided in the study. Tumor incidence data were analyzed using Fisher's exact and Cochran-Armitage chi-square (χ^2) trend tests for the purposes of this review.

[2]The peer-review status of this study is uncertain but assumed to be "non-peer-reviewed."
[3]Reported doses of 0, 0.05, 0.13, 0.32, 0.8, and 2 µL/day were converted to 0, 3.2, 8.4, 21, 51, or 130 mg/kg per treatment using the following formula: dose (mg/kg-day) = reported dose (µL/day) ÷ 1,000 µL/mL × *p*-α,α,α-tetrachlorotoluene density (1,446.3 mg/mL) ÷ body weight (kg). Measured body weights were not provided in the study. A reference body weight of 0.0225 kg was used for female mice in a subchronic-duration study [in the absence of reference body weights for ICR-SLC mice, the average of values for $B6C3F_1$ and BAF_1 mice from U.S. EPA (1988) was used].
[4]The ADDs of 0, 0.2060, 0.5357, 1.319, 3.296, and 8.241 mg/kg-day were calculated by multiplying the nominal doses in mg/kg by 2/7 days and 17.5/78 weeks, and to HEDs of 0, 0.028, 0.072, 0.18, 0.44, and 1.1 mg/kg-day (calculated by multiplying the ADD × DAF, where DAF = $[BW_a \div BW_h]^{1/4}$ = 0.134, using a reference body weight of 70 kg for humans).

The study authors reported that the highest dose group reached 50% mortality by 4.7 months of age, while 50% of the animals dosed with 51 mg/kg died by 12.3 months of age. Mortality in the other dose groups did not reach 50% prior to scheduled sacrifice at 18 months.

Statistically significant increases in the incidences of benign, malignant, and total tumors were observed at doses ≥8.4 mg/kg, compared with controls (see Table B-8). Tumors that occurred with the highest incidence were adenocarcinoma and adenoma in the lung, squamous cell carcinoma in the forestomach, malignant lymphoma, thymoma, and squamous cell carcinoma in the skin.

In general, tumors developed earlier in animals exposed to the highest dose compared with the other treatment groups; the average ages of affected animals were 6.2 months in the highest dose group, 14.8 months at 51 mg/kg, and 16.9–17.9 months at the lower doses. The earliest appearing tumors were malignant lymphoma and thymoma, which first appeared in the highest-dose group at around 4 months and reached their maximum incidence of 45% at around 9 months, and forestomach carcinoma, which first appeared in the highest-dose group at around 5 months and reached its maximum incidence of 25% at around 10 months. In contrast, lung adenocarcinomas were first seen in the highest-dose group at around 10 months and in the 51and 21-mg/kg groups at 13–14 months.

Lung adenocarcinomas were observed in 0/26, 3/22, 7/28, 10/22, 15/29, and 2/29 mice at 0, 3.2, 8.4, 21, 51, and 130 mg/kg, respectively. Incidences were significantly increased relative to controls in the 8.4-, 21-, and 51-mg/kg groups. The low incidence of lung adenocarcinomas in the highest dose group was not discussed by the study authors, but likely reflects the relatively late development of this tumor and the high early mortality in this group due to more quickly developing tumors (malignant lymphoma, thymoma, forestomach carcinoma). Excluding the highest dose, the incidence of lung adenocarcinomas followed a significant dose-related trend ($p < 0.005$). The incidences of multiple adenomas in the lung were also significantly increased at ≥21 mg/kg.

In the forestomach, incidences of squamous cell carcinomas and carcinomas in situ also followed dose-related trends ($p < 0.001$). The incidences of squamous cell carcinomas were statistically significant, reaching 21 and 24% of animals in the two highest treatment groups, respectively. Multiple papillomas in the forestomach were observed in all treatment groups, and incidences were statistically significant at 21 mg/kg, but with reduced incidence at the two highest dose groups, resulting in a lack of dose-response trend with the two high doses included ($p = 0.83$), or with the highest dose dropped ($p = 0.40$). The reduced incidence was not discussed by the study authors and it is uncertain if early mortality was a factor; the reduced incidence could possibly be a result of transformation of papillomas to carcinomas. Excluding the two highest doses, the incidence of forestomach multiple papillomas followed a significant dose-related trend ($p = 0.0075$). There were no cancers of the forestomach in controls. The study authors described a few non-neoplastic observations, including marked keratinization of the forestomach epithelium in groups "receiving higher doses" and atypical epithelia in the lower dose groups.

Other tumors with significant dose-related trends included thymomas (observed in 4/29 mice at 51 mg/kg and 8/29 mice at 130 mg/kg), malignant lymphomas (observed in

5/29 mice at 130 mg/kg), and squamous cell carcinomas in the skin (observed in 6/29 mice at 130 mg/kg).

Single incidences of mammary adenocarcinoma, ear canal squamous cell carcinoma, ovary glanulosa cell tumor, glandular stomach carcinoma, spindle cell carcinoma and sebaceous gland carcinoma in the skin, and two incidences of salivary gland adenocarcinomas were observed in different treatment groups, but these cancers did not show dose dependence and were not significantly increased compared with controls.

Reproductive and Developmental Studies

No oral-route reproductive or developmental studies on *p*-α,α,α-tetrachlorotoluene in animals have been identified.

Inhalation Exposures

Short-Term-Duration Studies

Rose et al. (1984)

Toxicities in albino (CR:WI BR) rats resulting from exposure to *p*-α,α,α-tetrachlorotoluene vapors were reported in an unpublished, non-peer-reviewed study by Rose et al. (1984). Albino rats (10/sex/group) were exposed to *p*-α,α,α-tetrachlorotoluene (purity not specified) at mean measured concentrations of 0, 3.98, 18.9, or 94.5 mg/m^3 by inhalation, for 6 hours/day, 5 days/week, for a period of 30 days. Control animals were exposed to air-only under the same experimental conditions. The method of exposure was specified to be whole-body. All animals were observed twice daily for clinical signs. Body weights were measured twice prior to the start of exposures, and then weekly; food consumption was measured weekly, and water intake was recorded daily. Hematology, blood chemistry, and urinalysis were performed on all rats before the start of exposure, and on five animals/sex/group on Day 24. At sacrifice, brain, pituitary, heart, lungs, liver, spleen, thymus, uterus, kidneys, thyroids, adrenals, and gonads were weighed, and >30 tissues were processed for microscopic examination from 5−6 animals/sex in the control and exposed groups. Bone marrow was extracted from the femurs of five males and five females per group for myelography. Statistical analyses included Bartlett's test for heterogeneity of variance, Kruskal-Wallis analysis of ranks, Fisher's exact test to detect differences among treatment groups, and Mantel's test for identifying exposure-related trends.

Three animals in the 94.5-mg/m^3 group died during the study. One male was found dead in the exposure chamber following exposure on Day 17. Another male and one female were found dead just before scheduled necropsies; the causes of death were not discussed. Clinical signs and behavioral changes were observed in animals in the 94.5-mg/m^3 group. The signs were consistent with those expected following exposure to an irritant atmosphere; they included irregular breathing/gasping, sneezing, rubbing snout with forepaws, partial closing of eyes, abnormal body posture, and increased fighting between cage mates. Individual rats in this group exhibited brown discharge or red staining around the nose and/or eyes and fur loss around the snout and jaws. The appearance and behaviors in other exposure groups were similar to control rats.

Body weights were depressed relative to controls throughout the study in both males and females exposed to 94.5 mg/m^3 *p*-α,α,α-tetrachlorotoluene (see Table B-9). Animals exposed at this level lost weight over the 4 weeks of the study. The loss in body weight was accompanied

by significant reductions in cumulative food and water consumption in these animals. There were no effects on body weight, body-weight gain, or food or water intake in the lower exposure groups.

Hematological analysis on Day 24, for animals exposed to 94.5 mg/m^3, showed large, statistically significant decreases in total white blood cells (WBCs) (39 and 61% decreases), circulating lymphocytes (48 and 73% decreases), and total cells in bone marrow (50 and 69% decreases) in males and females, respectively; eosinophils were reduced by 100% in males (see Table B-10). However, although not statistically significant, there was a 40% increase in WBCs for males exposed to 18.9 mg/m^3, but no corresponding increase for females. Males in the 18.9- and 94.5-mg/m^3 groups also showed statistically significant increases in red blood cell (RBC) count, Hb, and Hct relative to controls. Serum chemistry changes included statistically significant reductions in alanine aminotransferase (ALT), albumin, and albumin:globulin (A:G) ratio relative to controls in male rats at ≥18.9 mg/m^3, as well as statistically significant reductions in aspartate aminotransferase (AST), calcium, and creatinine at 94.5 mg/m^3. There were no biologically significant changes in other blood chemistry values, including alkaline phosphatase, lactate dehydrogenase, glucose, or total proteins. Females in the high-exposure group had increased serum phosphorous, reduced serum cholesterol, and reduced levels of protein in the urine relative to controls. The biological significance of these serum chemistry changes is uncertain.

Large changes in absolute organ weights were reported for the gonads (−63%), spleen (−60%), liver (−42%) and thymus (−83%) in male rats and for the uterus (−60%) in female rats at 94.5 mg/m^3 (see Table B-11). Smaller weight changes were seen in other organs in high-exposure group males and females, generally decreases in absolute organ weights and increases in body weight-adjusted organ weights, which the study authors thought reflected the large decreases in body weight in these groups.

Necropsy findings included high incidence of small testes (9/9) in males at 94.5 mg/m^3 and small thymus in both males (8/9) and females (10/10) at this concentration (see Table B-12). Other reported effects in the animals at 94.5 mg/m^3 were minimal adipose tissue, alopecia, and stained or badly groomed fur. There were no significant gross findings in animals from other exposure groups.

Microscopic examination showed decreased cellularity in the red and white pulp of the spleen, thymic involution in both males and females, and lesions in reproductive organs, including tubular atrophy/aspermatogenesis in the testes of males and reduced endometrial width in the uterus of females at 94.5 mg/m^3 (see Table B-13). These organs were not examined for histopathology in the mid- and low-exposure groups. No lesions in these tissues were seen in controls.

Microscopic lesions were also found in the respiratory tract, including the nasal passages, larynx, trachea, tracheal carina, and bronchiolar epithelium. Specific lesions and incidences are listed in Table B-14 for the upper respiratory tract, and Table B-15 for the lower respiratory tract. These lesions occurred primarily in the 18.9- and 94.5-mg/m^3 groups for both males and females, and incidence and/or severity of the lesions generally increased with exposure concentration. For example, atrophy of the olfactory epithelium was focal in 1/5 and 3/5 males and 0/5 and 5/5 females at 3.98 and 18.9 mg/m^3, respectively, and severe in 6/6 males and 5/5 females at

94.5 mg/m^3. Severe lesions, including severe atrophy of the olfactory epithelium in the nasal passages, severe epithelial ulceration of the trachea and carina, and severe ulceration of the bronchiolar epithelium occurred only in the 94.5-mg/m^3 groups of both sexes. Lesions in the 18.9-mg/m^3 males and females were generally characterized as minimal, moderate, or focal. The location of the lesions within the nasal passages was not reported.

The respiratory lesions were the most sensitive endpoints in rats exposed to *p*-α,α,α-tetrachlorotoluene vapor for 30 days. Respiratory lesions were significantly increased at ≥18.9 mg/m^3 in both males and females, and some of these lesions (e.g., atrophy of the olfactory epithelium in males and keratinizing epithelial hyperplasia in the larynx in females) also occurred at low incidence at 3.98 mg/m^3. The lesions showed a dose-response, with severe lesions occurring only at the high concentration of 94.5 mg/m^3. Microscopic lesions in other tissues, such as decreased splenic cellularity, thymic involution, and testicular atrophy were also seen at this concentration, as were gross depletion of the thymus and testes and decreases in absolute weights of these and other organs, as well as associated changes such as decreased lymphocytes, all likely affected by weight loss and malnutrition in these animals due to their low food and water intake. Gross clinical signs of toxicity and mortality were also observed at this concentration. The respiratory tract lesions identify a NOAEL of 3.98 mg/m^3 and a LOAEL of 18.9 mg/m^3 for male and female rats in this study, based on analytical concentrations.

The analytical concentrations of 3.98. 18.9, and 94.5 mg/m^3 (6 hours/day, 5 days/week) correspond to human equivalent concentrations (HECs) of 0.711, 3.38, and 16.9 mg/m^3 for systemic (extrarespiratory [ER]) effects (HEC_{ER}); 0.142, 0.675, and 2.53 mg/m^3 for males and 0.107, 0.506, and 2.03 mg/m^3 for females for upper (extrathoracic [ET]) respiratory effects (HEC_{ET}); and 1.49, 6.75, and 23.6 mg/m^3 for males and 0.995, 4.73, and 20.3 mg/m^3 for females for tracheobronchial [TB] respiratory effects (HEC_{TB}), using (U.S. EPA, 1994) methods.[5] Considering the HEC conversions, the most sensitive effects in the study were upper respiratory lesions, with a NOAEL (HEC_{ET}) of 0.107 mg/m^3 and a LOAEL (HEC_{ET}) of 0.506 mg/m^3 based on female rats.

Subchronic-Duration Studies

No subchronic-duration inhalation studies of *p*-α,α,α-tetrachlorotoluene in animals were identified.

[5]Measured exposure concentrations of 0, 3.98, 18.9, and 94.5 µg/L 6 hours/day, 5 days/week were converted to continuous concentrations of 0, 0.711, 3.38, and 16.9 mg/m^3 using the following equation: exposure concentration (mg/m^3) × hours/day (6 hours/24 hours) × days/week (5 days/7 days). *p*-α,α,α-Tetrachlorotoluene has characteristics of a highly reactive, Category 1 gas that often results in portal-of-entry effects in the ET and TB regions as well as less reactive Category 3 gas for ER effects. As HEC equations for a Category 2 gas are currently unavailable, the HECs are calculated using both Category 1 and Category 3 gas equations. The HEC_{ER} for extrarespiratory effects was calculated as per U.S. EPA (1994) by treating p-α,α,α tetrachlorotoluene as a Category 3 gas and multiplying the continuous concentration in mg/m^3 × ratio of animal:human blood-gas partition coefficients (default value of 1 applied in the absence of experimental data). HEC values for ET and TB regions were calculated by treating p-α,α,α-tetrachlorotoluene as a Category 1 gas and using the following equation from U.S. EPA (1994): HEC = continuous concentration (mg/m^3) × RGDR, where RGDR is the regional gas dose ratio (animal:human). RGDR (ET) and RGDR (TB) were calculated as per U.S. EPA (1994) using default human minute volume (V_E) and human and animal respiratory tissue surface area values and animal V_E values calculated from time-weighted average body weights for each dose group in the study.

Chronic-Duration/Carcinogenicity Studies

No chronic-duration studies or cancer bioassays on *p*-α,α,α-tetrachlorotoluene by inhalation exposure in animals were identified.

Reproductive and Developmental Studies

Edwards et al. (1985)

In an unpublished and non-peer-reviewed study, Edwards et al. (1985) investigated the potential effects of *p*-α,α,α-tetrachlorotoluene vapor on pregnancy and in utero development in CD (SD) BR strain rats. Mated female rats (25 per group) were exposed to mean measured concentrations of 4.1, 10.4, or 25.2 mg/m^3 for 6 hours/day on Gestation Days (GDs) 6–19. Control animals were transferred to exposure chambers but exposed to air only. The method of exposure was not specified but was clearly whole-body via examination of the exposure chamber diagram. Examinations for clinical signs were performed twice daily. Water consumption was measured daily; food consumption was measured between recordings of body weight. Body weights of dams were measured on GDs 1, 3, 6, 10, 14, and 17, and at sacrifice on GD 20. Pregnancy rates were recorded. After gross necropsy, ovaries and uteri were examined to determine litter parameters, including number of corpora lutea, number and distribution of live young, number and distribution of embryonic/fetal deaths, individual fetal weights, and fetal abnormalities. Pre- and postimplantation losses were determined. Half of the pups in each litter were examined for visceral abnormalities and the other half were examined for macroscopic and skeletal abnormalities and variations. For statistical analysis on litter data and skeletal deviations, the study authors performed Jonckheere and Kruskal-Wallis nonparametric tests and used the litter as the basic sampling unit.

There were no mortalities or adverse clinical signs in treated dams. Water consumption was not affected by treatment. Food consumption was reduced (6–14%) in the 25.2-mg/m^3 group but was similar to controls in the two lower exposure groups. At 25.2 mg/m^3, maternal group mean body weights were significantly reduced beginning on GD 14 (−5%) and continuing through sacrifice on GD 20 (−9%) (see Table B-16). Body-weight gain in this group was significantly reduced by 27–35% relative to controls throughout the study. No significant changes in body weight or body-weight gain were observed in the other exposure groups. There were no treatment-related gross abnormalities in exposed dams. Treatment had no significant effects on pregnancy rates, number of implants, or number of live young (see Table B-17). Intergroup differences in postimplantation losses did not appear to be related to exposure. Specifically, the percentage of postimplantation loss decreased with increased concentration and was statistically significantly decreased compared to control at 25.2 mg/m^3. Therefore, this effect is not biologically relevant.

Mean fetal weights were statistically significantly reduced by 8% at 25.2 mg/m^3, relative to controls (see Table B-17). There were no significant effects on the incidences of malformations, or visceral or skeletal anomalies. The only skeletal variation affected was a significant increase in the incidence of fetuses with unossified sternebrae in the 25.2-mg/m^3 exposure group (see Table B-18). The study authors suggested that the increase in unossified sternebrae could be associated with the lower mean fetal weight observed at this concentration.

Based on unadjusted analytical concentrations, the maternal NOAEL is 25.2 mg/m^3 based on the lack of significant treatment-related effects. The fetal NOAEL and LOAEL are 10.4 and 25.2 mg/m^3 for decreased mean fetal weight and increased incidence of unossified sternebrae.

The analytical concentrations of 10.4 and 25.2 mg/m^3 correspond to HECs (HEC_{ER})[6] of 2.60 and 6.30 mg/m^3.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Genotoxicity

No information has been located on the genotoxicity of *p*-α,α,α-tetrachlorotoluene.

Supporting Animal Studies

A letter from Hooker Chemical Co (1981a) and Hooker Chemical Co (1981b) reported a median lethal dose (LD_{50}) (95% confidence interval [CI]) of 820 (730–910) mg/kg in rats orally exposed to *p*-α,α,α-tetrachlorotoluene. Symptoms described included tremors, decreased motor activity, diarrhea, chromodacryorrhea, and piloerection. At necropsy, irritation to the gastrointestinal tract was noted. The letter also noted that a rat LD_{50} of 805 mg/kg was listed in a product data sheet issued by Ihara Chemical Industry Co., Ltd.

A dermal LD_{50} of >2,000 mg/kg was reported in rabbits (Hooker Chemical Co, 1981a, b). There were no signs of toxicity or test-article-related gross tissue changes. Skin reactions were described as mild to moderate. Although not corrosive, exposure caused skin erythema and edema during testing. Skin reactions scored by the Draize method gave a primary skin irritation value of 1.58. In the eye, *p*-α,α,α-tetrachlorotoluene induced irritation to the conjunctival tissue, but not the cornea or iris in rabbits.

Fukuda et al. (1980) mentioned a dermal carcinogenicity skin-painting study in mice by Matsushita et al., which reportedly resulted in skin tumors, but no such study was found in the literature.

Metabolism/Toxicokinetic Studies

The metabolism and excretion of *p*-α,α,α-tetrachlorotoluene were studied in female S-D rats administered a single dose of 1.5 (two rats) or 102 (one rat) mg/kg of radiolabeled (^{14}C) *p*-α,α,α-tetrachlorotoluene (98% purity) by gavage (Quistad et al., 1985). Immediately after dosing, the animals were housed in glass metabolism chambers for collection of urine, feces, and expired carbon dioxide (CO_2); urine was collected daily. Metabolites were analyzed by thin-layer chromatography and/or gas-liquid chromatography-mass spectrometry. The animals were sacrificed 4–6 days after dosing, and select organs and tissues were dissected, weighed, and used for quantification of ^{14}C residues.

Following administration of radiolabeled (^{14}C) *p*-α,α,α-tetrachlorotoluene, most of the radiolabel was excreted in the urine (77–87%) and a smaller amount in the feces (9–14%), with only 4% remaining in the carcass after 4–6 days, regardless of dose. *p*-α,α,α-Tetrachlorotoluene was primarily hydrolyzed to *p*-chlorobenzoic acid, which was excreted in urine as *p*-chlorohippuric acid. α,α′,4,4′-Tetrachlorostilbene was identified as a metabolite in feces.

[6]Analytical concentrations of 0, 4.1, 10.4, and 25.2 mg/m^3 administered 6 hours/day on GDs 6–19 were converted to continuous concentrations of 0, 1.0, 2.60, and 6.30 mg/m^3 using the following equation: reported concentration (mg/m^3) × hours/day (6 hours/24 hours) × days/week (7 days/7 days). HEC_{ER} values of 0, 1.0, 2.60, and 6.30 mg/m^3 were calculated by treating *p*-α,α,α-tetrachlorotoluene as a Category 3 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ER} = continuous concentration (mg/m^3) × ratio of blood-gas partition coefficients animal:human. Because blood-gas coefficients for this chemical are unknown, a default ratio of 1 was used.

There was no evidence of any selective concentration of ^{14}C residues in any tissues, although some deposition in fat was detected in the animal dosed with 102 mg/kg.

Mode-of-Action/Mechanistic Studies

No information has been located.

DERIVATION OF PROVISIONAL VALUES

Tables 4 and 5 present summaries of noncancer and cancer references values, respectively, for *p*-α,α,α-tetrachlorotoluene.

Table 4. Summary of Noncancer Reference Values for *p*-α,α,α-Tetrachlorotoluene (CASRN 5216-25-1)

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD (HED/HEC)	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-d)	Rat/M	Tubular atrophy and aspermatogenesis in testes	6×10^{-4}	$BMDL_{10}$	0.167	300	Liao (1989a, 1989c)
Screening chronic p-RfD (mg/kg-d)	Rat/M	Tubular atrophy and aspermatogenesis in testes	6×10^{-5}	$BMDL_{10}$	0.167	3,000	Liao (1989a, 1989c)
Screening subchronic p-RfC (mg/m^3)	Rat/M	Atrophy of the olfactory epithelium	5×10^{-5}	$BMCL_{10}$	0.0141	300	Rose et al. (1984)
Chronic p-RfC (mg/m^3)	NDr						

BMCL = 95% lower confidence limit on the benchmark concentration (subscripts denote benchmark response: i.e., 10 = concentration associated with 10% extra risk); BMDL = 95% lower confidence limit on the benchmark dose; HEC = human equivalent concentration; HED = human equivalent dose; M = male(s); NDr = not determined; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; UF_C = composite uncertainty factor.

Table 5. Summary of Cancer Reference Values for *p*-α,α,α-Tetrachlorotoluene (CASRN 5216-25-1)

Toxicity Type (units)	Species/ Sex	Tumor Type(s)	Cancer Value	Principal Study
Screening p-OSF $(mg/kg\text{-}d)^{-1}$	Mouse/F	Adenocarcinomas and multiple adenomas in the lungs, thymomas, malignant lymphomas, multiple papillomas, squamous cell carcinomas and carcinomas in situ in the forestomach, and squamous cell carcinomas in the skin	1.6×10^1	Fukuda et al. (1980); Fukuda et al. (1979)
p-IUR $(mg/m^3)^{-1}$	NDr			

F = female(s); NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

DERIVATION OF PROVISIONAL ORAL REFERENCE DOSES

No data have been located on the effects of oral exposure to *p*-α,α,α-tetrachlorotoluene in humans. Information on the toxicity of repeated oral exposure to *p*-α,α,α-tetrachlorotoluene is limited to an unpublished, non-peer-reviewed, 90-day gavage study in rats (Liao, 1989a, c) that

was preceded by an unpublished 14-day range-finding study by the same investigators (Liao, 1989b, c). There is also a translated version of a publication originally reported in Japanese that describes a study in which mice were treated for 17.5 weeks by gavage and monitored for tumor development up to 18 months of age, but it did not report on any non-neoplastic endpoints (Fukuda et al., 1980, 1979). None of these studies were suitable for the use in deriving provisional noncancer toxicity values, either because they were unpublished and not peer reviewed, or because they did not provide suitable data. Although it could not be used to develop provisional toxicity values, the unpublished 90-day study by Liao (1989a) and Liao (1989c) was well conducted and reported adequate information with which to derive screening-level provisional reference doses (p-RfDs) for *p*-α,α,α-tetrachlorotoluene (see Appendix A).

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Studies on the inhalation toxicity of *p*-α,α,α-tetrachlorotoluene vapors are limited to a 30-day study of systemic toxicity in rats and a developmental toxicity study in rats, neither of which was published or peer reviewed. For this reason, both studies were considered inadequate to derive provisional reference concentrations (p-RfCs). The studies did, however, provide adequate information with which to derive a screening-level subchronic p-RfC for *p*-α,α,α-tetrachlorotoluene (see Appendix A).

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Following U.S. EPA (2005) *Guidelines for Carcinogen Risk Assessment*, *p*-α,α,α-tetrachlorotoluene is *"Likely to Be Carcinogenic to Humans"* by oral exposure (see Table 6). Although there are no human studies to indicate cancer risk, a single oral cancer study in mice (Fukuda et al., 1980, 1979) included multiple dose levels but was limited by testing of a single sex, dosing only twice a week, a short exposure period of 17.5 weeks, a less-than-lifetime observation period of 18 months, relatively small group sizes of 26–31 mice, and marginally adequate reporting of methods and results. However, this study distinctly showed that after a relatively short duration of exposure (17.5 weeks) to *p*-α,α,α-tetrachlorotoluene, tumors formed at multiple sites, developed quickly, had a high proportion of malignancy, and displayed dose-related increases.

There is *"Inadequate Information to Assess Carcinogenic Potential"* of *p*-α,α,α-tetrachlorotoluene by inhalation exposure. No suitable human or animal data are available by this route (see Table 6).

Table 6. Cancer WOE Descriptor for *p*-α,α,α-Tetrachlorotoluene			
Possible WOE Descriptor	**Designation**	**Route of Entry (oral, inhalation, or both)**	**Comments**
"Carcinogenic to Humans"	NS	NA	No human data are available.
"Likely to Be Carcinogenic to Humans"	**Selected**	**Oral**	**A single oral cancer bioassay in animals was located. The study found dose-related increases in lung adenocarcinomas and adenomas, as well as cancers of the forestomach, skin, and lymphatic organs in female mice exposed to *p*-α,α,α-tetrachlorotoluene for 17.5 wk and observed for up to 18 mo (Fukuda et al., 1980, 1979).**
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	Evidence of the carcinogenic potential of *p*-α,α,α-tetrachlorotoluene supports a stronger descriptor by oral exposure, and there are no data available to support this descriptor by inhalation exposure.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Inhalation**	**This descriptor is selected due to the lack of any information on the carcinogenicity of *p*-α,α,α-tetrachlorotoluene by inhalation exposure.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	The available data do not support this descriptor.

NA = not applicable; NS = not selected; WOE = weight of evidence.

MODE-OF-ACTION DISCUSSION

The *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 2005) define mode of action (MOA) "…as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation." Examples of possible modes of carcinogenic action for any given chemical include "mutagenicity, mitogenesis, programmed cell death, cytotoxicity with reparative cell proliferation, and immune suppression."

Although *p*-α,α,α-tetrachlorotoluene has been classified as *"Likely to Be Carcinogenic to Humans,"* there are no data available to support a hypothesis of a MOA, including the absence of any genotoxic or mechanistic studies. Therefore, a detailed MOA discussion for *p*-α,α,α-tetrachlorotoluene is precluded.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of a Provisional Oral Slope Factor

No data have been located on the carcinogenic effects of exposure to *p*-α,α,α-tetrachlorotoluene in humans. The only information on the carcinogenicity of repeated oral exposure to *p*-α,α,α-tetrachlorotoluene is from Fukuda et al. (1980), who reported significant dose-related trends for increased incidence of multiple tumor types in female mice exposed to *p*-α,α,α-tetrachlorotoluene by gavage for 17.5 weeks and observed for up to 18 months, including

adenocarcinomas and multiple adenomas in the lungs, thymomas, malignant lymphomas, multiple papillomas, squamous cell carcinomas and carcinomas in situ in the forestomach, and squamous cell carcinomas in the skin (see Tables A-8 and B-8). Because the 17.5-week study duration was less than lifetime for mice (2 years), a less-than-lifetime adjustment factor is generally applied to the oral slope factor (OSF) (U.S. EPA, 1980). However, a provisional oral slope factor (p-OSF) is not derived here because the Fukuda et al. (1980) study did not undergo a formal peer-review process. In addition, the study duration was much less than lifetime, requiring the application of an adjustment factor to account for the expected increase in the tumor incidence rate with increasing age (U.S. EPA, 1980), with attendant increased uncertainty. A screening p-OSF, which may be useful for some applications, is derived in Appendix A.

APPENDIX A. SCREENING PROVISIONAL VALUES

For reasons noted in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) document, it is inappropriate to derive provisional reference doses (p-RfDs), provisional reference concentrations (p-RfCs), or a provisional oral slope factor (p-OSF) for *p*-α,α,α-tetrachlorotoluene. 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 Center for Public Health and Environmental Assessment (CPHEA) 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 main 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 CPHEA.

DERIVATION OF SCREENING PROVISIONAL ORAL REFERENCE DOSES

As discussed in the main body of this PPRTV assessment, the 90-day study by Liao (1989a) and Liao (1989c) could not be used to derive provisional reference values because it has not been peer reviewed. The study did, however, appear to be adequately designed and conducted, and it provided dose-response information on a wide range of endpoints suitable for use in quantitative toxicity assessment. To account for the uncertainty associated with basing a toxicity assessment on an unpublished study that has not been peer reviewed, the assessment is considered a screening-level assessment.

A no-observed-adverse-effect level (NOAEL) of 1.25 mg/kg-day and a lowest-observed-adverse-effect level (LOAEL) of 12.5 mg/kg-day were identified from the Liao (1989a) and Liao (1989c) study based on decreased body weights, decreased leukocyte and lymphocyte counts, increased incidence of testicular atrophy and aspermatogenesis, and decreased absolute and relative testis weights in male rats orally exposed to *p*-α,α,α-tetrachlorotoluene for 90 days. Females were less sensitive than males, showing only the decreases in leukocyte and lymphocyte counts and an increase in altered eosinophilic foci in the liver at the high dose of 25.0 mg/kg-day. There is supportive evidence for body weight, testicular, and lymphocyte effects from other studies described below (Liao, 1989b, c; Edwards et al., 1985; Rose et al., 1984).

Support for the effect on body weight is provided by the range-finding study performed by the same investigators (Liao, 1989b, c). A LOAEL of 75.0 mg/kg-day with a corresponding NOAEL of 25.0 mg/kg-day for reduced body weight were identified from this range-finding study, based on significantly decreased body weight (−21%) in male rats treated by gavage for 14 days. In addition, significant decreases in body weight were observed in both female and male rats at the high concentration (human equivalent concentration for systemic extrarespiratory effects [HEC_{ER}]) of 16.9 mg/m^3 in a 30-day inhalation study and in pregnant female rats at the high concentration (HEC_{ER}) of 6.30 mg/m^3 in a gestational exposure study (Edwards et al., 1985; Rose et al., 1984).

Testicular effects were prominent at the LOAEL of 12.5 mg/kg-day in the 90-day gavage study (increased incidence of seminiferous tubular atrophy and aspermatogenesis, with corresponding decreases in both absolute and relative testes weights) (Liao, 1989a, c). Data from other studies provide support for identifying degenerative changes in the testes as a critical effect of exposure to *p*-α,α,α-tetrachlorotoluene: small testes were noted in the 14-day range-finding study at 150 mg/kg-day (Liao, 1989b, c), and in a 30-day inhalation study in albino rats (Rose et al., 1984), significant increases in testicular tubular atrophy and decreased absolute testis weights were observed in males exposed to a concentration of 16.9 mg/m^3 (HEC_{ER}) of *p*-α,α,α-tetrachlorotoluene for 30 days.

The 90-day gavage study reported significant reductions in leukocyte, and specifically lymphocyte, populations in male rats at ≥12.5 mg/kg-day and female rats at 25.0 mg/kg-day (Liao, 1989a, c), implying that the immune system is another potential target of *p*-α,α,α-tetrachlorotoluene toxicity. Similar significant reductions in lymphocyte and total leukocyte counts were observed in male and female rats following exposure to an HEC_{ER} concentration of 16.9 mg/m^3 of *p*-α,α,α-tetrachlorotoluene vapor for 30 days (Rose et al., 1984). Related observations in this study were significant reductions in absolute spleen and thymus weights in males, and grossly small thymuses and histological findings of thymic involution and decreased splenic cellularity in both males and females, at 16.9 mg/m^3. In the 90-day gavage study, thymus and spleen weights were not measured, but there were no gross or microscopic pathology findings in these organs (Liao, 1989a, c). Immune tissues were also among the affected tissues in the oral cancer bioassay by Fukuda et al. (1980) and Fukuda et al. (1979), which found significant increases in incidences of thymomas and malignant lymphomas at 4.9 mg/kg-day (human equivalent dose [HED]), and these were some of the first tumors to form in exposed animals. The potential mechanisms of carcinogenesis for these immune-related tumors is unclear, but the tumors provide further evidence that the immune system is a potential target of *p*-α,α,α-tetrachlorotoluene.

Data for the most sensitive endpoints in the 90-day gavage study (increased tubular atrophy and aspermatogenesis in the testes, decreased absolute and relative testis weights, and decreased body weights in males, and reduced lymphocyte counts in both males and females) were modeled using all available continuous or dichotomous models, as appropriate, in the Benchmark Dose Software (BMDS; Version 2.6). The modeled data are shown in Table A-1. HEDs in mg/kg-day were used as the dose metric. Benchmark responses (BMRs) were chosen for each data set in accordance with standard U.S. EPA practice.

Table A-1. Data for Sensitive Endpoints in Male and Female S-D Rats Exposed Daily to *p*-α,α,α-Tetrachlorotoluene by Gavage for 90 Days[a]

	ADD (HED) (mg/kg-d)[b]			
Male	**0 (0)**	**1.25 (0.342)**	**12.5 (3.38)**	**25.0 (6.70)**
Male body weight at Week 14 (g); mean ± SD (*n* = 10)	543 ± 38.8	526 ± 64.0	484 ± 45.1	459 ± 34.8
Absolute testis weight (g); mean ± SD (*n* = 10)	3.41 ± 0.399	3.73 ± 0.713	2.19 ± 0.922	1.25 ± 0.138
Relative testis weight (% BW); mean ± SD (*n* = 10)	0.662 ± 0.086	0.762 ± 0.174	0.477 ± 0.203	0.291 ± 0.048
Total incidence of tubular atrophy and aspermatogenesis in the testes (*n* = 10)	0	0	7	10
Incidence of marked tubular atrophy and aspermatogenesis in the testes (*n* = 10)	0	0	5	7
Lymphocytes (10^3/µL); mean ± SD (*n* = 10)	9.73 ± 2.65	9.54 ± 2.28	6.17 ± 1.4	5.27 ± 2.04
Female	**0 (0)**	**1.25 (0.299)**	**12.5 (2.94)**	**25.0 (5.89)**
Lymphocytes (10^3/µL); mean ± SD (*n* = 10)	7.06 ± 2.9	6.16 ± 1.73	5.28 ± 1.9	3.6 ± 1.29

[a]Liao (1989a, 1989c).
[b]HEDs were calculated as recommended by U.S. EPA (2011b). HED = ADD × DAF. The DAF is calculated as follows: DAF = ($BW_a^{1/4} \div BW_h^{1/4}$), where BW_a = animal body weight and BW_h = human body weight. A reference body weight recommended by U.S. EPA (1988) for humans, (70 kg), and study-specific TWA body weights for male (0.392, 0.375, and 0.362 kg at low, medium, and high doses, respectively) and female (0.229, 0.214, and 0.215 kg at low, medium, and high doses, respectively) rats from each dose group were used for BW_h and BW_a. The calculated DAFs for low, medium, and high doses were: 0.274, 0.271, and 0.268 (males) and 0.239, 0.235, and 0.235 (females).

ADD = adjusted daily dose; BW = body weight; DAF = dosimetric adjustment factor; HED = human equivalent dose; S-D = Sprague-Dawley; SD = standard deviation; TWA = time-weighted average.

Table A-2 summarizes the benchmark dose (BMD) modeling results and provides candidate points of departure (PODs) for the modeled endpoints. Details of model fit for each data set are presented in Appendix C.

Table A-2 Potential PODs in Rats Administered p-α,α,α-Tetrachlorotoluene by Gavage for 90 Days[a]

Endpoint	NOAEL (HED) mg/kg-d	LOAEL (HED) mg/kg-d	BMDL (HED)[b] mg/kg-d	POD (HED) mg/kg-d
Decreased body weight (M)	0.342	3.38	0.351	0.351 ($BMDL_{10}$)
Decreased absolute testis weight (M)	0.342	3.38	NA	0.342 (NOAEL)
Decreased relative testis weight (M)	0.342	3.38	NA	0.342 (NOAEL)
Increased total incidence of tubular atrophy and aspermatogenesis in the testes (M)	**0.342**	**3.38**	**0.167**	**0.167 ($BMDL_{10}$)**
Increased incidence of marked tubular atrophy and aspermatogenesis in the testes (M)	0.342	3.38	0.261	0.261 ($BMDL_{10}$)
Decreased lymphocyte count (M)	0.342	3.38	0.491	0.491 ($BMDL_{10}$)
Decreased lymphocyte count (F)	3.38	6.70	3.03	3.03 ($BMDL_{10}$)

[a]Liao (1989a, 1989c).
[b]Modeling results are described in more detail in Appendix C.

BMDL = benchmark dose lower confidence limit; F = female(s); HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; M = male(s); NA = not applicable; NOAEL = no-observed-adverse-effect level; POD = point of departure.

Derivation of a Screening Subchronic Provisional Reference Dose

Of the most sensitive endpoints in the 90-day gavage study by (Liao, 1989a, c) that provided adequate BMD modeling results, the lowest POD is a 10% benchmark dose lower confidence limit human equivalent dose ($BMDL_{10}$ [HED]) of 0.167 mg/kg-day for increased total incidence of tubular atrophy and aspermatogenesis. The data for decreased absolute and relative testis weight did not provide adequate BMD model fits; thus, the POD for these effects is a NOAEL of 0.342 mg/kg-day. The $BMDL_{10}$ (HED) of 0.167 mg/kg-day for increased total incidence of tubular atrophy and aspermatogenesis in the 90-day gavage study (Liao, 1989a, c) was selected as the POD for derivation of the screening subchronic provisional reference dose (p-RfD), because it is the lowest of the prospective PODs and is therefore expected to be protective against all testicular effects, as well as any potential effects on body weight and the immune system, following oral exposure to *p*-α,α,α-tetrachlorotoluene.

The screening subchronic p-RfD is derived by applying a composite uncertainty factor (UF_C) of 300 (reflecting an interspecies uncertainty factor [UF_A] of 3, an intraspecies uncertainty factor [UF_H] of 10, and a database uncertainty factor [UF_D] of 10) to the selected POD (HED) of 0.167 mg/kg-day.

Screening Subchronic p-RfD = POD (HED) ÷ UF_C
= 0.167 mg/kg-day ÷ 300
= **6×10^{-4} mg/kg-day**

Table A-3 summarizes the uncertainty factors for the screening subchronic p-RfD for *p*-α,α,α-tetrachlorotoluene.

Table A-3. Uncertainty Factors for the Screening Subchronic p-RfD for *p*-α,α,α-Tetrachlorotoluene

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for remaining uncertainty associated with extrapolating from animals to humans when cross-species dosimetric adjustment (HED calculation) is performed.
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. Relevant oral studies are limited to a single subchronic-duration toxicity study in rats (Liao, 1989a, c) and a 14-d range-finding study performed by the same researchers (both studies unpublished and not peer reviewed), although some support is also provided by a short-term-duration inhalation study in rats (also unpublished) that found effects consistent with those identified in the subchronic-duration oral study. An oral cancer bioassay in mice is also available but contains no information on noncancer endpoints. There are no reproductive or developmental studies available by oral exposure. An unpublished developmental toxicity study by inhalation exposure is available, but the results (fetal effects suggestive of developmental delay at a concentration that also affected body weight in dams) are of uncertain significance for oral exposure. Additionally, the thymus has been identified as a potential toxicity target after inhalation exposure to *p*-α,α,α-tetrachlorotoluene, suggesting the possibility of immunotoxicity as a systemic effect; however, an immunotoxicity study is lacking in the database.
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of *p*-α,α,α-tetrachlorotoluene in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a BMDL.
UF_S	1	A UF_S of 1 is applied because the POD comes from a subchronic-duration study.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMDL = benchmark dose lower confidence limit; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Derivation of Screening Chronic Provisional Reference Dose

There are no chronic-duration studies on *p*-α,α,α-tetrachlorotoluene that provide adequate data on noncancer effects. Thus, the screening chronic p-RfD for *p*-α,α,α-tetrachlorotoluene is derived using the same POD (HED) as the screening subchronic p-RfD (0.167 mg/kg-day) with a UF_C of 3,000 (reflecting a UF_A of 3, a UF_H of 10, a UF_D of 10, and a subchronic-to-chronic uncertainty factor [UF_S] of 10 for the use of a subchronic POD).

Screening Chronic p-RfD = POD (HED) ÷ UF_C
= 0.167 mg/kg-day ÷ 3,000
= **6×10^{-5} mg/kg-day**

Table A-4 summarizes the uncertainty factors for the screening chronic p-RfD for *p*-α,α,α-tetrachlorotoluene.

Table A-4. Uncertainty Factors for the Screening Chronic p-RfD for *p*-α,α,α-Tetrachlorotoluene

UF	Value	Justification
UF_A	3	A UF_A of 3 is applied to account for remaining uncertainty associated with extrapolating from animals to humans when cross-species dosimetric adjustment (HED calculation) is performed.
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. Relevant oral studies are limited to a single subchronic-duration toxicity study in rats (Liao, 1989a, c) and a 14-d range-finding study performed by the same researchers (both studies unpublished and not peer reviewed), although some support is also provided by a short-term-duration inhalation study in rats (also unpublished) that found effects consistent with those identified in the subchronic-duration oral study. An oral cancer bioassay in mice is also available but contains no information on noncancer endpoints. There are no chronic-duration noncancer, reproductive, or developmental studies available by oral exposure. An unpublished developmental toxicity study is available by inhalation exposure, but the results (fetal effects suggestive of developmental delay at a concentration that also affected body weight in dams) are of uncertain significance for oral exposure. Additionally, the thymus has been identified as a potential toxicity target after inhalation exposure to *p*-α,α,α-tetrachlorotoluene, suggesting the possibility of immunotoxicity as a systemic effect; however, an immunotoxicity study is lacking from the database.
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of *p*-α,α,α-tetrachlorotoluene in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a BMDL.
UF_S	10	A UF_S of 10 is applied because of the lack of a chronic-duration study, and a subchronic POD is being used to estimate a chronic point of departure for the derivation of a screening chronic p-RfD.
UF_C	3,000	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMDL = benchmark dose lower confidence limit; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

DERIVATION OF SCREENING INHALATION REFERENCE CONCENTRATIONS

The main body of this PPRTV assessment noted that, because they have not been peer reviewed, neither the 30-day rat inhalation study by Rose et al. (1984), nor the rat inhalation developmental toxicity study by Edwards et al. (1985) could be used to derive provisional reference values. Both studies did, however, appear to be adequately designed and conducted, and provided dose-response information on endpoints suitable for use in quantitative toxicity assessment. To account for the uncertainty associated with basing a toxicity assessment on unpublished studies that have not been peer reviewed, the assessment is considered a screening-level assessment.

A NOAEL of 3.98 mg/m^3 and a LOAEL of 18.9 mg/m^3 (analytical vapor concentrations) were identified for rats in the 30-day inhalation study (Rose et al., 1984), based on significantly increased incidence of upper and lower respiratory tract lesions in male and female rats exposed to *p*-α,α,α-tetrachlorotoluene vapors. The lesions showed a dose-response, with severe lesions occurring only at the high concentration of 94.5 mg/m^3. Other significant effects at this high exposure level were decreases in food and water intake, body and organ weights, and lymphocyte counts; and increases in incidence of degenerative lesions in the testes, spleen, and thymus. Gross clinical signs of toxicity and mortality were also observed at this concentration.

In considering the relative sensitivity of the different respiratory lesions, exposure levels were converted to HECs for both the extrathoracic (ET) region (for upper respiratory lesions) and for the tracheobronchial (TB) region (for lower respiratory lesions), according to U.S. EPA (1994) methodology. HEC_{ET} values (0.142, 0.675, and 2.53 mg/m^3 in males, and 0.107, 0.506, and 2.03 mg/m^3 in females) were roughly 10-fold lower than HEC_{TB} values. Thus, based on HECs, the upper respiratory lesions are a more sensitive basis for toxicity assessment than the lower respiratory lesions. Of the observed upper respiratory lesions, only two lesions occurred at all exposure levels: atrophy of olfactory epithelium in males and keratinizing epithelial hyperplasia over arytenoid projections in the larynx in females. Data for both of these lesions were modeled by all available dichotomous models in BMDS (Version 2.6), using the corresponding HEC_{ET} values. Other lesions considered for modeling were epithelial hyperplasia/metaplasia in the ventrolateral region of the larynx of males, and focal atrophy of the olfactory epithelium in females. Neither of these lesions occurred in the low-exposure group, but both were significantly increased in the middle-exposure group. However, neither of these data sets was suitable for BMD modeling because incidence jumped from 0% in the control and low-exposure groups, to 80–100% in the middle- and high-exposure groups, with no intermediate values to inform the shape of the dose-response curve in the low-dose region.

The modeled data are shown in Table A-5. For atrophy of the olfactory epithelium in male rats, incidences were reported by severity grade in the original study. Those data were combined to give total incidence of the lesion, which was the data set modeled here. Modeling was performed using the standard reporting BMR for dichotomous data of 10% extra risk.

Table A-5. Data for Sensitive Endpoints in Male and Female Albino (CR:WI BR) Rats Exposed to *p*-α,α,α-Tetrachlorotoluene Vapor 5 Days/Week, 6 Hours/Day, for 30 Days[a]

	HEC_{ET} (mg/m^3)[b]			
Males	**0**	**0.142**	**0.675**	**2.53**
Atrophy of olfactory epithelium				
Focal	0/5	1/5	3/5	0/6
Severe	0/5	0/5	1/5	6/6
Total[c]	0/5	1/5	4/5*	6/6*
Females	**0**	**0.107**	**0.506**	**2.03**
Keratinizing epithelial hyperplasia in the larynx	0/5	1/5	2/5	5/5*

[a]Rose et al. (1984).
[b]HEC_{ET} was calculated using the equation for ET effects from a Category 1 gas (U.S. EPA, 1994). HEC_{ET} = TWA concentration (mg/m^3) × $RGDR_{ET}$, where $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human). $RGDR_{ET}$ was calculated as per U.S. EPA (1994) using default human V_E and human and animal respiratory tissue surface area values and animal V_E values calculated from TWA body weights for each dose group in the study. TWA body weights (grams) for the 0, 3.98, 18.9, and 94.5 mg/m^3 groups, respectively, were: males = 303.6, 304.7, 298.1, and 201.2; female = 203.2, 203.4, 202.5, and 159.5.
[c]Total incidence was modeled by EPA.
*Statiscially significant ($p < 0.05$) based on Fisher's exact test, as conducted for this review.

ET = extrathoracic; HEC = human equivalent concentration; RGDR = regional gas dose ratio; TWA = time-weighted average; V_E = minute volume.

In the developmental toxicity study (Edwards et al., 1985), a maternal NOAEL of 6.30 mg/m^3 (HEC) was identified. Although absolute maternal body weight was reduced at 6.30 mg/m^3, this reduction was less than 10%. Thus, a maternal LOAEL was not identified. The fetal NOAEL and LOAEL were established at 2.60 mg/m^3 and 6.30 mg/m^3 (HEC), respectively, based on decreased mean fetal weight and increased incidence of unossified sternebrae in the fetuses of dams exposed to *p*-α,α,α-tetrachlorotoluene for 6 hours/day on GDs 6–19. Fetal-weight data were not reported in sufficient detail to perform BMD modeling, but the study did include individual animal data that were used to perform BMD modeling of the incidence of fetal unossified sternebrae by the nested models in BMDS. A BMR of 5% extra risk was used. The individual animal data used to perform the modeling are shown in Appendix C.

Table A-6 summarizes the BMD modeling results and provides candidate PODs for the modeled endpoints. Details of model fit for each data set are presented in Appendix C.

Table A-6. Potential PODs in Rats Administered p-α,α,α-Tetrachlorotoluene by Inhalation Exposure

Endpoint	NOAEL (HEC) mg/m^3	LOAEL (HEC) mg/m^3	BMCL (HEC)[a] mg/m^3	POD (HEC) mg/m^3
Increased total incidence of atrophy of the olfactory epithelium (M)[b]	**0.142**	**0.675**	**0.0141**	**0.0141 ($BMCL_{10}$)**
Increased incidence of keratinizing epithelial hyperplasia in the larynx (F)[b]	0.506	2.03	0.0182	0.0182 ($BMCL_{10}$)
Increased incidence of unossified sternebrae[c]	2.60	6.30	0.385	0.385 ($BMCL_{05}$)

[a]Modeling results are described in more detail in Appendix C.
[b]Rose et al. (1984).
[c]Edwards et al. (1985).

BMCL = benchmark concentration lower confidence limit; F = female(s); HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; POD = point of departure.

Derivation of a Screening Subchronic Provisional Reference Concentration

Of the most sensitive endpoints observed following inhalation exposure to *p*-α,α,α-tetrachlorotoluene that provided adequate BMD modeling results, the lowest POD is a $BMCL_{10}$ (HEC) of 0.0141 mg/m^3 for increased incidence of atrophy of the olfactory epithelium in male rats in the 30-day inhalation study (Rose et al., 1984). Thus, the $BMCL_{10}$ (HEC) of 0.0141 mg/m^3 was selected as the POD for derivation of the screening subchronic p-RfC. The POD based on increased incidence of atrophy of the olfactory epithelium was slightly lower than the potential POD based on laryngeal hyperplasia in females in this same study, and an order of magnitude lower than the potential POD based on unossified sternebrae in the developmental toxicity study (Edwards et al., 1985). Thus, the POD based on increased incidence of atrophy of the olfactory epithelium is expected to be protective against all respiratory effects, as well as any potential developmental effects, following inhalation exposure to *p*-α,α,α-tetrachlorotoluene.

The screening subchronic p-RfC is derived by applying a UF_C of 300 (reflecting a UF_A of 3, a UF_H of 10, and a UF_D of 10) to the selected POD of 0.0141 mg/m^3.

$$\textbf{Screening Subchronic p-RfC} = \text{POD (HEC)} \div UF_C$$
$$= 0.0141 \text{ mg/m}^3 \div 300$$
$$= \mathbf{5 \times 10^{-5} \text{ mg/m}^3}$$

Table A-7 summarizes the uncertainty factors for the screening subchronic p-RfC for *p*-α,α,α-tetrachlorotoluene.

Table A-7. Uncertainty Factors for the Screening Subchronic p-RfC for *p*-α,α,α-Tetrachlorotoluene

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for remaining uncertainty associated with extrapolating from animals to humans when cross-species dosimetric adjustment (HEC calculation) is performed.
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. The inhalation database for *p*-α,α,α-tetrachlorotoluene is limited to one 30-d toxicity study and one developmental toxicity study in rats (Edwards et al., 1985; Rose et al., 1984), neither of which was published or peer reviewed. No longer, subchronic- or chronic-duration inhalation studies were located. The inhalation database is also lacking a multigenerational reproductive study and a developmental toxicity study in a second species. Additionally, the thymus has been identified as a potential toxicity target after inhalation exposure to *p*-α,α,α-tetrachlorotoluene; however, an immunotoxicity study is lacking from the database.
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of *p*-α,α,α-tetrachlorotoluene in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a BMCL.
UF_S	1	A UF_S of 1 is applied because the POD was derived from a 30-d study.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMCL = 95% lower confidence limit on the benchmark concentration; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Derivation of a Screening Chronic Provisional Reference Concentration

There are no chronic-duration inhalation studies on *p*-α,α,α-tetrachlorotoluene. The 30-day study used for deriving the screening subchronic p-RfC (Rose et al., 1984) is too limited in duration to support derivation of a screening chronic p-RfC. Use of a less-than-subchronic-duration study is highly uncertain with respect to deriving chronic toxicity values unless there are chronic toxicity data available to suggest that the critical effect observed in the short-term-duration study will not increase in severity or become more sensitive based on dose-response analysis following longer treatment duration. In the absence of any supporting chronic toxicity data, it is unclear that a POD based on the short-term-duration inhalation study by Rose et al. (1984) or the developmental toxicity study by Edwards et al. (1985) would protect against chronic effects. Therefore, a screening chronic p-RfC was not derived for *p*-α,α,α-tetrachlorotoluene.

DERIVATION OF PROVISIONAL SCREENING CANCER POTENCY VALUES

Derivation of a Screening Provisional Oral Slope Factor

As discussed in the main body of the report, a provisional oral slope factor (p-OSF) was not derived because U.S. EPA could find no evidence that the Fukuda et al. (1980) study was peer reviewed. In addition the study duration was much less than lifetime duration, requiring the application of an adjustment factor to account for the expected increase in the tumor incidence rate with increasing age (U.S. EPA, 1980), substantially increasing the uncertainty.

Fukuda et al. (1980) observed significant dose-related trends for increased incidence of multiple tumor types in female mice exposed to *p*-α,α,α-tetrachlorotoluene by gavage for 17.5 weeks and observed for up to 18 months, including adenocarcinomas and multiple adenomas in the lungs, thymomas, malignant lymphomas, multiple papillomas, squamous cell carcinomas and carcinomas in situ in the forestomach, and squamous cell carcinomas in the skin (see Tables A-8 and B-8).

Table A-8. Incidence Data for Significantly Increased Tumors in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks[a]

Endpoint	HED (mg/kg-d)					
	0	0.028	0.072	0.18	0.44	1.1
Tumor incidence/total effective number of animals						
Forestomach:						
Squamous cell carcinoma	0/26	0/22	0/28	0/22	6/29	7/29
Carcinoma in situ	0/26	0/22	0/28	1/22	4/29	3/29
Multiple papilloma	0/26	2/22	4/28	5/22	2/29	1/29
Lung:						
Adenocarcinoma	0/26	3/22	7/28	10/22	15/29	2/29
Multiple adenoma	1/26	2/22	1/28	6/22	10/29	17/29
Thymoma	0/26	0/22	0/28	0/22	4/29	8/29
Malignant lymphoma	1/26	0/22	1/28	0/22	0/29	5/29
Skin:						
Squamous cell carcinoma	0/26	0/22	0/28	0/22	0/29	6/29

[a]Fukuda et al. (1980); Fukuda et al. (1979).

HED = human equivalent dose.

BMD modeling was performed for each of these tumor types individually. It was not possible to combine data for multiple tumor types in a given tissue because tumor data from individual animals were not provided, and the reporting of multiple tumor types in a single animal could not be ruled out. The MS_Combo model was used to evaluate the composite risk for developing any combination of tumors at any site within a single study. The MS_Combo model was run using the incidence data for the individual tumor types and the polydegrees identified in the model runs for the individual tumor types. Including all tumor types in the combined tumor BMD analysis using the MS_Combo model could result in an overestimate of the screening p-OSF. The potential for "double-counting" of related tumors in the forestomach exists primarily at the highest two doses, where there is more than one tumor of each type. There is a greater potential for double-counting in the lung, with multiple tumors of each type at most exposure levels. Also, despite the observed differences in survival (reported as months to 50% mortality) across groups, it was not possible to perform any adjustments for differential mortality across groups due to the lack of individual animal data. Multistage cancer models in the U.S. EPA BMDS (Version 2.6) were fit to the incidence data for each tumor. The BMR used was 10% extra risk. The HED in mg/kg-day was used as the dose metric, and modeling results are summarized in Table A-9 (see additional BMD details in Appendix C).

Table A-9. Modeling Results Based on the Incidence of Tumors in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks[a]

Tumor Endpoint	Selected Model	BMD_{10} (HED) (mg/kg-d)	$BMDL_{10}$ (HED) (mg/kg-d)	Potential p-OSF $(mg/kg\text{-}d)^{-1}$
Lung adenocarcinoma	Multistage (1-degree); high-dose group dropped	0.047	0.033	3.0×10^{0}
Lung multiple adenoma	Multistage (1-degree)	0.127	0.092	1.1×10^{0}
Thymoma	Multistage (1-degree)	0.402	0.258	3.9×10^{-1}
Malignant lymphoma	Multistage (1-degree)	0.979	0.727	1.5×10^{-1}
Forestomach multiple papillomas	Multistage (1-degree)	0.0569	0.0359	2.8×10^{0}
Forestomach squamous cell carcinoma	Multistage (1-degree)	0.372	0.243	4.1×10^{-1}
Forestomach carcinoma in situ	Multistage (1-degree)	0.640	0.376	2.7×10^{-1}
Skin squamous cell carcinoma	Multistage (1-degree)	0.957	0.721	1.5×10^{-1}
Combined tumors	**MS_Combo**	**0.019**	**0.015**	**6.8×10^{0}**

[a]Fukuda et al. (1980); Fukuda et al. (1979).

BMD = benchmark dose; BMDL = 95% lower confidence limit on the benchmark dose (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); HED = human equivalent dose; p-OSF = provisional oral slope factor.

The Multistage cancer model (1-degree) provided an adequate fit to the data sets for lung adenocarcinomas, lung multiple adenomas, forestomach carcinoma in situ, carcinomas in the forestomach, and thymomas (see Table A-9). The higher degree polynomial models took the form of the 1-degree models for these tumors. For lung adenocarcinomas, it was necessary to drop the high-dose data to obtain an adequate fit. This is due to the low incidence of these tumors in the highest-dose group, which reflects the relatively late development of this tumor and the high early mortality observed in this group due to quicker developing tumors (malignant lymphoma, thymoma, and forestomach carcinomas). Similarly, the forestomach multiple papilloma data could be fit adequately only by dropping the two highest doses (1-degree Multistage model). Although two doses had to be dropped, forestomach multiple papillomas were included in the multiple tumor analysis because of the strong dose-response trend ($p = 0.0075$) for the lower doses and the second highest potential unadjusted screening p-OSF.

From the Multistage cancer models, predicted BMDs associated with 10% extra risk (BMD_{10}) and their 95% lower confidence limits ($BMDL_{10}$) for the individual tumor types ranged from 0.047 and 0.033 mg/kg-day (HED), respectively, for lung adenocarcinoma to 0.979 and 0.727 mg/kg-day (HED) for malignant lymphoma. The combined tumor model resulted in BMD_{10} and $BMDL_{10}$ estimates of 0.019 and 0.015 mg/kg-day (HED). The lowest $BMDL_{10}$ value of 0.015 mg/kg-day (HED) based on the combined tumor risk was selected as the point of departure (POD) for deriving the screening p-OSF.

In the absence of data for the MOA of *p*-α,α,α-tetrachlorotoluene-induced tumorigenesis, the unadjusted screening p-OSF for *p*-α,α,α-tetrachlorotoluene, based on the $BMDL_{10}$ (HED) of

0.015 mg/kg-day for combined tumors in female mice treated with *p*-α,α,α-tetrachlorotoluene for 17.5 weeks, was derived using a linear approach as follows:

$$\begin{aligned} \textbf{Screening p-OSF (Unadjusted)} &= \text{BMR} \div \text{BMDL}_{10}\text{ (HED)} \\ &= 0.1 \div 0.015\text{ mg/kg-day} \\ &= \mathbf{6.8 \times 10^{0}\ (mg/kg\text{-}day)^{-1}} \end{aligned}$$

An adjustment was applied to account for the shorter-than-lifetime observation period (U.S. EPA, 1980). The Fukuda et al. (1980) bioassay was terminated after 18 months (compared to the reference mouse lifespan of 24 months) due to early mortality associated with tumor formation. Due to the less-than-lifetime duration of the study, it cannot be known how an increased duration (i.e., the full 2-year lifetime exposure) might have influenced the tumor incidence in the low-dose treated rats. Therefore, an adjustment factor of $(L \div L_e)^3$ was applied to the unadjusted screening p-OSF, where L = the lifetime of the animal and L_e = the duration of experimental dosing (U.S. EPA, 1980). Using this adjustment, an adjusted screening p-OSF is derived as follows:

$$\begin{aligned} \textbf{Screening p-OSF (Adjusted)} &= \text{Screening p-OSF (unadjusted)} \times (L \div L_e)^3 \\ &= 6.8 \times 10^{0}\ (\text{mg/kg-day})^{-1} \times (24\text{ months} \div 18\text{ months})^3 \\ &= \mathbf{1.6 \times 10^{1}\ (mg/kg\text{-}day)^{-1}} \end{aligned}$$

The adjusted screening p-OSF should not be used with exposure exceeding the POD (0.015 mg/kg-day) because at doses higher than this value, the fitted dose-response model better characterizes the dose-response relationship. As mentioned previously, there is considerable uncertainty associated with the screening p-OSF due to the large difference between actual exposure time and study duration, with respect to dose averaging, and application of a less-than-lifetime adjustment factor. Averaging the doses over the full study duration is a common practice that assumes that the carcinogenic outcome is a linear function of total dose, rather than dose rate; that is, a large dose over a short time period is equivalent to a smaller dose over a longer time period (U.S. EPA, 2005). An alternative that uses the 17.5-week average exposure (not averaging over 18 months) would result in a much larger less-than-lifetime adjustment factor. As some adjustment to the effective dose is necessary based on both the 2005 *Cancer Guidelines* and the unique, short treatment duration in the study by Fukuda et al. (1980) [necessitating a less-than-lifetime adjustment factor per U.S. EPA (1980)], the selected approach was determined to be the least uncertain.

Derivation of a Provisional Inhalation Unit Risk

Derivation of quantitative estimates of cancer risk following inhalation exposure to *p*-α,α,α-tetrachlorotoluene is precluded by the absence of inhalation data for this compound.

APPENDIX B. DATA TABLES

Table B-1. Body Weight and Body-Weight Gain in Male and Female Rats Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 14 Days[a]

	Study Day		
	1	**8**	**15**
Dose (mg/kg-d)	**Male Body Weight (g)[b, c]**		
0	187 ± 13.6	230 ± 14.7	273 ± 12.6
1.25[d]	201 ± 11.7 (+8%)	262 ± 11.7** (+14%)	309 ± 18.4** (+13%)
12.5[d]	201 ± 16.2 (+8%)	263 ± 17.7** (+14%)	312 ± 19.2** (+14%)
25.0	185 ± 11.9 (−1%)	220 ± 11.8 (−4%)	249 ± 11.3 (−9%)
75.0	187 ± 9.2 (0%)	197 ± 10.3** (−14%)	217 ± 17.8** (−21%)
150	186 ± 10.8 (−1%)	167 ± 18** (−27%)	169 ± 10** (−38%)
300[e]	183 ± 10.5 (−2%)	NDr	NDr
Dose (mg/kg-d)	**Female Body Weight (g)**		
0	133 ± 8.0	159 ± 11.7	175 ± 18.4
1.25[d]	137 ± 9.3 (+3%)	159 ± 10.08 (0%)	172 ± 16.8 (−2%)
12.5[d]	136 ± 7.5 (+2%)	158 ± 7.4 (−1%)	172 ± 5.8 (−2%)
25.0	136 ± 6.3 (+2%)	156 ± 10.4 (−2%)	168 ± 8.9 (−4%)
75.0	134 ± 7.4 (+1%)	140 ± 10.3* (−12%)	156 ± 11.6 (−11%)
150	132 ± 7.4 (−1%)	124 ± 14.7** (−22%)	132 ± 18** (−25%)
300[e]	134 ± 8.4 (+1%)	NDr	NDr

Table B-1. Body Weight and Body-Weight Gain in Male and Female Rats Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 14 Days[a]

	Body-Weight Gain (g)			
	Male		Female	
Dose (mg/kg-d)	Week 1 (D 1−7)	Week 2 (D 8−15)	Week 1 (D 1−8)	Week 2 (D 8−15)
0	43 ± 4.7	43 ± 3.1	26 ± 5.8	17 ± 7.8
1.25[d]	61 ± 3.9* (+42%)	47 ± 11.9 (+9%)	22 ± 5.5 (−15%)	14 ± 8.7 (−18%)
12.5[d]	62 ± 7.3** (+44%)	49 ± 8.3 (+14%)	22 ± 2.5 (−15%)	14 ± 3.5 (−18%)
25.0	36 ± 4.2* (−16%)	29 ± 10** (−33%)	20 ± 5.7 (−23%)	13 ± 6.1 (−24%)
75.0	10 ± 3** (−77%)	20 ± 7.8** (−54%)	7 ± 11.3** (−73%)	16 ± 3.6 (−6%)
150	−17 ± 18.5** (−141%)	2 ± 10.8** (−95%)	−8 ± 14.7** (−131%)	8 ± 8.2 (−53%)
300[e]	NDr	NDr	NDr	NDr

[a]Liao (1989b, 1989c).
[b]Data are mean ± SD; *n* = 6/group on Day 1, and 5/group at 150 mg/kg-day, and 6/group for other dose groups on Days 8 and 15.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Data from these doses were obtained from a second experiment (Experiment 2) without a concurrent control. Comparisons and statistical analysis shown here were done for this review using the control data shown from Experiment 1.
[e]All animals from the 300-mg/kg-day group died prior to Day 8.
*Significantly different from controls at the same time point by unpaired *t*-test ($p < 0.05$), as conducted for this review.
**Significantly different from controls at the same time point by unpaired *t*-test ($p < 0.01$), as conducted for this review.

NDr = not determined (all animals from the 300-mg/kg-day group died prior to Day 8); SD = standard deviation.

Table B-2. Weekly Food Consumption in Male and Female Rats Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 14 Days[a]

	Study Day	
	1−8 (Week 1)	**8−15 (Week 2)**
Dose (mg/kg-d)	**Male Food Consumption (g/animal-d)[b, c]**	
0	22 ± 1	22 ± 1.3
1.25[d]	28 ± 1.4** (+27.3%)	27 ± 2.5** (+22.7%)
12.5[d]	28 ± 2.2** (+27.3%)	28 ± 2.2** (+27.3%)
25.0	21 ± 0.6 (−4.5%)	20 ± 1.1 (−9.1%)
75.0	17 ± 1.8** (−22.7%)	16 ± 2.6** (−27.3%)
150	12 ± 4** (−45.5%)	12 ± 1.3** (−45.5%)
300[e]	NDr	NDr
Dose (mg/kg-d)	**Female Food Consumption (g/animal-d)**	
0	17 ± 1.5	16 ± 2
1.25[d]	18 ± 1.3 (+5.9%)	17 ± 1.6 (+6.3%)
12.5[d]	17 ± 0.6 (0%)	18 ± 0.8 (+12.5%)
25.0	16 ± 0.9 (−5.9%)	16 ± 1.1 (0%)
75.0	13 ± 2.6** (−23.5%)	15 ± 2 (−6.3%)
150	10 ± 2.3** (−41.2%)	11 ± 2.5** (−31.3%)
300[e]	NDr	NDr

[a]Liao (1989b, 1989c).
[b]Data are mean ± SD; *n* = 5/group at 150 mg/kg-day and 6/group for other dose groups.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Data from these doses were obtained from a second experiment (Experiment 2) without a concurrent control. Comparisons and statistical analysis shown here were done for this review using the control data shown from Experiment 1.
[e]All animals from the 300-mg/kg-day group died prior to Day 8.
*Significantly different from controls at the same time point by unpaired *t*-test ($p < 0.05$), as conducted for this review.
**Significantly different from controls at the same time point by unpaired *t*-test ($p < 0.01$), as conducted for this review.

NDr = not determined (all animals from the 300-mg/kg-day group died prior to Day 8); SD = standard deviation.

Table B-3. Absolute and Relative Organ Weights in Male and Female Rats Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 14 Days[a]

Male Absolute Organ Weights (g)[b, c]				
Dose (mg/kg-d)	**Adrenals**	**Testes**	**Kidneys**	**Liver**
0	0.0507 ± 0.01405	2.56 ± 0.207	2.88 ± 0.251	14.91 ± 1.047
1.25[d]	0.0738 ± 0.01355* (+46%)	2.74 ± 0.193 (+7%)	3.51 ± 0.345** (+22%)	18.14 ± 1.954** (+22%)
12.5[d]	0.0780 ± 0.01707* (+54%)	2.78 ± 0.068 (+9%)	3.44 ± 0.413* (+19%)	19.02 ± 1.903** (+28%)
25.0	0.0554 ± 0.01229 (+9%)	2.67 ± 0.191 (+4%)	2.75 ± 0.244 (−5%)	13.21 ± 1.301* (−11%)
75.0	0.0582 ± 0.00949 (+15%)	2.28 ± 0.157* (−11%)	2.41 ± 0.221** (−16%)	12.93 ± 1.075** (−13%)
150	0.0761 ± 0.01355* (+50%)	1.77 ± 0.203** (−31%)	2.44 ± 0.180** (−15%)	11.54 ± 0.503** (−23%)
300[e]	NDr	NDr	NDr	NDr
Male Relative Organ Weights (% BW)				
Dose (mg/kg-d)	**Adrenals**	**Testes**	**Kidneys**	**Liver**
0	0.019 ± 0.0049	0.940 ± 0.0657	1.055 ± 0.0767	5.478 ± 0.4811
1.25[d]	0.024 ± 0.0044 (+26%)	0.892 ± 0.0937 (−5%)	1.139 ± 0.0933 (+8%)	5.867 ± 0.2998 (+7%)
12.5[d]	0.025 ± 0.0060 (+32%)	0.893 ± 0.0659 (−5%)	1.098 ± 0.0916 (+4%)	6.089 ± 0.4582* (+11%)
25.0	0.022 ± 0.0050 (+16%)	1.074 ± 0.0836* (+14%)	1.104 ± 0.0676 (+5%)	5.304 ± 0.3541 (−3%)
75.0	0.027 ± 0.0038* (+42%)	1.053 ± 0.0974* (+12%)	1.112 ± 0.0900 (+5%)	5.978 ± 0.4699 (+9%)
150	0.045 ± 0.0081** (+137%)	1.053 ± 0.1391 (+12%)	1.448 ± 0.0922** (+37%)	6.845 ± 0.3294** (+25%)
300[e]	NDr	NDr	NDr	NDr
Female Absolute Organ Weights (g)				
Dose (mg/kg-d)	**Adrenals**	**Ovaries**	**Kidneys**	**Liver**
0	0.0587 ± 0.00881	0.0853 ± 0.01852	1.99 ± 0.222	9.35 ± 1.628
1.25[d]	0.0818 ± 0.01559** (+39%)	0.1216 ± 0.02334* (+43%)	2.13 ± 0.216 (+7%)	9.24 ± 1.292 (−1%)
12.5[d]	0.0771 ± 0.01956 (+31%)	0.1236 ± 0.01680** (+45%)	2.09 ± 0.101 (+5%)	9.34 ± 0.367 (0%)
25.0	0.0694 ± 0.01464 (+18%)	0.0913 ± 0.03204 (+7%)	2.03 ± 0.195 (+2%)	9.16 ± 0.759 (−2%)
75.0	0.0641 ± 0.01199 (+9%)	0.0990 ± 0.02423 (+16%)	1.97 ± 0.089 (−1%)	9.64 ± 0.569 (+3%)

Table B-3. Absolute and Relative Organ Weights in Male and Female Rats Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 14 Days[a]

Male Absolute Organ Weights (g)[b, c]				
Dose (mg/kg-d)	**Adrenals**	**Testes**	**Kidneys**	**Liver**
150	0.0762 ± 0.01593* (+30%)	0.0607 ± 0.01741* (−29%)	1.85 ± 0.154 (−7%)	9.12 ± 1.072 (−3%)
300[e]	NDr	NDr	NDr	NDr
Female Relative Organ Weights (% BW)				
Dose (mg/kg-d)	**Adrenals**	**Ovaries**	**Kidneys**	**Liver**
0	0.034 ± 0.0067	0.049 ± 0.0129	1.142 ± 0.1211	5.317 ± 0.5665
1.25[d]	0.047 ± 0.0070** (+38%)	0.07 ± 0.0110** (+43%)	1.236 ± 0.0761 (+8%)	5.345 ± 0.3393 (+1%)
12.5[d]	0.045 ± 0.0122 (+32%)	0.072 ± 0.0098** (+47%)	1.213 ± 0.0365 (+6%)	5.435 ± 0.2357 (+2%)
25.0	0.041 ± 0.0090 (+21%)	0.055 ± 0.0188 (+12%)	1.210 ± 0.1093 (+6%)	5.450 ± 0.3490 (+3%)
75.0	0.042 ± 0.0095 (+24%)	0.064 ± 0.0176 (+31%)	1.268 ± 0.0753 (+11%)	6.201 ± 0.4663* (+17%)
150	0.059 ± 0.0188* (+74%)	0.046 ± 0.0106 (−6.1%)	1.415 ± 0.1015** (+24%)	6.944 ± 0.3126** (+31%)
300[e]	NDr	NDr	NDr	NDr

[a]Liao (1989b, 1989c).
[b]Data are mean ± SD; *n* = 5/group at 150 mg/kg-day and 6/group for other dose groups.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Data from these doses were obtained from a second experiment (Experiment 2) without a concurrent control. Comparisons and statistical analysis shown here were done for this review using the control data shown from Experiment 1.
[e]All animals from the 300-mg/kg-day group died prior to Day 15 necropsy.
*Significantly different from controls by unpaired *t*-test ($p < 0.05$), as conducted for this review.
**Significantly different from controls by unpaired *t*-test ($p < 0.01$), as conducted for this review.

BW = body weight; NDr = not determined (all animals from the 300-mg/kg-day group died prior to Day 15 necropsy); SD = standard deviation.

Table B-4. Select Weekly Body Weight and Body-Weight Gain Data of Male and Female Rats Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 90 Days[a]

	Dose (mg/kg-d)			
	0	**1.25**	**12.5**	**25.0**
Male Body Weight (g)[b, c]				
Wk 7	412 ± 26.6	398 ± 48.1 (−3%)	383 ± 32.7 (−7%)	373 ± 25.1* (−10%)
Wk 8	436 ± 28.3	420 ± 45.8 (−4%)	402 ± 32.6 (−8%)	389 ± 28.7* (−11%)
Wk 9	453 ± 30.6	441 ± 43.2 (−3%)	418 ± 36.9 (−8%)	405 ± 31.6* (−11%)
Wk 10	479 ± 31.3	464 ± 50.9 (−3%)	436 ± 38.5* (−9%)	422 ± 27.9** (−12%)
Wk 11	496 ± 34.9	482 ± 56.3 (−3%)	452 ± 39.5 (−9%)	434 ± 28.4** (−13%)
Wk 12	514 ± 35.8	495 ± 60.2 (−4%)	466 ± 41.2* (−9%)	444 ± 28.4** (−14%)
Wk 13	530 ± 37.9	512 ± 63.4 (−3%)	477 ± 43.5* (−10%)	453 ± 32.4** (−15%)
Wk 14	543 ± 38.8	526 ± 64.0 (−3%)	484 ± 45.1* (−11%)	459 ± 34.8** (−15%)
Female Body Weight (g)				
Wk 7	239 ± 19.4	238 ± 19.3 (−0.4%)	220 ± 12.3 (−8%)	221 ± 17.7 (−8%)
Wk 8	247 ± 21.4	245 ± 20.4 (−0.8%)	227 ± 13.7 (−8%)	226 ± 18.9* (−9%)
Wk 9	252 ± 20.4	250 ± 22.2 (−0.8%)	230 ± 13.7* (−9%)	230 ± 19.8* (−9%)
Wk 10	261 ± 22.7	257 ± 21.6 (−2%)	235 ± 12.9* (−10%)	239 ± 21.6 (−8%)
Wk 11	267 ± 24	265 ± 21.8 (−0.7%)	240 ± 12.6* (−10%)	246 ± 25.5 (−8%)
Wk 12	271 ± 24.4	268 ± 23.1 (−1%)	246 ± 14.5 (−9%)	254 ± 33.3 (−6%)
Wk 13	273 ± 24	270 ± 23.6 (−1%)	247 ± 14.6 (−10%)	258 ± 38 (−6%)
Wk 14	279 ± 26	275 ± 23.4 (−1%)	252 ± 13.1 (−10%)	263 ± 39 (−6%)
Male Body-Weight Gain (g)				
Wk 7−8	24 ± 3.1	22 ± 10.2 (−8%)	19 ± 4.3 (−21%)	17 ± 5.2* (−29%)
Wk 8−9	17 ± 8.5	21 ± 7.0 (+23%)	16 ± 6.4 (−6%)	16 ± 5.3 (−6%)
Wk 9−10	26 ± 6.1	22 ± 10.2 (−15%)	18 ± 5.1 (−31%)	17 ± 7.8* (−35%)
Wk 10−11	17 ± 6.1	19 ± 6.4 (+13%)	17 ± 4.6 (0%)	12 ± 4.0 (−29%)
Wk 11−12	18 ± 2.9	13 ± 7.6 (−28%)	13 ± 6.5 (−28%)	11 ± 3.5* (−39%)
Wk 12−13	16 ± 3.4	16 ± 6.1 (0%)	12 ± 5.9 (−25%)	8.0 ± 8.1* (−50%)
Wk 13−14	13 ± 2.9	14 ± 6.1 (+8%)	7.0 ± 5.7* (−46%)	6.0 ± 5.3* (−54%)
Female Body-Weight Gain (g)[d]				
Wk 1−2	23 ± 3.3	19 ± 3.8 (−17%)	17 ± 5.4* (−26%)	14 ± 5.8** (−39%)
Wk 5−6	16 ± 3.5	13 ± 5.5 (−19%)	7 ± 2.5** (−56%)	7 ± 5.2** (−56%)

[a]Liao (1989a, 1989c).
[b]Data are mean ± SD; *n* = 10/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Select treatment weeks with statistically significant differences, compared with controls.
*Significantly different from control ($p < 0.05$), as reported by the study authors.
**Significantly different from control ($p < 0.01$), as reported by the study authors.

SD = standard deviation.

Table B-5. Terminal Hematology Data in Male and Female Rats Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 90 Days[a, b]

Endpoint	Dose (mg/kg-d)[c, d]			
	0	1.25	12.5	25.0
Male				
Erythrocytes (10^6/µL)	9.34 ± 0.506	9.45 ± 0.295 (+1%)	9.4 ± 0.35 (+1%)	8.82 ± 0.305* (−6%)
Hct (%)	48.59 ± 1.98	49.44 ± 1.68 (+2%)	48.9 ± 1.09 (+1%)	46.51 ± 1.53* (−4%)
Hb (g/dL)	16.24 ± 0.66	16.74 ± 0.67 (+3%)	16.62 ± 0.51 (+2%)	15.70 ± 0.64 (−3%)
Leukocytes (10^3/µL)	11.66 ± 2.59	12 ± 3.29 (+3%)	7.63 ± 1.37** (−35%)	7.86 ± 2.19** (−33%)
Lymphocytes (10^3/µL)	9.73 ± 2.65	9.54 ± 2.28 (−2%)	6.17 ± 1.4** (−37%)	5.27 ± 2.04** (−46%)
Female				
Leukocytes (10^3/µL)	8.11 ± 2.81	7.25 ± 2.17 (−11%)	6.29 ± 1.99 (−22%)	4.25 ± 1.36** (−48%)
Lymphocytes (10^3/µL)	7.06 ± 2.9	6.16 ± 1.73 (−13%)	5.28 ± 1.9 (−25.2%)	3.6 ± 1.29** (−49%)

[a]Liao (1989a, 1989c).
[b]No statistically significant changes in hematology parameters between treated and control animals were observed on Day 5 prior to study initiation.
[c]Data are mean ± SD; n = 10/group.
[d]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control ($p < 0.05$), as reported by the study authors.
**Significantly different from control ($p < 0.01$), as reported by the study authors.

Hb = hemoglobin; Hct = hematocrit; SD = standard deviation.

Table B-6. Absolute and Relative Organ Weights in Male and Female Rats Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 90 Days[a]

Endpoint	Dose (mg/kg-d)[b, c]			
	0	**1.25**	**12.5**	**25.0**
Male Absolute Organ Weights (g)				
Brain	2.22 ± 0.072	2.21 ± 0.151 (−1%)	2.18 ± 0.139 (−2%)	2.20 ± 0.121 (−1%)
Adrenal glands	0.0705 ± 0.00811	0.0712 ± 0.01491 (+0.9%)	0.0648 ± 0.01807 (−8%)	0.0676 ± 0.02004 (−4%)
Testes	3.41 ± 0.399	3.73 ± 0.713 (+9%)	2.19 ± 0.922** (−36%)	1.25 ± 0.138** (−63%)
Kidneys	3.78 ± 0.528	4.02 ± 0.351 (+6%)	3.87 ± 0.636 (+2%)	3.96 ± 0.437 (+5%)
Liver	16.99 ± 2.184	16.92 ± 3.026 (0%)	16.62 ± 3.364 (−2%)	16.63 ± 2.11 (−2%)
Necropsy body weight	517 ± 38.4	498 ± 62.4 (−4%)	461 ± 44.3† (−11%)	434 ± 33.1† (−16%)
Male Relative Organ Weights (% BW)				
Brain	0.431 ± 0.0327	0.448 ± 0.0453 (+4%)	0.476 ± 0.0396* (+10%)	0.510 ± 0.0335** (+18%)
Adrenal glands	0.014 ± 0.0019	0.014 ± 0.0034 (0%)	0.014 ± 0.0046 (0%)	0.015 ± 0.0045 (+7%)
Testes	0.662 ± 0.086	0.762 ± 0.174 (+15%)	0.477 ± 0.203* (−28%)	0.291 ± 0.048** (−56%)
Kidneys	0.731 ± 0.083	0.814 ± 0.085 (+11%)	0.838 ± 0.102* (+15%)	0.915 ± 0.093** (+25%)
Liver	3.283 ± 0.319	3.394 ± 0.431 (+3%)	3.578 ± 0.465 (+9%)	3.829 ± 0.372* (+17%)
Female Absolute Organ Weights (g)				
Brain	2.00 ± 0.080	2.04 ± 0.119 (+2%)	1.96 ± 0.085 (−2%)	2.01 ± 0.092 (+1%)
Adrenal glands	0.0774 ± 0.01955	0.0833 ± 0.01448 (+8%)	0.0786 ± 0.01091 (+2%)	0.0820 ± 0.01741 (+6%)
Ovaries	0.0966 ± 0.03528	0.1223 ± 0.03781 (+27%)	0.0837 ± 0.016 (−13%)	0.1119 ± 0.03584 (+15%)
Kidneys	2.20 ± 0.277	2.23 ± 0.230 (+1%)	2.18 ± 0.267 (−1%)	2.18 ± 0.247 (−1%)
Liver	8.77 ± 1.227	8.52 ± 0.862 (−2.9%)	8.37 ± 1.212 (−4.6%)	9.22 ± 1.607 (+5.1%)
Necropsy body weight	263 ± 26.0	257 ± 21.9 (−3%)	237 ± 12.8† (−10%)	245 ± 36.6 (−7%)

Table B-6. Absolute and Relative Organ Weights in Male and Female Rats Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 90 Days[a]

Endpoint	Dose (mg/kg-d)[b, c]			
	0	**1.25**	**12.5**	**25.0**
Female Relative Organ Weights (% BW)				
Brain	0.767 ± 0.073	0.800 ± 0.083 (+4%)	0.830 ± 0.034 (+8%)	0.835 ± 0.109 (+9%)
Adrenal glands	0.030 ± 0.0077	0.033 ± 0.0057 (+10%)	0.033 ± 0.0045 (+10%)	0.033 ± 0.0047 (+10%)
Ovaries	0.037 ± 0.014	0.048 ± 0.014 (+30%)	0.035 ± 0.007 (−5%)	0.046 ± 0.012 (+24%)
Kidneys	0.837 ± 0.082	0.870 ± 0.072 (+4%)	0.922 ± 0.112 (+10%)	0.898 ± 0.073 (+7%)
Liver	3.353 ± 0.454	3.325 ± 0.320 (−1%)	3.534 ± 0.419 (+5%)	3.761 ± 0.278 (+12%)

[a]Liao (1989a, 1989c).
[b]Data are mean ± SD; *n* = 10/group, except *n* = 9 for adrenal gland weight in high-dose males (one lost at necropsy).
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control ($p < 0.05$), as reported by the study authors.
**Significantly different from control ($p < 0.01$), as reported by the study authors.
†Statistical analysis not provided by study authors; significantly different from controls by unpaired *t*-test ($p < 0.05$), as conducted for this review.

BW = body weight; SD = standard deviation.

Table B-7. Incidence of Selected Non-neoplastic Lesions in Male and Female Rats Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 90 Days[a]

Endpoint	Dose (mg/kg-d)[b]			
	0	**1.25**	**12.5**	**25.0**
Male				
Epididymis				
Aspermia	0/10	0/10	0/10	10/10** (100%)
Testis				
Total tubular atrophy, aspermatogenesis:	0/10	0/10	7/10** (70%)	10/10** (100%)
Mild	0/10	0/10	2/10 (20%)	1/10 (10%)
Moderate	0/10	0/10	0/10	2/10 (20%)
Marked	0/10	0/10	5/10* (50%)	7/10** (70%)
Syncytial giant cells, tubules:	0/10	0/10	3/10 (30%)	0/10
Mild	0/10	0/10	1/10 (10%)	0/10
Moderate	0/10	0/10	1/10 (10%)	0/10
Marked	0/10	0/10	1/10 (10%)	0/10
Female				
Liver				
Altered foci, eosinophilic:	0/10	0/10	0/10	4/10* (40%)
Minimal	0/10	0/10	0/10	3/10 (30%)
Mild	0/10	0/10	0/10	1/10 (10%)

[a]Liao (1989a, 1989c).
[b]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
*Significantly different from control by Fisher's exact test (one-sided; $p < 0.05$), as conducted for this review.
**Significantly different from control by Fisher's exact test (one-sided; $p < 0.01$), as conducted for this review.

Table B-8. Tumor Incidence in ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks[a]

Endpoint	Dose (HED) (mg/kg-d)[b]					
	0	**0.21 (0.028)**	**0.54 (0.072)**	**1.3 (0.18)**	**3.3 (0.44)**	**8.2 (1.1)**
Initial number of animals	30	30	30	26	31	31
Effective number of animals[c]	26	22	28	22	29	29
Average age (months) of affected animals	17.5	17.9	16.9	16.9	14.8	6.2
Occurrence of 50% mortality (months)	>18	>18	>18	>18	12.3	4.7
Number of animals with tumors ÷ effective number of animals (% incidence)						
Tumors types:						
Malignant	1/26 (4%)	4/22 (18%)	8/28* (30%)	10/22** (45%)	20/29** (69%)	16/29** (55%)
Benign	1/26 (4%)	2/22 (9%)	2/28 (7%)	7/22* (32%)	7/29* (24%)	9/29* (31%)
Total	2/26 (8%)	6/22 (27%)	10/28* (36%)	17/22** (77%)	27/29** (93%)	25/29** (86%)
Forestomach:						
Squamous cell carcinoma	0/26†	0/22	0/28	0/22	6/29* (21%)	7/29** (24%)
Carcinoma in situ	0/26†	0/22	0/28	1/22 (5%)	4/29 (14%)	3/29 (10%)
Multiple papilloma	0/26	2/22 (9%)	4/28 (14%)	5/22* (23%)	2/29 (7%)	1/29 (3%)
Glandular stomach carcinoma	0/26	1/22 (5%)	0/28	0/22	0/29	0/29
Lung:						
Adenocarcinoma	0/26[d], †	3/22 (14%)	7/28* (23%)	10/22** (45%)	15/29** (52%)	2/29 (7%)
Multiple adenoma	1/26† (4%)	2/22 (9%)	1/28 (3%)	6/22* (27%)	10/29** (34%)	17/29** (59%)
Malignant lymphoma	1/26† (4%)	0/22	1/28 (3%)	0/22	0/29	5/29 (17%)
Thymoma	0/26†	0/22	0/28	0/22	4/29 (14%)	8/29** (28%)
Skin tumor:						
Squamous cell carcinoma	0/26†	0/22	0/28	0/22	0/29	5/29* (21%)
Spindle cell carcinoma	0/26	0/22	0/28	1/22 (5%)	1/29 (3%)	0/29
Sebaceous gland carcinoma	0/26	0/22	0/28	0/22	1/29 (3%)	0/29

Table B-8. Tumor Incidence in ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks[a]

Endpoint	Dose (HED) (mg/kg-d)[b]					
	0	**0.21 (0.028)**	**0.54 (0.072)**	**1.3 (0.18)**	**3.3 (0.44)**	**8.2 (1.1)**
Other tumors:						
Mammary adenocarcinoma	0/26	0/22	1/28 (3%)	0/22	0/29	1/29 (3%)
Ear canal squamous cell carcinoma	0/26	0/22	0/28	0/22	1/29 (3%)	0/29
Ovary glanulosa cell tumor	0/26	0/22	0/28	1/22 (5%)	0/29	0/29
Salivary gland adenocarcinoma	0/26	0/22	0/28	0/22	2/29 (7%)	0/29

[a]Fukuda et al. (1980); Fukuda et al. (1979).
[b]The nominal treatment doses of 0, 3.2, 8.4, 21, 51 and 130 mg/kg were converted to daily doses averaged over the study duration of 18 months; calculated HEDs appear in brackets.
[c]This number presumably represents number of animals available to develop tumors but was not defined in the study report.
[d]Test for trend only significant with top dose removed.
*Significantly different from control ($p < 0.05$) by two-tailed Fisher's exact test, as conducted for this review.
**Significantly different from control $p < 0.01$) by two-tailed Fisher's exact test, as conducted for this review.
†Significant trend ($p < 0.005$) by Cochran-Armitage χ^2 test, as conducted for this review.

HED = human equivalent dose.

Table B-9. Weekly Body Weights, Food Consumption, and Water Intake in Male and Female Albino Rats Exposed to *p*-α,α,α-Tetrachlorotoluene Vapor via Inhalation for 30 Days[a]

Endpoint	Exposure Concentration (HEC_{ER}) (mg/m^3)[b, c]			
	0	**3.98 (0.711)**	**18.9 (3.38)**	**94.5 (16.9)**
Male Body Weights (g)				
Week −1.0	161	159 (−1%)	159 (−1%)	159 (−1%)
Week 0.1	208	209 (+0.5%)	207 (−0.5%)	212 (+2%)
Week 1.0	264	264 (0%)	260 (−2%)	209 (−21%)
Week 2.0	312	313 (+0.3%)	307 (−2%)	196 (−37%)
Week 3.0	347	349 (+0.6%)	340 (−2%)	196 (−44%)
Week 4.0	375	377 (+0.5%)	364 (−3%)	196 (−48%)
Body-weight gain (Weeks 0.1–4)	167	168 (+1%)	158 (−6%)	−16** (−110%)
Male Cumulative Intakes (g/rat)				
Food consumption	746	766 (+3%)	737 (−1%)	411** (−45%)
Water consumption	930	966 (+4%)	943 (+1%)	700* (−25%)
Female Body Weights (g)				
Week −1.0	131	132 (+0.8%)	132 (+0.8%)	132 (+1%)
Week 0.1	160	159 (−0.6%)	158 (−1%)	160 (0%)
Week 1.0	183	184 (+0.5%)	184 (+0.5%)	156 (−15%)
Week 2.0	207	207 (0%)	208 (+0.5%)	161 (−22%)
Week 3.0	224	226 (+1%)	221 (−1%)	164 (−27%)
Week 4.0	238	234 (−2%)	236 (−0.8%)	154 (−35%)
Body-weight gain (Weeks 0.1–4)	78	75 (−4%)	78 (0%)	−6** (−108%)
Female Cumulative Intakes (g/rat)				
Food consumption	543	540 (−1%)	537 (−1%)	357** (−34%)
Water consumption	851	876 (+3%)	813 (−5%)	700* (−18%)

[a]Rose et al. (1984).
[b]Data are means (SD not reported); n = 10/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control using the method of least significant differences ($p < 0.05$), as reported by the study authors.
**Significantly different from control using the method of least significant differences ($p < 0.01$), as reported by the study authors.

ER = extrarespiratory; HEC = human equivalent concentration; SD = standard deviation.

Table B-10. Select Day 24 Group Mean Hematology, Serum Chemistry, and Urinalysis Results in Male and Female Albino Rats Exposed to *p*-α,α,α-Tetrachlorotoluene Vapor by Inhalation for 30 Days[a]

Endpoint	Exposure Concentration (HEC_{ER}) (mg/m^3)[b, c]			
	0	3.98 (0.711)	18.9 (3.38)	94.5 (16.9)
Male				
Hematology				
Packed cell volume (%)	45 ± 1.1	47 ± 2.4 (+4%)	47 ± 1.7 (+4%)	48 ± 2.3* (+7%)
Hb (g/dL)	15.2 ± 0.47	15.6 ± 0.49 (+3%)	16.5 ± 0.35** (+9%)	17.7 ± 0.69** (+16%)
Hct (%)	33.4 ± 0.83	33.0 ± 0.82 (0%)	35.5 ± 1.14** (+6%)	36.6 ± 0.91** (+10%)
RBC (10^6/µL)	7.3 ± 0.44	7.3 ± 0.75 (0%)	8.0 ± 0.28* (+10%)	9.0 ± 0.40** (+23%)
Total WBC (10^3/µL)	9.0 ± 1.77	10.5 ± 2.65 (+17%)	12.6 ± 0.78 (+40%)	5.5 ± 2.36* (−39%)
Lymphocytes (10^3/µL)	6.84 ± 1.12	8.66 ± 2.43 (+27%)	10.06 ± 1.32 (+47%)	3.53 ± 2.0* (−48%)
Total cells in bone marrow (10^3)	109 ± 23.1	183 ± 74.7 (+68%)	93 ± 26.1 (−15%)	55 ± 9.5* (−50%)
Serum chemistry				
Albumin (g/d)	3.7 ± 0.08	3.6 ± 0.15 (−3%)	3.5 ± 0.1* (−5%)	3.5 ± 0.09** (−5%)
A:G	1.36 ± 0.11	1.23 ± 0.14 (−10%)	1.09 ± 0.06** (−20%)	1.12 ± 0.09** (−18%)
ALT (mU/mL)	27 ± 10.9	19 ± 3.1 (−30%)	17 ± 4.3* (−37%)	17 ± 3.3* (−37%)
AST (mU/mL)	65 ± 25	53 ± 6.0 (−18%)	50 ± 7.4 (−23%)	41 ± 3.2** (−37%)
Creatinine (mg/dL)	0.8 ± 0.07	0.8 ± 0.04 (0%)	0.7 ± 0.05 (−13%)	0.6 ± 0.04** (−25%)
Calcium (mEq/L)	5.4 ± 0.18	5.6 ± 0.08 (+3%)	5.5 ± 0.16 (+2%)	5.2 ± 0.09* (−4%)
Female				
Hematology				
Packed cell volume (%)	45 ± 1.7	45 ± 1.4 (0%)	44 ± 0.8 (−2%)	45 ± 2.5 (0%)
Hb (g/dL)	15.7 ± 0.98	15.0 ± 0.16 (−4%)	14.7 ± 0.34 (−6%)	15.0 ± 0.76 (−4%)
RBC (10^6/µL)	7.6 ± 0.32	7.6 ± 0.22 (0%)	6.8 ± 0.25* (−11%)	7.0 ± 0.56* (−8%)
Hct (%)	34.5 ± 1.23	33.4 ± 1.06 (−3%)	33.6 ± 0.77 (−3%)	33.8 ± 1.52 (−2%)
Total WBC (10^3/µL)	7.7 ± 1.23	8.8 ± 1.7 (+14%)	7.2 ± 2.08 (0%)	3.0 ± 1.22* (−61%)

Table B-10. Select Day 24 Group Mean Hematology, Serum Chemistry, and Urinalysis Results in Male and Female Albino Rats Exposed to *p*-α,α,α-Tetrachlorotoluene Vapor by Inhalation for 30 Days[a]

Endpoint	Exposure Concentration (HEC_{ER}) (mg/m^3)[b, c]			
	0	**3.98 (0.711)**	**18.9 (3.38)**	**94.5 (16.9)**
Lymphocytes ($10^3/\mu L$)	6.84 ± 1.09	7.18 ± 1.57 (+5%)	5.94 ± 1.58 (−13%)	1.87 ± 0.58** (−73%)
Eosinophils ($10^3/\mu L$)	0.12 ± 0.106	0.08 ± 0.087 (−33%)	0.05 ± 0.074 (−58%)	0.00 ± 0.000* (−100%)
Total cells in bone marrow (10^3)	111 ± 38.8	81 ± 44.2 (−27%)	119 ± 50.7 (+7%)	34 ± 18.9** (−69%)
Serum chemistry				
Phosphorus (mEq/L)	4.2 ± 0.29	3.9 ± 0.19 (−7%)	3.8 ± 0.29 (−7%)	4.7 ± 0.21** (+12%)
Cholesterol (mg/dL)	64 ± 6.7	60 ± 8.7 (−6%)	66 ± 5.0 (+10%)	51 ± 4.7* (−20%)
Urinalysis				
Protein in urine (mg/dL)	28 ± 26.8	0.0 ± 0.0* (−100%)	0.0 ± 0.0* (−100%)	14 ± 19.5* (−50%)

[a]Rose et al. (1984).
[b]Data are mean ± SD; *n* = 10/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control using Williams' test ($p < 0.05$), as reported by the study authors.
**Significantly different from control using Williams' test ($p < 0.01$), as reported by the study authors.

A:G = albumin:globulin ratio; ALT = alanine transaminase; AST = aspartate aminotransferase; ER = extrarespiratory; Hb = hemoglobin; Hct = hematocrit; HEC = human equivalent concentration; RBC = red blood cell; SD = standard deviation; WBC = white blood cell.

Table B-11. Group Mean Absolute Organ Weights in Male and Female Albino Rats Exposed to *p*-α,α,α-Tetrachlorotoluene Vapor by Inhalation for 30 Days[a]

Endpoint	Organ Weights (g)			
	Exposure Concentration (HEC_{ER}) (mg/m^3)			
	0	3.98 (0.711)	18.9 (3.38)	94.5 (16.9)
Male[b, c]				
Brain, adjusted[d]	1.82	1.82 (0%)	1.85 (+2%)	1.90 (+4%)
Pituitary	0.014	0.012 (−12%)	0.013 (−7%)	0.010** (−29%)
Heart	1.1	1.2 (+9%)	1.1 (0%)	0.8** (−27%)
Lungs[e]	0.91	0.93 (+2%)	0.91 (0%)	0.88 (−3%)
Liver	16.7	16.2 (−3%)	15.7 (−6%)	9.7 (−42%)[f]
Liver, adjusted[d]	14.2	13.7 (−4%)	14.2 (0%)	17.4* (+23%)
Spleen	1.0	1.0 (0%)	0.9 (−10%)	0.4** (−60%)
Thymus	0.6	0.6 (0%)	0.5* (−17%)	0.1** (−83%)
Kidney, adjusted[d]	2.5	2.5 (0%)	2.6 (+4%)	2.9 (+16%)
Thyroid	0.024	0.024 (0%)	0.026 (+8%)	0.017** (−29%)
Adrenals	0.066	0.064 (−3%)	0.069 (+4%)	0.070 (+6%)
Gonads	4.1	4.2 (+2%)	4.2 (+2%)	1.5** (−63%)
Necropsy body weight	371	371 (0%)	355 (−4%)	190 (−49%)[f]
Female[b, c]				
Brain	1.70	1.75 (+3%)	1.71 (+1%)	1.61* (−5%)
Pituitary, adjusted[d]	0.013	0.012 (−8%)	0.012 (−8%)	0.016 (+29%)
Heart	0.9	0.9 (0%)	1.0 (+11%)	0.7 (−23%)
Lungs	1.2	1.1 (−8%)	1.2 (0%)	1.2 (0%)
Lungs, adjusted[d, e]	0.71	0.69 (−3%)	0.71 (0%)	0.99** (+39%)
Liver	10.1	9.6 (−4%)	9.9 (−2%)	7.0 (−31%)[f]
Liver, adjusted[d]	8.7	8.3 (−5%)	8.5 (−2%)	11.0* (+26%)
Spleen, adjusted[d, e]	0.5	0.5 (0%)	0.4 (−20%)	0.4 (−20%)
Thymus, adjusted[d, e]	0.3	0.3 (0%)	0.3 (0%)	0.3 (0%)
Uterus	0.5	0.6 (+20%)	0.6 (+20%)	0.2** (−60%)
Kidney, adjusted[d]	1.6	1.7 (+6%)	1.7 (+6%)	1.9 (+19%)
Thyroid	0.021	0.017 (−19%)	0.022 (+5%)	0.017 (−19%)

Table B-11. Group Mean Absolute Organ Weights in Male and Female Albino Rats Exposed to *p*-α,α,α-Tetrachlorotoluene Vapor by Inhalation for 30 Days[a]

Endpoint	Organ Weights (g)			
	Exposure Concentration (HEC_{ER}) (mg/m^3)			
	0	**3.98 (0.711)**	**18.9 (3.38)**	**94.5 (16.9)**
Adrenals	0.088	0.088 (0%)	0.082 (−7%)	0.092 (+5%)
Gonads	102	100 (−2%)	96 (−6%)	84 (−18%)
Necropsy body weight	235	233 (−1%)	234 (−0.4%)	139 (−41%)[f]

[a]Rose et al. (1984).
[b]Data are means (SD not reported); n = 10/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Organ weights were "adjusted for final body weights where appropriate," as reported by the study authors (no further details were provided).
[e]Data were log-transformed for statistical analysis, as reported by the study authors.
[f]Statistical analysis was not provided by study authors, and insufficient data were provided to perform statistical analysis for this review.
*Significantly different from control using Williams' test ($p < 0.05$), as reported by the study authors.
**Significantly different from control using Williams' test ($p < 0.01$), as reported by the study authors.

ER = extrarespiratory; HEC = human equivalent concentration; SD = standard deviation.

Table B-12. Incidence of Macroscopic Observations in Male and Female Albino Rats Exposed to *p*-α,α,α-Tetrachlorotoluene Vapor by Inhalation for 30 Days[a]

Endpoint	Exposure Concentration (HEC_{ER}) (mg/m^3)			
	0	3.98 (0.711)	18.9 (3.38)	94.5 (16.9)
Male[b]				
Thymus:				
Small	0/10	0/10	0/10	8/9** (89%)
Congested	0/10	0/10	0/10	1/9 (11%)
Adipose tissue:				
Minimal	0/10	0/10	0/10	7/9** (78%)
Testes:				
Small	0/10	0/10	0/10	9/9† (100%)
Skin:				
Alopecia	0/10	0/10	0/10	4/9* (44%)
Fur:				
Stained	0/10	0/10	1/10 (10%)	1/9 (11%)
Badly groomed	0/10	0/10	0/10	4/9* (44%)
Female[b]				
Thymus:				
Small	0/10	0/10	0/10	10/10† (100%)
Congested	0/10	0/10	0/10	0/10
Adipose tissue:				
Minimal	0/10	0/10	0/10	9/10** (90%)
Skin:				
Alopecia	0/10	0/10	0/10	3/10 (30%)
Fur:				
Stained	0/10	0/10	0/10	4/10 (40%)
Badly groomed	0/10	0/10	0/10	0/10

[a]Rose et al. (1984).
[b]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
*Significantly different from control by Fisher's exact test (two-tailed $p < 0.05$) conducted for this review.
**Significantly different from control by Fisher's exact test (two-tailed $p < 0.01$) conducted for this review.
†Significantly different from control by Fisher's exact test (two-tailed $p < 0.001$) conducted for this review.

ER = extrarespiratory; HEC = human equivalent concentration.

Table B-13. Incidence of Selected Non-neoplastic Lesions in Extrarespiratory Tissues in Albino Rats Exposed to *p*-α,α,α-Tetrachlorotoluene Vapor by Inhalation for 30 Days[a]

Endpoint	Exposure Concentration (HEC_{ER}) (mg/m^3)[b]			
	0	3.98 (0.711)	18.9 (3.38)	94.5 (16.9)
Male				
Spleen:				
Decreased cellularity of white pulp	0/5	NA	NA	4/6* (67%)
Decreased cellularity of red pulp	0/5	NA	NA	5/6* (83%)
Thymus:				
Marked involution	0/5	NA	NA	4/6* (67%)
Severe involution	0/5	NA	NA	1/6 (17%)
Testes:				
Marked tubular atrophy	0/5	NA	NA	4/6* (67%)
Severe tubular atrophy	0/5	NA	NA	1/6 (17%)
Arrest of spermatogenesis	0/5	NA	NA	1/6 (17%)
Female[c]				
Spleen:				
Decreased cellularity of white pulp	0/5	NA	NA	3/5 (60%)
Decreased cellularity of red pulp	0/5	NA	NA	5/5* (100%)
Thymus:				
Moderate involution	0/5	NA	NA	2/5 (20%)
Marked involution	0/5	NA	NA	2/5 (20%)
Severe involution	0/5	NA	NA	0/5
Uterus:				
Reduction in endometrial width	0/5	NA	NA	4/5* (80%)

[a]Rose et al. (1984).
[b]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
[c]One female rat in the high-dose group was found dead immediately prior to postmortem examination; tissues from this animal were not examined microscopically.
*Significantly different from control by Fisher's exact test (one-sided $p < 0.05$), as conducted for this review.

ER = extrarespiratory; HEC = human equivalent concentration; NA = not applicable.

Table B-14. Incidence of Selected Non-neoplastic Lesions in the Upper Respiratory Tract in Albino Rats Exposed to *p*-α,α,α-Tetrachlorotoluene Vapor by Inhalation for 30 Days[a]

Endpoint	Exposure Concentration (HEC_{ET}) (mg/m^3)[b]			
	0	3.98 (0.142 [M], 0.107 [F])	18.9 (0.675 [M], 0.506 [F])	94.5 (2.53 [M], 2.03 [F])
Male[c]				
Nasal passages:				
Focal atrophy of olfactory epithelium	0/5	1/5 (20%)	3/5 (60%)	0/6
Severe atrophy of olfactory epithelium	0/5	0/5	1/5 (20%)	6/6* (100%)
Extensive squamous keratinizing epithelial metaplasia	0/5	0/5	0/5	4/6* (67%)
Inflammatory exudate in chamber	0/5	0/5	0/5	6/6* (100%)
Larynx:				
Epithelial hyperplasia in ventrolateral region	0/5	0/5	4/5* (80%)	0/6
Squamous keratinizing epithelial metaplasia in:				
Ventrolateral region	0/5	0/5	0/5	6/6* (100%)
Tracheo-larangeal junction	0/5	0/5	0/5	5/6* (83%)
Keratinizing epithelial hyperplasia over arytenoid projections	0/5	0/5	0/5	6/6* (100%)
Pharynx:				
Squamous keratinizing epithelial metaplasia	0/5	NA	NA	2/6 (33%)
Female[c, d]				
Nasal passages:				
Focal atrophy of olfactory epithelium	0/5	0/5	5/5* (100%)	0/5
Severe atrophy of olfactory epithelium	0/5	0/5	0/5	5/5* (100%)
Extensive squamous keratinizing epithelial metaplasia	0/5	0/5	0/5	5/5* (100%)
Inflammatory exudate in chambers	0/5	0/5	0/5	5/5* (100%)
Larynx:				
Epithelial hyperplasia in ventrolateral region	0/5	0/5	1/5 (20%)	0/5
Squamous keratinizing epithelial metaplasia in:				
Ventrolateral region	0/5	0/5	0/5	5/5* (100%)
Tracheo-larangeal junction	0/5	0/5	0/5	4/5* (80%)
Keratinizing epithelial hyperplasia over arytenoid projections	0/5	1/5 (20%)	2/5 (40%)	5/5* (100%)

Table B-14. Incidence of Selected Non-neoplastic Lesions in the Upper Respiratory Tract in Albino Rats Exposed to *p*-α,α,α-Tetrachlorotoluene Vapor by Inhalation for 30 Days[a]

Endpoint	Exposure Concentration (HEC_{ET}) (mg/m^3)[b]			
	0	**3.98 (0.142 [M], 0.107 [F])**	**18.9 (0.675 [M], 0.506 [F])**	**94.5 (2.53 [M], 2.03 [F])**
Pharynx:				
Squamous keratinizing epithelial metaplasia	0/5	NA	NA	3/5 (60%)

[a]Rose et al. (1984).
[b]HEC_{ET} values calculated using TWA body weights for each dose group in the study.
[c]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
[d]One female rat in the high-dose group was found dead immediately prior to postmortem examination; tissues from this animal were not examined microscopically.
*Significantly different from control by Fisher's exact test (one-sided $p < 0.05$), as conducted for this review.

ET = extrathoracic; F = female(s); HEC = human equivalent concentration; M = male(s); NA = not applicable; TWA = time-weighted average.

Table B-15. Incidence of Selected Non-neoplastic Lesions in the Lower Respiratory Tract in Albino Rats Exposed to *p*-α,α,α-Tetrachlorotoluene Vapor by Inhalation for 30 Days[a]

Male				
	Exposure Concentration (HEC_{TB}) (mg/m^3)[b, c]			
Endpoint	**0**	**3.98 (1.49)**	**18.9 (6.75)**	**94.5 (23.6)**
Trachea:				
Minimal epithelial hyperplasia	0/5	0/5	4/5* (80%)	0/6
Moderate epithelial hyperplasia	0/5	0/5	1/5 (20%)	1/6 (17%)
Extensive epithelial hyperplasia	0/5	0/5	0/5	1/6 (17%)
Regeneration of tracheal epithelium	0/5	0/5	0/5	2/6 (33%)
Severe epithelial ulceration	0/5	0/5	0/5	3/6 (50%)
Tracheal carina:				
Severe epithelial ulceration	0/5	NA	NA	6/6* (100%)
Marked inflammatory cell exudate and mucus in lumen	0/5	NA	NA	1/6 (17%)
Bronchioles:				
Severe ulceration of bronchiolar epithelium	0/5	NA	NA	6/6* (100%)
Focal regeneration of bronchiolar epithelium	0/5	NA	NA	6/6* (100%)
Female[d]				
	Exposure Concentration (HEC_{TB}) (mg/m^3)[b, c]			
Endpoint	**0**	**3.98 (0.995)**	**18.9 (4.73)**	**94.5 (20.3)**
Trachea:				
Minimal epithelial hyperplasia	0/5	0/5	2/5 (40%)	0/5
Moderate epithelial hyperplasia	0/5	0/5	1/5 (20%)	1/5 (20%)
Extensive epithelial hyperplasia	0/5	0/5	0/5	0/5
Regeneration of tracheal epithelium	0/5	0/5	0/5	2/5 (40%)
Severe epithelial ulceration	0/5	0/5	0/5	2/5 (20%)

Table B-15. Incidence of Selected Non-neoplastic Lesions in the Lower Respiratory Tract in Albino Rats Exposed to *p*-α,α,α-Tetrachlorotoluene Vapor by Inhalation for 30 Days[a]

Tracheal carina:				
Severe epithelial ulceration	0/5	NA	NA	5/5* (100%)
Inflammatory cell exudate in lumen	0/5	NA	NA	4/5* (80%)
Bronchioles:				
Severe ulceration of bronchiolar epithelium	0/5	NA	NA	5/5* (100%)
Focal regeneration of bronchiolar epithelium	0/5	NA	NA	4/5* (80%)

[a]Rose et al. (1984).
[b]HEC_{TB} values calculated using TWA body weights for each dose group in the study.
[c]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
[d]One female rat in the high-dose group was found dead immediately prior to postmortem examination; tissues from this animal were not examined microscopically.
*Significantly different from control by Fisher's exact test (one-sided $p < 0.05$), as conducted for this review.

F = female(s); HEC = human equivalent concentration; M = male(s); NA = not applicable; TB = tracheobronchial; TWA = time-weighted average.

Table B-16. Group Mean Body Weights and Mean Body-Weight Changes in Pregnant Female Rats Exposed by Inhalation to *p*-α,α,α-Tetrachlorotoluene Vapor on GDs 6–19[a]

Time point	Exposure Concentration (HEC_{ER}) (mg/m^3)[b, c]			
	0 (*n* = 19)	**4.1 (1.0) (*n* = 19)**	**10.4 (2.60) (*n* = 21)**	**25.2 (6.30) (*n* = 22)**
GD	**Body Weight (g)**			
6	236.1 ± 17.4	238.0 ± 13.1 (+1%)	236.6 ± 16.1 (−1%)	235.2 ± 13.1 (−1%)
10	258.9 ± 18.7	259.0 ± 14.7 (0%)	257.9 ± 17.4 (0%)	250.0 ± 14.7 (−3%)
14	284.7 ± 19.7	285.6 ± 16.1 (0%)	284.8 ± 19.7 (0%)	269.9 ± 15.1* (−5%)
17	314.2 ± 21.0	316.5 ± 18.7 (+1%)	314.7 ± 22.0 (−1%)	290.9 ± 17.5** (−8%)
20	354.3 ± 24.2	356.3 ± 22.1 (+1%)	353.1 ± 27.1 (−1%)	321.2 ± 20.5** (−9%)
GD	**Body-Weight Change (g)**			
6−10	22.9 ± 4.7	21 ± 4.4 (−8%)	21.3 ± 4.4 (−7%)	14.8 ± 5.6** (−35%)
6−14	48.7 ± 6.2	47.6 ± 6.1 (−2%)	48.1 ± 6.6 (−1%)	34.7 ± 7.5** (−29%)
6−17	78.2 ± 8.3	78.5 ± 9.3 (0%)	78.0 ± 8.7 (0%)	55.6 ± 11.9** (−29%)
6−20	118.3 ± 11.3	118.3 ± 12.9 (0%)	116.5 ± 15.1 (−2%)	86.0 ± 17.4** (−27%)

[a]Edwards et al. (1985).
[b]Data are mean ± SD (SD calculated for this review from individual body-weight data).
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control ($p < 0.01$) by unpaired Student's *t*-test (two-tailed), as conducted for this review.
**Significantly different from control ($p < 0.001$) by unpaired Student's *t*-test (two-tailed), as conducted for this review.

ER = extrarespiratory; GD = gestation day; HEC = human equivalent concentration; SD = standard deviation.

Table B-17. Group Mean Litter Data from Pregnant Female Rats Exposed by Inhalation to *p*-α,α,α-Tetrachlorotoluene Vapor on GDs 6–19[a]

Endpoint	Exposure Concentration (HEC_{ER}) (mg/m^3)[b, c]			
	0	**4.1 (1.0)**	**10.4 (2.60)**	**25.2 (6.30)**
Number of animals with live young	19	19	21	22
Corpora lutea	14.8	14.2 (−4%)	13.9 (−6%)	13.8 (−7%)
Implants	12.5	13.0 (+4%)	12.7 (+2%)	11.6 (−7%)
Live young	11.5	12.1 (+5%)	12.0 (+4%)	11.2 (−3%)
Embryonic deaths: Early Late Total	 1.0 0.0 1.0†	 0.8 (−20%) 0.2 0.9 (−10%)	 0.6 (−40%) 0.0 0.6 (−40%)	 0.4 (−60%) 0.0 0.4* (−60%)
Preimplant loss (%)[d]	13.1	7.8 (−40%)	10.0 (−24%)	16.2 (+24%)
Postimplant loss (%)[e]	7.8†	7.0 (−10%)	4.7 (−40%)	3.3* (−58%)
Litter weight (g)	37.94	39.43 (+4%)	38.44 (+1%)	34.24 (−10%)
Mean fetal weight (g)	3.30††‡	3.27 (−1%)	3.21 (−3%)	3.05** (−8%)

[a]Edwards et al. (1985).
[b]Data are means of litter values (SD not reported).
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]([Number of corpora lutea – number of implantations] ÷ [number of corpora lutea]) × 100.
[e]([Number of implantations – number of live young] ÷ [number of implantations]) × 100.
*Intergroup differences from control statistically significant in the absence of significant "H" statistic ($p < 0.05$), as reported by the study authors.
**Statistically significant intergroup differences from control using the Kruskal-Wallis test ($p < 0.01$), as reported by the study authors.
†Significant trend using Jonckheere "J" statistic ($p < 0.05$), as reported by the study authors.
††Significant trend using Jonckheere "J" statistic ($p < 0.01$), as reported by the study authors.
‡Significant difference among groups using the Kruskal-Wallis "H" statistic ($p < 0.01$), as reported by the study authors.

ER = extrarespiratory; GD = gestation day; HEC = human equivalent concentration; SD = standard deviation.

Table B-18. Incidence of Skeletal Variants in Fetuses from Female Rats Exposed by Inhalation to *p*-α,α,α-Tetrachlorotoluene Vapor on GDs 6–19[a]

Endpoint	Exposure Concentration (HEC_{ER}) (mg/m^3)			
	0	**4.1 (1.0)**	**10.4 (2.60)**	**25.2 (6.30)**
Number of fetuses examined	107	111	123	121
Sternebrae				
Normal	29†‡ (27.1%)	13 (12.2%)	17 (13.7%)	4* (3.1%)
Unossified	55†‡ (51.8%)	74 (67%)	80 (65.6%)	105** (84.6%)
Reduced	42 (38.4%)	57 (51.1%)	56 (43.4%)	50 (44.1%)
Total variant	78†‡ (72.9%)	98 (87.8%)	106 (86.3%)	117** (96.9%)

[a]Edwards et al. (1985).
*Statistically significant intergroup differences from control using the Kruskal-Wallis test ($p < 0.01$), as reported by the study authors using the litter as the basic sampling unit.
**Statistically significant intergroup differences from control using the Kruskal-Wallis test ($p < 0.001$), as reported by the study authors using the litter as the basic sampling unit.
†Significant trend using Jonckheere "J" statistic ($p < 0.001$), as reported by the study authors using the litter as the basic sampling unit.
‡Significant difference among groups using the Kruskal-Wallis "H" statistic ($p < 0.01$), as reported by the study authors using the litter as the basic sampling unit.

ER = extrarespiratory; GD = gestation day; HEC = human equivalent concentration.

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

MODELING PROCEDURE

Dichotomous Noncancer Data

The benchmark dose (BMD) modeling of dichotomous data is conducted with the U.S. EPA's Benchmark Dose Software (BMDS, Version 2.6 was used for this document). For these data, the Gamma, Logistic, Log-Logistic, Log-Probit, Multistage, Probit, and Weibull dichotomous models available within the software are fit using a benchmark response (BMR) of 10% extra risk. Alternative BMRs may also be used where appropriate, as outlined in the *Benchmark Dose Technical Guidance* (U.S. EPA, 2012b). In general, the BMR should be near the low end of the observable range of increased risk in the study. BMRs that are too low can result in widely disparate benchmark dose lower confidence limit (BMDL) estimates from different models (high model-dependence). Adequacy of model fit is judged based on the χ^2 goodness-of-fit *p*-value ($p > 0.1$), magnitude of scaled residuals (absolute value < 2.0), and visual inspection of the model fit. Among all models providing adequate fit, the BMDL from the model with the lowest Akaike's information criterion (AIC) is selected as a potential point of departure (POD), if the BMDLs are sufficiently close (less than approximately threefold); if the BMDLs are not sufficiently close (greater than approximately threefold), model dependence is indicated, and the model with the lowest reliable BMDL is selected.

Nested Dichotomous Data

The BMD modeling of nested dichotomous data from a developmental toxicity study is conducted using the NLogistic model within the BMDS (Version 2.6). This model requires the individual animal data showing the number of offspring experiencing the effect in question per exposed dam in each dose group. Modeling of developmental endpoints uses a BMR of 5% extra risk (U.S. EPA, 2018b). The model is run with and without an exposure-independent litter-specific covariate (the theta [θ] coefficients in the models), meant to account for intralitter similarity due to the condition of the dam prior to treatment (U.S. EPA, 2018b). The model is also run with and without intralitter correlations (the phi [Φ] coefficients in the models), meant to account for similarity of responses to treatment among pups in the same litter (U.S. EPA, 2018b). The adequacy of model fit is judged based on the χ^2 goodness-of-fit *p*-value ($p > 0.1$), magnitude of scaled residuals (absolute value < 2.0), and visual inspection of the model fit. A decision to include the litter-specific covariate and/or intralitter correlation in the final model is based on whether the θ or Φ coefficients are estimated by BMDS to be nonzero, and if the model fit is improved (e.g., per AIC or scaled residual comparison) when the litter-specific covariate and/or intralitter correlation are included.

Cancer Data

The model-fitting procedure for dichotomous cancer incidence is as follows. The Multistage cancer model in the U.S. EPA's BMDS (Version 2.6) is fit to the incidence data using the extra risk option. The Multistage cancer model is run for all polynomial degrees up to $n - 1$ (where n is the number of dose groups including control). An adequate model fit is judged by three criteria: (1) goodness-of-fit *p*-value ($p < 0.1$), (2) visual inspection of the dose-response curve, and (3) scaled residual at the data point (except the control) closest to the predefined BMR (absolute value < 2.0). Among all the models providing adequate fit to the data, the BMDL for the model with the lowest AIC is selected as the POD. In accordance with U.S. EPA (2012b) and U.S. EPA (2005) guidance, BMD and BMDL values associated with an extra risk of 10%

are calculated, which should be within the observable range of increased risk in a cancer bioassay. The best fitting model (i.e., the polydegrees) is identified based on the process used for noncancer data mentioned above. Modeling is performed for each individual tumor type with at least a statistically significant trend. Where applicable, the MS_Combo model is used to evaluate the combined cancer risk of multiple tumor types. MS_Combo is run using the incidence data for the individual tumor types and the polydegrees from the best fitting model identified in the model runs for the individual tumor types.

Continuous Data

BMD modeling of continuous data is conducted with U.S. EPA's BMDS (Version 2.6) as well. All continuous models available within the software (Exponential, Hill, Linear, Polynomial, and Power models) are fit using a standard reporting BMR of 1 standard deviation (SD) relative risk. Alternate BMRs may also be used (e.g., BMR = 10% relative deviation [RD] for body weight based on a biologically significant weight loss of 10%), as outlined in the *Benchmark Dose Technical Guidance* (U.S. EPA, 2012b). In general, the BMR should be near the low end of the observable range of increased risk in the study. BMRs that are too low can result in widely disparate BMDL estimates from different models (high model dependence). An adequate fit is judged based on the χ^2 goodness-of-fit *p*-value ($p > 0.1$), magnitude of the scaled residuals near the BMR (absolute value < 2.0), and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination is made as to whether the variance across dose groups is homogeneous. If a homogeneous variance model is deemed appropriate based on the statistical test provided by BMDS (i.e., Test 2), the final BMD results are estimated from a homogeneous variance model. If the test for homogeneity of variance is rejected (*p*-value < 0.1), the model is run again while modeling the variance as a power function of the mean to account for this nonhomogeneous variance. If this nonhomogeneous variance model does not adequately fit the data (i.e., Test 3; *p*-value < 0.1), the data set is considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest BMDL is selected if the BMDL estimates from different models vary more than approximately threefold (indicating model dependence); otherwise, the BMDL from the model with the lowest AIC is selected as a potential POD from which to derive the reference value.

Dropping the High Dose

In the absence of a mechanistic understanding of the biological response to a toxic agent, data from exposures much higher than the study lowest-observed-adverse-effect level (LOAEL) do not provide reliable information regarding the shape of the response at low doses. Such exposures, however, can have a strong effect on the shape of the fitted model in the low-dose region of the dose-response curve. Thus, if lack of fit is due to characteristics of the dose-response data for high doses, then the *Benchmark Dose Technical Guidance* document allows for data to be adjusted by eliminating the high-dose group (U.S. EPA, 2012b). Because the focus of BMD analysis is on the low-dose regions of the response curve, elimination of the high-dose group may be reasonable for certain data sets.

BMD Modeling to Identify Potential PODs for Derivation of a Provisional Reference Dose

The most sensitive endpoints showing treatment-related changes in the principal study of rats administered *p*-α,α,α-tetrachlorotoluene by gavage daily for 90 days (Liao, 1989a, c) were reduced male body weights and absolute and relative testis weights, increased incidences of testicular tubular atrophy and aspermatogenesis, and decreased lymphocyte counts in both males

and females (see Tables B-4 to B-7 in Appendix B). Data sets for these endpoints were selected to determine potential PODs for the provisional reference dose (p-RfD) using BMD analysis. Data for these endpoints were fit to all available models for continuous or dichotomous data, as appropriate. Summaries of modeling approaches and results (see Tables C-1 to C-7) are described below.

Decreased Terminal Body Weight in Male Sprague-Dawley (S-D) Rats Exposed Daily to p-α,α,α-Tetrachlorotoluene by Gavage for 90 Days (Liao, 1989a, c)

The procedure outlined above for continuous data was applied to the data for decreased body weight in male rats exposed daily to *p*-α,α,α-tetrachlorotoluene by gavage for 90 days (Liao, 1989a, c). The constant variance model provided an adequate fit (*p*-value > 0.1) to the variance data, and with that model applied, all the tested models provided adequate fit to the means (see Table C-1). BMDLs for these models differed by more than approximately threefold, so the model with the lowest BMDL was selected (Exponential Model 5). Figure C-1 shows the fit of the Exponential Model 5 to the data. Based on human equivalent doses (HEDs), the BMD_{10} and $BMDL_{10}$ were 3.11 and 0.351 mg/kg-day, respectively.

Table C-1. BMD Modeling Results for Decreased Terminal Body Weight in Male S-D Rats Exposed to *p*-α,α,α-Tetrachlorotoluene by Gavage for 90 Days[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{10} (HED) (mg/kg-d)	$BMDL_{10}$ (HED) (mg/kg-d)
BMR = 10% RD change from control						
Exponential (Model 2)[c]	0.21	0.64	−0.59	350.75	4.31	3.13
Exponential (Model 3)[c]	0.21	0.64	−0.59	350.75	4.31	3.13
Exponential (Model 4)[c]	0.21	0.65	0.12	352.05	3.11	0.549
Exponential (Model 5)[c, d]	**0.21**	**0.65**	**0.12**	**352.05**	**3.11**	**0.351**
Hill[c]	0.21	0.69	0.16	352.01	2.95	NDr
Linear[e]	0.21	0.59	−0.68	350.91	4.45	3.32
Polynomial (2-degree)[e]	0.21	0.59	−0.68	350.91	4.45	3.32
Polynomial (3-degree)[e]	0.21	0.59	−0.68	350.91	4.45	3.32
Power[c]	0.21	0.59	−0.68	350.91	4.45	3.32

[a]Liao (1989a, 1989c).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to ≥1.
[d]Selected model.
[e]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = benchmark dose (i.e., maximum likelihood estimates of the dose associated with the selected BMR); BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; HED = human equivalent dose; NDr = not determined; RD = relative deviation; S-D = Sprague-Dawley.

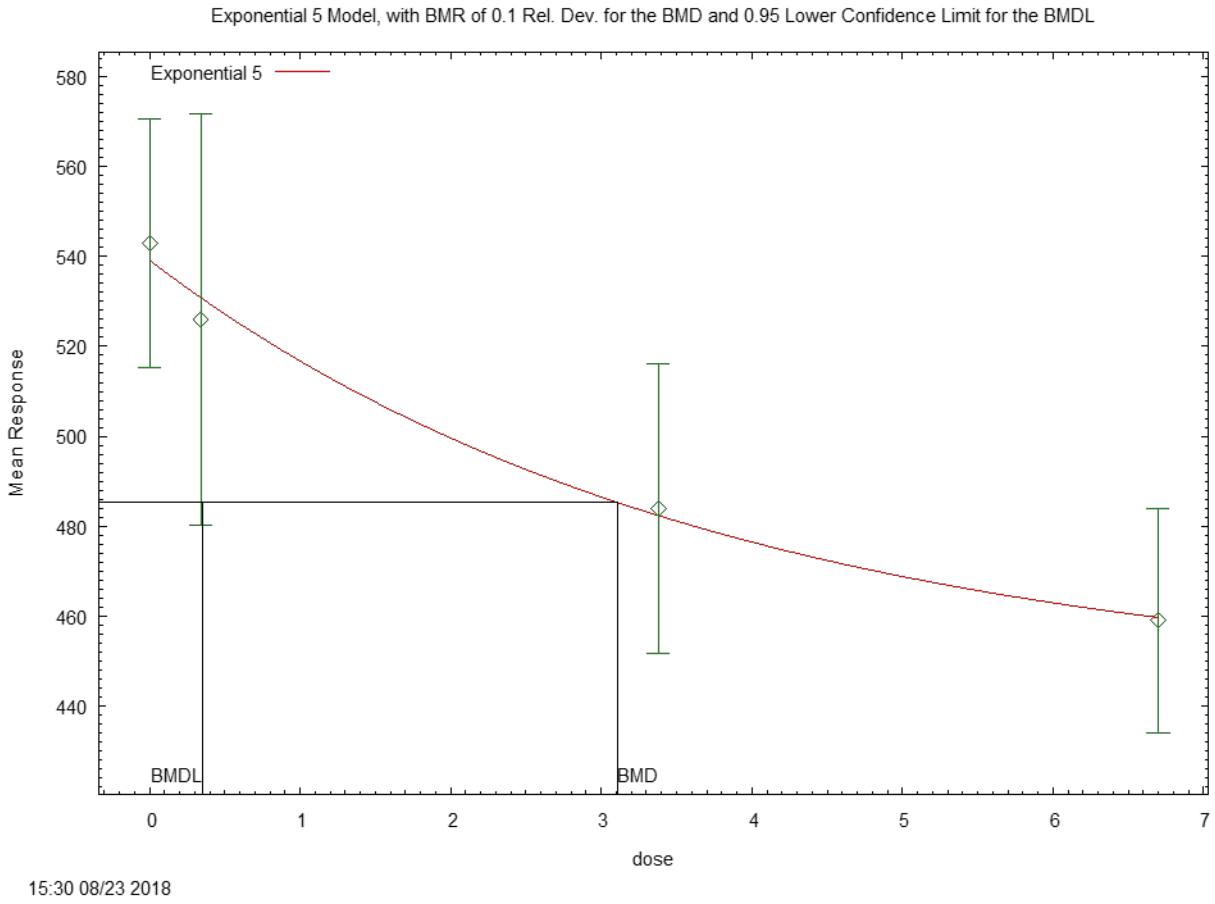


Figure C-1. Fit of Exponential (Model 5) to Data for Decreased Terminal Body Weight in Male S-D Rats Exposed Daily to *p*-α,α,α-Tetrachlorotoluene by Gavage for 90 Days (Liao, 1989a, c) (BMR = 10% RD)

BMD Model Output for Figure C-1:

```
================================================================
        Exponential Model. (Version: 1.11;  Date: 03/14/2017)
        Input Data File: E:/exp_bodyweight_Exp-ConstantVariance-BMR10-Down.(d)
        Gnuplot Plotting File:
                                          Thu Aug 23 15:30:31 2018
 ================================================================

 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]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 500
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 5
               --------          --------
                 lnalpha           7.59612
                     rho                 0 Specified
                       a            570.15
                       b          0.279342
                       c          0.766716
                       d                 1



                  Parameter Estimates

                Variable          Model 5          Std. Err.
                --------          -------          ---------
                 lnalpha           7.60126           447.373
                       a           539.164           11.4226
                       b          0.268311          0.343703
                       c           0.82328         0.0973331
                       d                 1              NA


        Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0     10          543          38.8
  0.342     10          526            64
   3.38     10          484          45.1
    6.7     10          459          34.8


              Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         539.2        44.73           0.2712
  0.342         530.8        44.73          -0.3401
   3.38         482.4        44.73           0.1163
    6.7         459.7        44.73         -0.04734
```

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	-171.9224	5	353.8448
A2	-169.6508	8	355.3016
A3	-171.9224	5	353.8448
R	-180.7635	2	365.5271
5	-172.0252	4	352.0503

Additive constant for all log-likelihoods = -36.76. 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 7a: Does Model 5 fit the data? (A3 vs 5)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	22.23	6	0.001102
Test 2	4.543	3	0.2085
Test 3	4.543	3	0.2085
Test 7a	0.2055	1	0.6503

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 7a is greater than .1. Model 5 seems to adequately describe the data.

```
Benchmark Dose Computations:

  Specified Effect = 0.100000

         Risk Type = Relative deviation

  Confidence Level = 0.950000

               BMD =      3.10984

              BMDL =     0.351213

              BMDU =        67000
```

Decreased Absolute Testis Weight in Male S-D Rats Exposed Daily to *p*-α,α,α-Tetrachlorotoluene by Gavage for 90 Days (Liao, 1989a, c)

The procedure outlined above for continuous data was applied to the data for decreased absolute testis weight in male rats exposed daily to *p*-α,α,α-tetrachlorotoluene by gavage for 90 days (Liao, 1989a, c). The data were not amenable to BMD modeling because neither the constant nor nonconstant variance model provided adequate fit to the variance data (see Table C-2). In an attempt to obtain an adequate fit, the highest dose was dropped because there was a significant difference at the mid dose. After dropping the highest dose, the variance data still were not adequately fit by either the constant or nonconstant variance models. No model was selected. The linear model is shown in Table C-2 to demonstrate the lack of fit to the variance data.

Table C-2. BMD Modeling Results for Decreased Absolute Testis Weight in Male S-D Rats Exposed to *p*-α,α,α-Tetrachlorotoluene by Gavage for 90 Days[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{1SD} (HED) (mg/kg-d)	$BMDL_{1SD}$ (HED) (mg/kg-d)
All Doses						
Constant variance						
Linear[c]	<0.0001	0.15	1.39	7.38	1.72	1.37
Nonconstant variance						
Linear[c]	<0.0001	0.24	−1.06	1.47	2.66	1.87
Highest Dose Dropped						
Constant variance						
Linear[c]	0.04	0.13	1.1	14.68	1.67	1.20
Nonconstant variance						
Linear[c]	0.05	0.13	1.33	14.24	1.42	0.94

[a]Liao (1989a, 1989c).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = benchmark dose (i.e., maximum likelihood estimates of the dose associated with the selected BMR); BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; HED = human equivalent dose; S-D = Sprague-Dawley; SD = standard deviation.

Decreased Relative Testis Weight in Male S-D Rats Exposed Daily to *p*-α,α,α-Tetrachlorotoluene by Gavage for 90 Days (Liao, 1989a, c)

The procedure outlined above for continuous data was applied to the data for decreased relative testis weight in male rats exposed daily to *p*-α,α,α-tetrachlorotoluene by gavage for 90 days (Liao, 1989a, c). The data were not amenable to BMD modeling because neither the constant nor nonconstant variance model provided adequate fit to the variance data (see Table C-3). In an attempt to obtain an adequate fit, the highest dose was dropped because there was a significant difference at the mid dose. After dropping the highest dose, the variance data were still not adequately fit by either the constant or nonconstant variance models. No model was selected. The linear model is shown in Table C-3 to demonstrate the lack of fit to the variance data.

Table C-3. BMD Modeling Results for Decreased Relative Testis Weight in Male S-D Rats Exposed to *p*-α,α,α-Tetrachlorotoluene by Gavage for 90 Days[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{1SD} (HED) (mg/kg-d)	$BMDL_{1SD}$ (HED) (mg/kg-d)
All Doses (*n* = 10)						
Constant Variance						
Linear[c]	0.0001	0.12	−0.467	−109.93	2.21	1.72
Nonconstant Variance						
Linear[c]	0.0008	0.11	−0.543	−114.19	3.00	2.17
Highest Dose Dropped						
Constant Variance						
Linear[c]	0.03	0.08	−0.129	−73.20	2.31	1.53
Nonconstant Variance						
Linear[c]	0.02	0.10	−0.214	−72.68	2.07	1.26

[a]Liao (1989a, 1989c).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = benchmark dose (i.e., maximum likelihood estimates of the dose associated with the selected BMR); BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; HED = human equivalent dose; S-D = Sprague-Dawley; SD = standard deviation.

Increased Testicular Tubular Atrophy and Aspermatogenesis in Male S-D Rats Exposed Daily to *p*-α,α,α-Tetrachlorotoluene by Gavage for 90 Days (Liao, 1989a, c)

Liao (1989a) and Liao (1989c) presented testicular tubular atrophy both as total incidences observed and as incidence by severity (mild, moderate, or marked). The incidence data for both "total" and "marked" tubular atrophy and aspermatogenesis exhibited a positive dose-related trend, and therefore, both data sets were separately fit to all available models in the BMDS (Version 2.6) using the procedure outlined above for dichotomous data.

Total Incidence of Tubular Atrophy and Aspermatogenesis in Male S-D Rats Exposed Daily to *p*-α,α,α-Tetrachlorotoluene via Gavage for 90 Days (Liao, 1989a, c)

For "total" incidence of tubular atrophy and aspermatogenesis in the testes, all models provided an adequate fit (*p*-value > 0.1; see Table C-4). BMDLs for models providing adequate fit were not sufficiently close (differed by more than approximately threefold), so the model with the lowest BMDL (1-degree Multistage) was selected. Fit of the 1-degree Multistage model to the data is shown in Figure C-2. Based on HEDs, the estimated BMD_{10} and $BMDL_{10}$ for total incidence of testicular tubular atrophy and aspermatogenesis were 0.267 and 0.167 mg/kg-day, respectively.

Table C-4. BMD Modeling Results for Increased Total Incidence of Tubular Atrophy and Aspermatogenesis in Testes of Male S-D Rats Exposed Daily to *p*-α,α,α-Tetrachlorotoluene by Gavage for 90 Days[a]

Model	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{10} (HED) (mg/kg-d)	$BMDL_{10}$ (HED) (mg/kg-d)
Gamma[c]	1.00	−0.001	14.22	2.17	0.410
Logistic	1.00	−0.00	16.22	2.91	0.980
LogLogistic[d]	1.00	−0.00	14.22	2.85	0.542
LogProbit[d]	1.00	0.00	16.22	2.66	0.482
Multistage (1-degree)[e, f]	**0.52**	**−1.20**	**18.46**	**0.267**	**0.167**
Multistage (2-degree)[e]	0.98	−0.36	14.63	0.981	0.311
Multistage (3-degree)[e]	1.00	−0.11	14.24	1.50	0.310
Probit	1.00	0.00	16.22	2.50	0.858
Weibull[c]	1.00	0.00	16.22	2.33	0.392

[a]Liao (1989a, 1989c).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model.

AIC = Akaike's information criterion; BMD = benchmark dose (i.e., maximum likelihood estimates of the dose associated with the selected BMR); BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; HED = human equivalent dose; S-D = Sprague-Dawley.

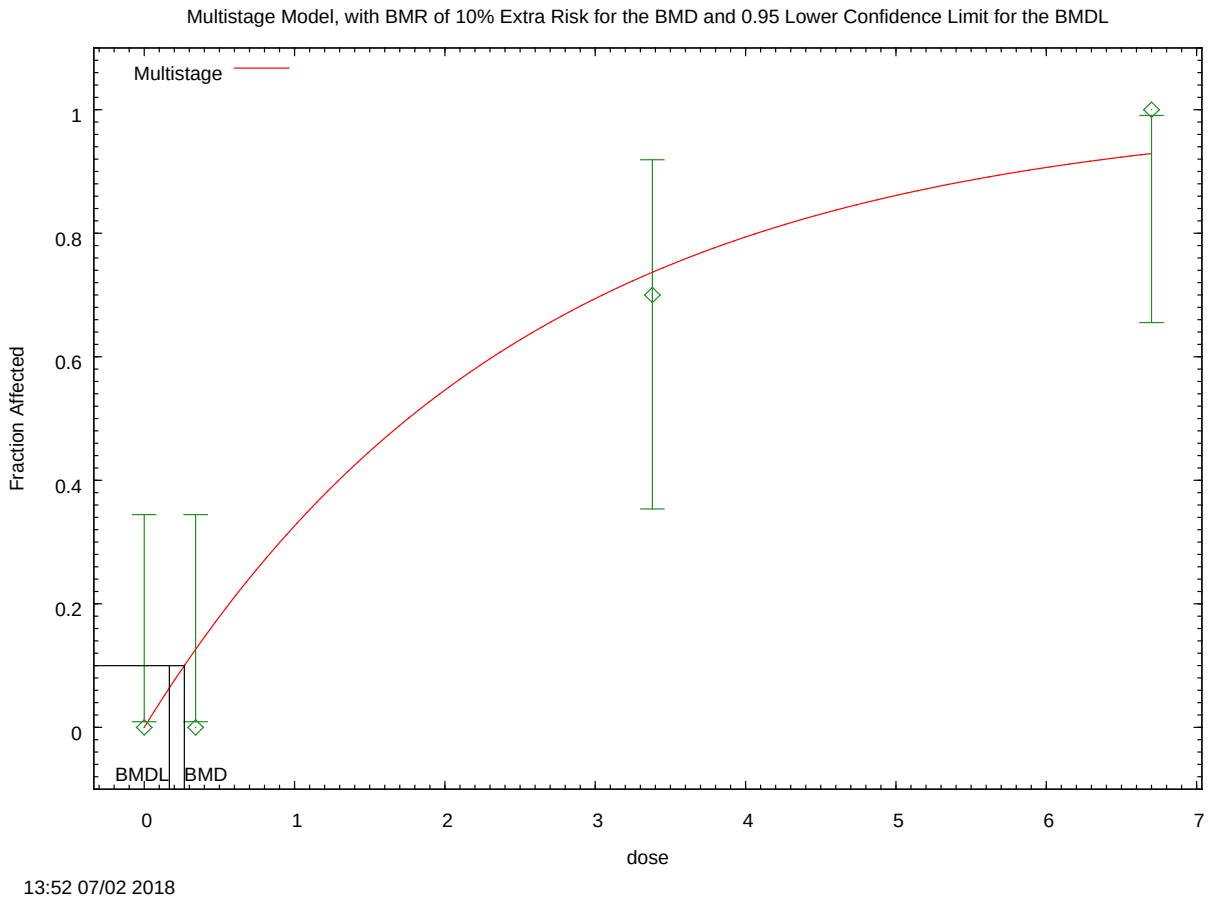


Figure C-2. Fit of the Multistage (1-Degree) Model to the Data for Increased Total Incidence of Tubular Atrophy and Aspermatogenesis in Testes of Male S-D Rats Exposed Daily to *p*-α,α,α-Tetrachlorotoluene by Gavage for 90 Days (Liao, 1989a, c)

BMD Model Output for Figure C-2:

```
================================================================
        Multistage Model. (Version: 3.4;  Date: 05/02/2014)
        Input Data File: C:/Users/sstevens/Documents/BMDS/BMDS2704/Input
data/mst_Liao_1989_Total_TubAtro_Mst1-BMR10-Restrict.(d)
        Gnuplot Plotting File:  C:/Users/sstevens/Documents/BMDS/BMDS2704/Input
data/mst_Liao_1989_Total_TubAtro_Mst1-BMR10-Restrict.plt
                                          Mon Jul 02 13:52:12 2018
 ================================================================
 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive

   Dependent variable = Effect
   Independent variable = Dose
```

```
 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1

 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008

                  Default Initial Parameter Values
                     Background =           0
                        Beta(1) = 1.39855e+019

           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(1)

   Beta(1)           1

                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0              NA
        Beta(1)         0.395021         0.115001            0.169623
0.620418

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

                       Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -6.10864         4
   Fitted model          -8.229         1       4.24072      3          0.2366
  Reduced model        -27.2742         1       42.3311      3         <.0001

           AIC:          18.458

                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
  ---------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000      10.000         0.000
    0.3420     0.1264         1.264     0.000      10.000        -1.203
    3.3800     0.7369         7.369     7.000      10.000        -0.265
    6.7000     0.9291         9.291    10.000      10.000         0.873

 Chi^2 = 2.28      d.f. = 3        P-value = 0.5164

   Benchmark Dose Computation

Specified effect =           0.1
```

```
Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =       0.266721

             BMDL =       0.167101

             BMDU =       0.437293

Taken together, (0.167101, 0.437293) is a 90     % two-sided confidence
interval for the BMD
```

Marked Tubular Atrophy and Aspermatogenesis in Male S-D Rats Exposed Daily to *p*-α,α,α-Tetrachlorotoluene by Gavage for 90 Days (Liao, 1989a, c)

For incidence of "marked" tubular atrophy and aspermatogenesis in the testes, all models provided an adequate fit (*p*-value > 0.1; see Table C-5). BMDLs for models providing adequate fit were not sufficiently close (differed by more than approximately threefold), so the model with the lowest BMDL (LogLogistic) was selected. Fit of the LogLogistic model to the data is shown in Figure C-3. Based on HEDs, the estimated BMD_{10} and $BMDL_{10}$ for increased incidence of marked testicular tubular atrophy and aspermatogenesis were 1.14 and 0.260 mg/kg-day, respectively.

Table C-5. BMD Modeling Results for Increased Incidence of Marked Tubular Atrophy and Aspermatogenesis in Testes of Male S-D Rats Exposed Daily to *p*-α,α,α-Tetrachlorotoluene by Gavage for 90 Days[a]

Model	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{10} (HED) (mg/kg-d)	$BMDL_{10}$ (HED) (mg/kg-d)
Gamma[c]	0.76	−0.397	30.78	1.12	0.389
Logistic	0.18	1.35	34.33	1.89	1.19
LogLogistic[d, e]	**0.85**	**−0.348**	**30.51**	**1.14**	**0.260**
LogProbit[d]	0.91	−0.236	30.32	1.12	0.649
Multistage (1-degree)[f]	0.87	−0.796	29.39	0.587	0.369
Multistage (2-degree)[f]	0.68	−0.665	31.27	0.798	0.373
Multistage (3-degree)[f]	0.68	−0.665	31.27	0.798	0.373
Probit	0.21	−0.662	33.71	1.82	1.16
Weibull[c]	0.73	−0.497	30.94	1.01	0.384

[a]Liao (1989a, 1989c).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model.
[f]Betas restricted to ≥0.

AIC = Akaike's information criterion; BMD = benchmark dose (i.e., maximum likelihood estimates of the dose associated with the selected BMR); BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; HED = human equivalent dose; S-D = Sprague-Dawley.

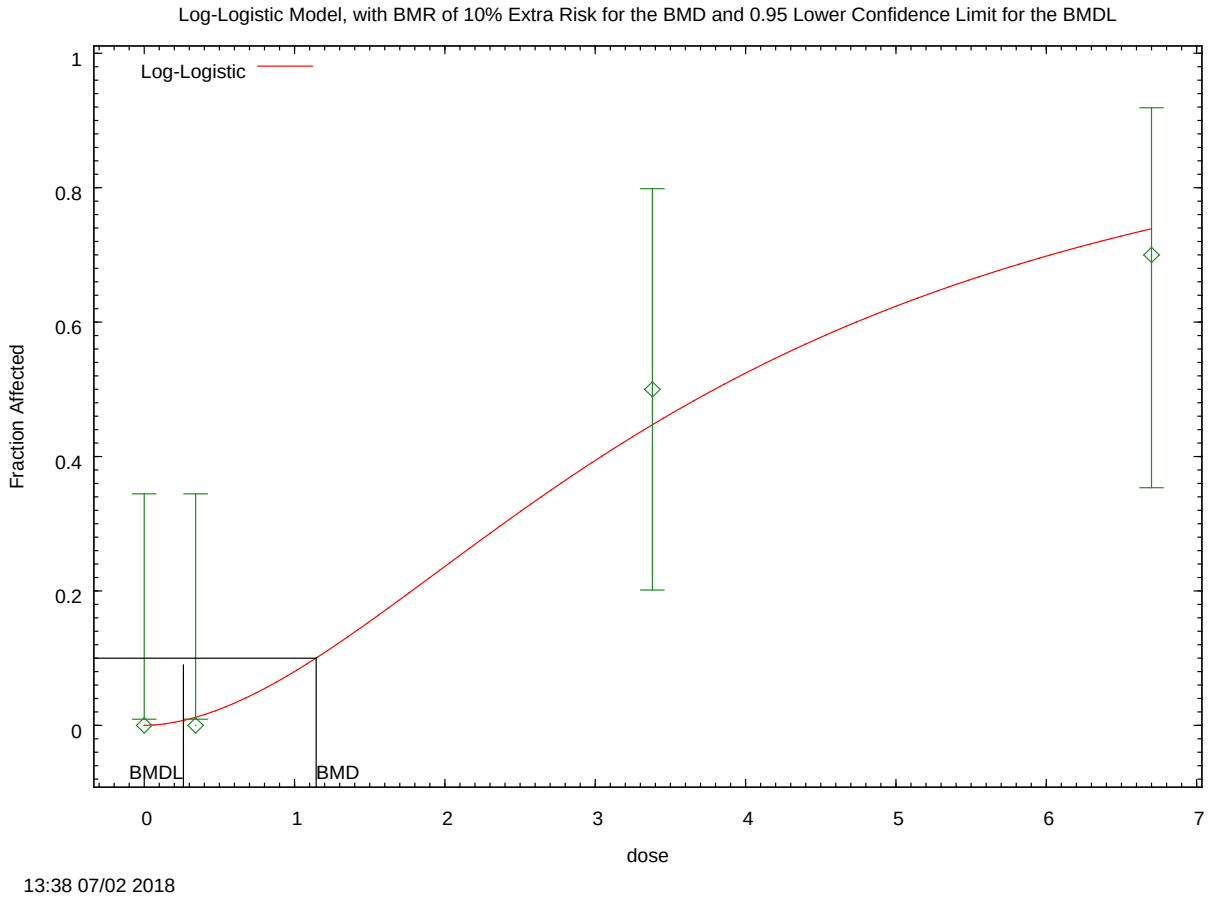


Figure C-3. Fit of LogLogistic Model to Data for Incidence of Marked Tubular Atrophy and Aspermatogenesis in Testes of Male S-D Rats Exposed Daily to *p*-α,α,α-Tetrachlorotoluene by Gavage for 90 Days (Liao, 1989a, c)

BMD Model Output for Figure C-3:

```
================================================================
        Logistic Model. (Version: 2.15; Date: 3/20/2017)
        Input Data File: C:/Users/sstevens/Documents/BMDS/BMDS2704/Input
data/lnl_Liao_1989_MarkedTubAtro_Lnl-BMR10-Restrict.(d)
        Gnuplot Plotting File:  C:/Users/sstevens/Documents/BMDS/BMDS2704/Input
data/lnl_Liao_1989_MarkedTubAtro_Lnl-BMR10-Restrict.plt
                                          Mon Jul 02 13:38:39 2018
 ================================================================
 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1
```

```
   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008

   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =           0
                      intercept =    -1.62862
                          slope =     1.31342

           Asymptotic Correlation Matrix of Parameter Estimates

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

              intercept        slope
 intercept            1        -0.94

     slope        -0.94            1

                                Parameter Estimates

                                                                    95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.  Lower Conf. Limit   Upper Conf.
Limit
     background                0              NA
      intercept         -2.44383         1.36492            -5.11903   0.231366
          slope          1.83497        0.883994            0.102376   3.56757

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

                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -13.0401         4
   Fitted model        -13.2557         2      0.431111      2          0.8061
  Reduced model        -24.4346         1       22.7889      3         <.0001

           AIC:         30.5113

                                  Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
  ---------------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000      10.000         0.000
    0.3420     0.0120         0.120     0.000      10.000        -0.348
    3.3800     0.4479         4.479     5.000      10.000         0.331
    6.7000     0.7401         7.401     7.000      10.000        -0.289

 Chi^2 = 0.31      d.f. = 2        P-value = 0.8545

   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk
```

```
Confidence level =           0.95

             BMD =        1.14384

            BMDL =       0.260665

            BMDU =        2.44074
```

Decreased Lymphocyte Counts in Male S-D Rats Exposed Daily to *p*-α,α,α-Tetrachlorotoluene by Gavage for 90 Days (Liao, 1989a, c)

The procedure outlined above for continuous data was applied to the data for decreased lymphocyte count in male rats exposed daily to *p*-α,α,α-tetrachlorotoluene by gavage for 90 days (Liao, 1989a, c). The constant variance model provided an adequate fit (*p*-value > 0.1) to the variance data, and with that model applied, each of the tested models provided adequate fit to the means, except for the Exponential 5 and Hill models (see Table C-6). BMDLs for models providing adequate fit were not sufficiently close (differed by more than approximately threefold), so the model with the lowest BMDL was selected (Exponential Model 4). Figure C-4 shows the fit of the Exponential Model 4 to the data. Based on HEDs, the estimated BMD_{1SD} and $BMDL_{1SD}$ for decreased lymphocyte count in males were 1.38 and 0.489 mg/kg-day, respectively.

Table C-6. BMD Modeling Results for Decreased Lymphocytes in Male S-D Rats Administered *p*-α,α,α-Tetrachlorotoluene by Gavage for 90 Days[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{1SD} (HED) (mg/kg-d)	$BMDL_{1SD}$ (HED) (mg/kg-d)
Exponential (model 2)[c]	0.27	0.46	−0.99	104.25	2.32	1.59
Exponential (model 3)[c]	0.27	0.46	−0.99	104.25	2.32	1.59
Exponential (model 4)[c, d]	**0.27**	**0.62**	**0.36**	**104.94**	**1.38**	**0.489**
Exponential (model 5)[c]	0.27	NA	1.12×10^{-7}	106.70	1.84	0.515
Hill[c]	0.27	NA	7.18×10^{-8}	106.70	1.65	NDr
Linear[e]	0.27	0.23	−1.44	105.67	3.00	2.23
Polynomial (2-degree)[e]	0.27	0.23	−1.44	105.67	3.00	2.23
Polynomial (3-degree)[e]	0.27	0.23	−1.44	105.67	3.00	2.23
Power[c]	0.27	0.23	−1.44	105.67	3.00	2.23

[a]Liao (1989a, 1989c).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to be ≥1.
[d]Selected model.
[e]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = benchmark dose (i.e., maximum likelihood estimates of the dose associated with the selected BMR); BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; DF = degree(s) of freedom; HED = human equivalent dose; NA = not applicable; NDr = not determined; S-D = Sprague-Dawley; SD = standard deviation.

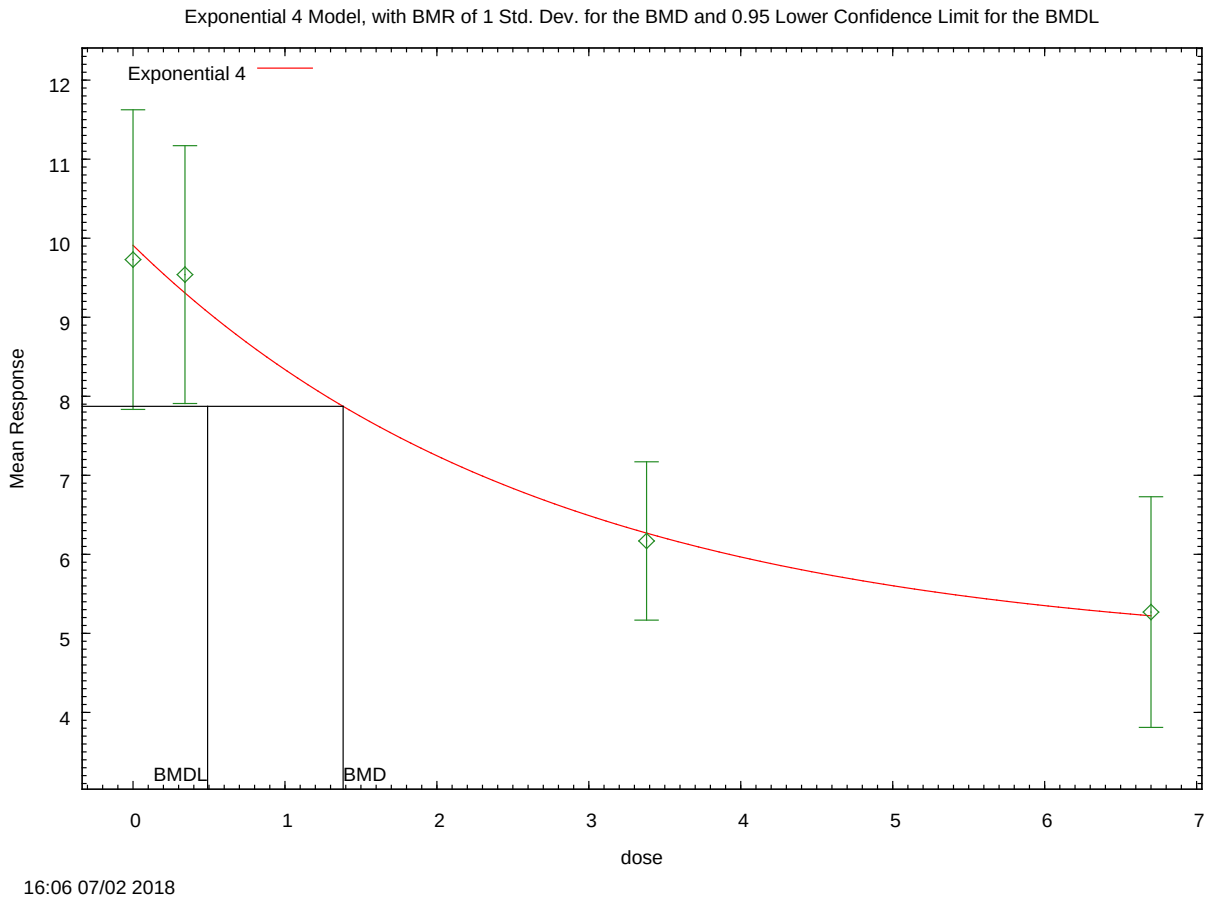


Figure C-4. Fit of Exponential (Model 4) to Data for Decreased Lymphocytes in Male S-D Rats Administered *p*-α,α,α-Tetrachlorotoluene by Gavage for 90 Days (Liao, 1989a, c)

BMD Model Output for Figure C-4:

```
================================================================
        Exponential Model. (Version: 1.11;  Date: 03/14/2017)
        Input Data File: C:/Users/sstevens/Documents/BMDS/BMDS2704/Input
data/exp_Liao_1989_lymphocytes_M_Exp-ConstantVariance-BMR1Std-Down.(d)
        Gnuplot Plotting File:
                                                Mon Jul 02 16:06:05 2018
 ================================================================
 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]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 500
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           1.41757
                     rho                 0 Specified
                       a           10.2165
                       b          0.450968
                       c          0.491269
                       d                 1 Specified

                  Parameter Estimates

                Variable          Model 4          Std. Err.
                --------          -------          ---------
                 lnalpha             1.42355           0.928377
                       a             9.91074           0.522831
                       b            0.366137            0.27681
                       c            0.482456           0.136117

         Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0     10         9.73         2.65
  0.342     10         9.54         2.28
   3.38     10         6.17          1.4
    6.7     10         5.27         2.04

               Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         9.911        2.038          -0.2805
  0.342         9.307        2.038           0.3615
   3.38         6.269        2.038          -0.1544
    6.7         5.223        2.038          0.07335

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       -48.35132            5      106.7026
                   A2       -46.37436            8      108.7487
                   A3       -48.35132            5      106.7026
                    R       -61.74976            2      127.4995
                    4       -48.47097            4      104.9419

Additive constant for all log-likelihoods =     -36.76.  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                       30.75            6           < 0.0001
  Test 2                       3.954            3             0.2665
  Test 3                       3.954            3             0.2665
 Test 6a                      0.2393            1             0.6247

  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 6a is greater than .1.  Model 4 seems
  to adequately describe the data.

Benchmark Dose Computations:

  Specified Effect = 1.000000

         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =       1.3827

              BMDL =     0.490844

              BMDU =       3.2753
```

Decreased Lymphocyte Counts in Female S-D Rats Exposed Daily to *p*-α,α,α-Tetrachlorotoluene by Gavage for 90 Days (Liao, 1989a, c)

The procedure outlined above for continuous data was applied to the data for decreased lymphocyte count in female rats exposed daily to *p*-α,α,α-tetrachlorotoluene by gavage for 90 days (Liao, 1989a, c). The constant variance model did not provide an adequate fit to the variance data (*p*-value < 0.1), but the nonconstant variance model did. With the nonconstant variance model applied, all models except Exponential Model 5 provided an adequate fit (*p*-value > 0.1) to the means (see Table C-7). BMDLs for models providing adequate fit were sufficiently close (differed by less than approximately threefold), so the model with the lowest AIC was selected (Linear). Figure C-5 shows the fit of the Linear model to the data. Based on HEDs, the estimated BMD_{1SD} and $BMDL_{1SD}$ for decreased lymphocyte count in females were 4.41 and 3.03 mg/kg-day, respectively.

Table C-7. BMD Modeling Results for Decreased Lymphocytes in Female S-D Rats Administered to *p*-α,α,α-Tetrachlorotoluene by Gavage for 90 Days[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{1SD} (HED) (mg/kg-d)	$BMDL_{1SD}$ (HED) (mg/kg-d)
Constant variance						
Linear[c]	0.07	0.68	0.16	99.66	3.72	2.57
Nonconstant variance						
Exponential (model 2)[d]	0.56	0.37	0.49	97.10	4.09	2.49
Exponential (model 3)[d]	0.56	0.16	0.26	99.05	4.32	2.50
Exponential (model 4)[d]	0.56	0.37	0.49	97.10	4.09	2.12
Exponential (model 5)[d]	0.56	NA	0.26	101.05	4.32	2.50
Hill[d]	0.56	0.18	0.18	98.89	4.41	3.17
Linear[c, e]	**0.56**	**0.41**	**0.18**	**96.89**	**4.41**	**3.03**
Polynomial (2-degree)[c]	0.56	0.18	−0.03	98.89	4.46	3.03
Polynomial (3-degree)[c]	0.56	0.18	−0.02	98.88	4.52	3.03
Power[d]	0.56	0.41	0.18	96.89	4.41	3.03

[a]Liao (1989a, 1989c).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Coefficients restricted to be negative.
[d]Power Restricted to ≥1
[e]Selected model.

AIC = Akaike's information criterion; BMD = benchmark dose (i.e., maximum likelihood estimates of the dose associated with the selected BMR); BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; HED = human equivalent dose; NA = not applicable; S-D = Sprague-Dawley; SD = standard deviation.

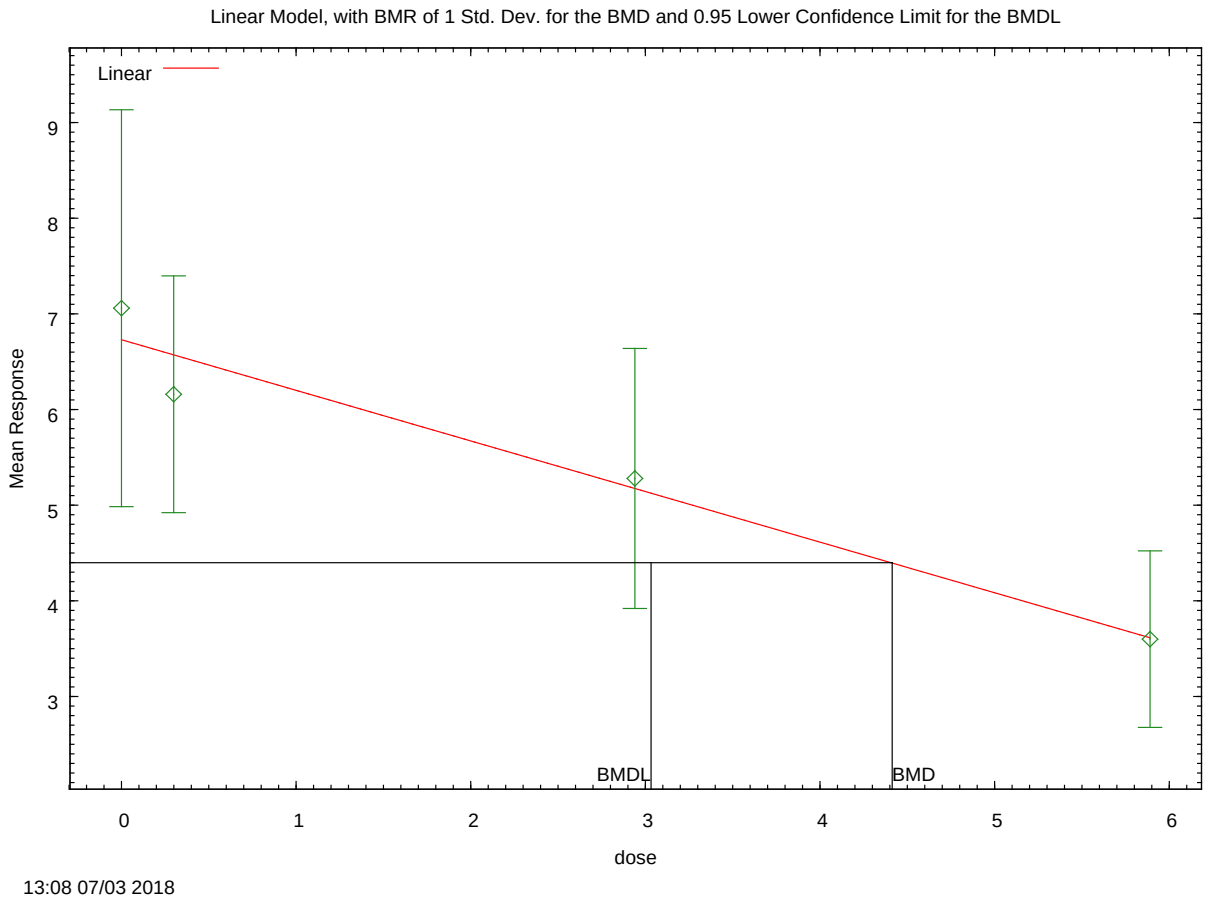


Figure C-5. Fit of Linear Model to Data for Decreased Lymphocytes in Female S-D Rats Administered *p*-α,α,α-Tetrachlorotoluene by Gavage for 90 Days (Liao, 1989a, c)

BMD Model Output for Figure C-5:

```
================================================================
        Polynomial Model. (Version: 2.21;  Date: 03/14/2017)
        Input Data File: C:/Users/sstevens/Documents/BMDS/BMDS2704/Input
data/lin_Liao_1989_lymphocytes_F_Lin-ModelVariance-BMR1Std.(d)
        Gnuplot Plotting File:  C:/Users/sstevens/Documents/BMDS/BMDS2704/Input
data/lin_Liao_1989_lymphocytes_F_Lin-ModelVariance-BMR1Std.plt
                                          Tue Jul 03 13:08:32 2018
 ================================================================
 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

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

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

   Total number of dose groups = 4
```

```
   Total number of records with missing values = 0
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008

                  Default Initial Parameter Values
                         lalpha =      1.42774
                            rho =            0
                         beta_0 =      6.72406
                         beta_1 =    -0.525385

           Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho       beta_0       beta_1

    lalpha             1        -0.99       -0.014         0.02

       rho         -0.99            1        0.014        -0.02

    beta_0        -0.014        0.014            1        -0.83

    beta_1          0.02        -0.02        -0.83            1


                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
         lalpha         -2.27713           1.5129            -5.24236
0.688109
            rho          2.08269         0.890533            0.337273
3.8281
         beta_0          6.73265          0.48421             5.78362
7.68168
         beta_1        -0.528656
0.110966           -0.746145           -0.311166

     Table of Data and Estimated Values of Interest

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

    0    10       7.06         6.73          2.9         2.33          0.444
0.299    10       6.16         6.57         1.73         2.28         -0.576
 2.94    10       5.28         5.18          1.9         1.78          0.181
 5.89    10        3.6         3.62         1.29         1.22        -0.0488

 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	-46.447513	5	102.895026
A2	-42.986072	8	101.972144
A3	-43.557729	6	99.115458
fitted	-44.444415	4	96.888830
R	-53.667146	2	111.334292

Explanation of Tests

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

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	21.3621	6	0.001579
Test 2	6.92288	3	0.0744
Test 3	1.14331	2	0.5646
Test 4	1.77337	2	0.412

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

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

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

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

Benchmark Dose Computation

Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 4.41348

BMDL = 3.03265

BMDU = 7.419

BMD Modeling to Identify Potential PODs for Derivation of a Provisional Reference Concentration

Data on suitable endpoints from the 30-day and developmental inhalation studies were modeled (Edwards et al., 1985; Rose et al., 1984). Modeled data from the 30-day study (Rose et al., 1984) were increased incidences of atrophy of olfactory epithelium in male rats and keratinizing epithelia hyperplasia in the larynx in female rats (see Table A-5 in Appendix A). The Edwards et al. (1985) developmental toxicity study observed an increased incidence of unossified sternebrae at the high-exposure concentration that could be modeled using individual animal data from the study (see Table C-10) with the nested dichotomous models of the BMDS. Summaries of modeling approaches and results (see Tables C-8 to C-11) are provided below.

Increased Atrophy of Olfactory Epithelium in Male Rats Exposed to *p*-α,α,α-Tetrachlorotoluene by Inhalation 6 Hours/Day, 5 Days/Week for 30 Days

The incidence data for atrophy of olfactory epithelium in male rats (Rose et al., 1984) were fit to all available dichotomous models in the BMDS (Version 2.6) using the procedure described above dichotomous data. HECs for extrathoracic effects (HEC_{ET}) were calculated using the equation for ET effects from a Category 1 gas (U.S. EPA, 1994). HEC_{ET} = TWA concentration (mg/m^3) × $RGDR_{ET}$, where $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) and TWA is the time-weighted average. $RGDR_{ET}$ was calculated as per U.S. EPA (1994) using default human minute volume (V_E), human and animal respiratory tissue surface area values, and animal V_E values calculated from TWA body weights for each dose group in the study. TWA body weights were calculated from weekly measured body weights given in Table 5 in Rose et al. (1984). TWA body weights (grams) for the 0, 3.98, 18.9, and 94.5 mg/m^3 groups, respectively, were: males = 303.6, 304.7, 298.1, and 201.2; females = 203.2, 203.4, 202.5, and 159.5. All models provided an adequate fit (*p*-value > 0.1; see Table C-8). Benchmark concentration lower confidence limits (BMCLs) for models providing adequate fit were not sufficiently close (differed by more than approximately threefold), so the model with the lowest BMCL was selected (LogLogistic). Figure C-6 shows the fit of the LogLogistic model to the data, using a BMR of 10% extra risk. Based on human equivalent concentrations (HECs), the BMC_{10} and $BMCL_{10}$ for increased incidence of atrophy of the olfactory epithelium in male rats were 0.0989 and 0.0141 mg/m^3, respectively.

Table C-8. BMC Modeling Results for Atrophy of Olfactory Epithelium in Male Albino Rats Exposed to *p*-α,α,α-Tetrachlorotoluene by Inhalation 6 Hours/Day, 5 Days/Week for 30 Days[a]

Model	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual at Dose Nearest BMC	AIC	BMC_{10} (HEC) (mg/m^3)	$BMCL_{10}$ (HEC) (mg/m^3)
Gamma[c]	1.00	0.011	14.02	0.0828	0.0245
Logistic	0.77	0.477	14.79	0.171	0.0777
LogLogistic[d, e]	**0.94**	**0.085**	**14.23**	**0.0989**	**0.0141**
LogProbit[d]	0.97	0.063	14.11	0.101	0.0409
Multistage (1-degree)[f]	0.98	−0.342	12.20	0.0720	0.0245
Multistage (2-degree)[f]	1.00	0.00	14.01	0.0714	0.0245
Multistage (3-degree)[f]	1.00	0.00	16.01	0.158	0.0781
Probit	0.79	0.469	14.70	0.0793	0.0245
Weibull[c]	1.00	0.01	14.01	0.0480	0.0239

[a]Rose et al. (1984).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model.
[f]Betas restricted to ≥0.

AIC = Akaike's information criterion; BMC = benchmark concentration (i.e., maximum likelihood estimates of the concentration associated with the selected BMR); BMCL = 95% lower confidence limit on the BMC (subscripts denote BMR: i.e., 10 = exposure concentration associated with 10% extra risk); BMR = benchmark response; HEC = human equivalent concentration.

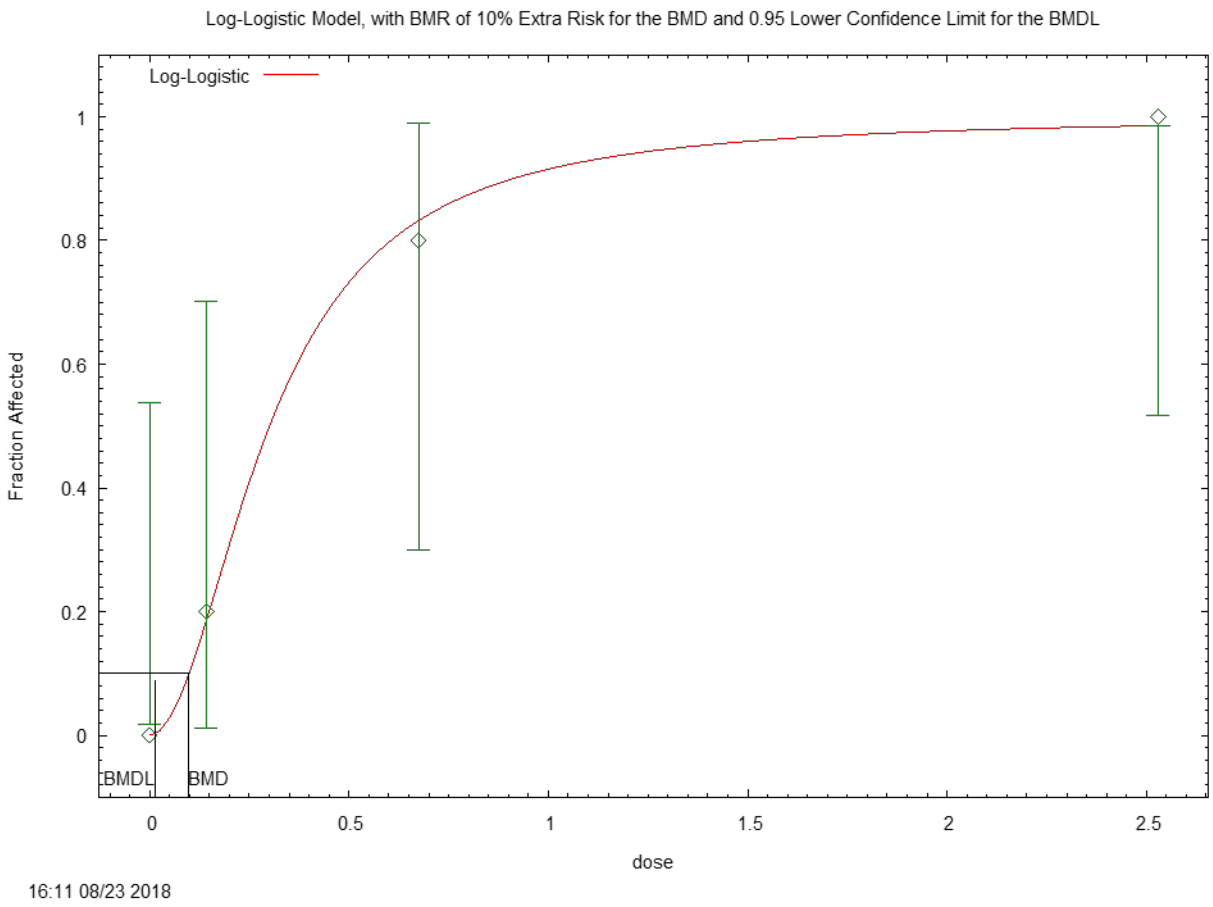


Figure C-6. Fit of LogLogistic Model to Data for Atrophy of Olfactory Epithelium in Male Albino Rats Exposed to *p*-α,α,α-Tetrachlorotoluene by Inhalation 6 Hours/Day, 5 Days/Week for 30 Days (Rose et al., 1984) (BMR = 10% Extra Risk)

BMD Model Output for Figure C-6:

```
================================================================
        Logistic Model. (Version: 2.15; Date: 3/20/2017)
        Input Data File: E:/lnl_olfactory_Lnl-BMR10-Restrict.(d)
        Gnuplot Plotting File:  E:/lnl_olfactory_Lnl-BMR10-Restrict.plt
                                          Thu Aug 23 16:11:10 2018
 ================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 4
```

```
   Total number of records with missing values = 0
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =           0
                     intercept =     1.50856
                         slope =     1.38397


          Asymptotic Correlation Matrix of Parameter Estimates

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

              intercept        slope

 intercept            1         0.77

     slope         0.77            1


                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background                0              NA
      intercept           2.3792          1.26067           -0.091669
4.85006
          slope          1.97791         0.894408            0.224899
3.73091

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


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -5.00402         4
   Fitted model        -5.11334         2      0.218628      2          0.8964
  Reduced model        -14.5323         1       19.0565      3       0.0002661

          AIC:         14.2267


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000       5.000        0.000
```

```
    0.1420     0.1852         0.926     1.000       5.000        0.085
    0.6750     0.8323         4.161     4.000       5.000       -0.193
    2.5300     0.9854         5.913     6.000       6.000        0.298

 Chi^2 = 0.13      d.f. = 2        P-value = 0.9356


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =      0.0988877

            BMDL =      0.0141224

            BMDU =       0.599202
```

Increased Keratinizing Epithelial Hyperplasia in the Larynx in Female Albino Rats Exposed to *p*-α,α,α-Tetrachlorotoluene by Inhalation 6 Hours/Day, 5 Days/Week for 30 Days

The incidence data for keratinizing epithelial hyperplasia in the larynx of female rats (Rose et al., 1984) were fit to all available dichotomous models in the BMDS (Version 2.6) using the procedure described above for dichotomous data. All models provided an adequate fit (*p*-value > 0.1; see Table C-9). BMCLs for models providing adequate fit were not sufficiently close (differed by more than approximately threefold), so the model with the lowest BMCL was selected (LogLogistic). Figure C-7 shows the fit of the LogLogistic model to the data, using a BMR of 10% extra risk. Based on HECs, the BMC_{10} and $BMCL_{10}$ for increased incidence of keratinizing epithelial hyperplasia in the larynx of female rats were 0.0932 and 0.0182 mg/m^3, respectively.

Table C-9. BMC Modeling Results for Keratinizing Epithelial Hyperplasia in the Larynx of Female Albino Rats Exposed to *p*-α,α,α-Tetrachlorotoluene by Inhalation 6 Hours/Day, 5 Days/Week for 30 Days[a]

Model	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual at Dose Nearest BMC	AIC	BMC_{10} (HEC) (mg/m^3)	$BMCL_{10}$ (HEC) (mg/m^3)
Gamma[c]	0.69	0.44	16.64	0.0808	0.0348
Logistic	0.66	0.67	16.84	0.211	0.105
LogLogistic[d, e]	**0.50**	**0.55**	**17.52**	**0.0932**	**0.0182**
LogProbit[d]	0.63	0.80	15.54	0.110	0.0566
Multistage (1-degree)[f]	0.87	0.31	14.67	0.0934	0.0361
Multistage (2-degree)[f]	0.74	0.60	16.34	0.0904	0.0371
Multistage (3-degree)[f]	0.80	0.57	16.15	0.196	0.0999
Probit	0.67	0.65	16.78	0.0907	0.0350
Weibull[c]	0.68	0.56	16.58	0.0689	0.0347

[a]Rose et al. (1984).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model.
[f]Betas restricted to ≥0.

AIC = Akaike's information criterion; BMC = benchmark concentration (i.e., maximum likelihood estimates of the concentration associated with the selected BMR); BMCL = 95% lower confidence limit on the BMC (subscripts denote BMR: i.e., 10 = exposure concentration associated with 10% extra risk); BMR = benchmark response; HEC = human equivalent concentration.

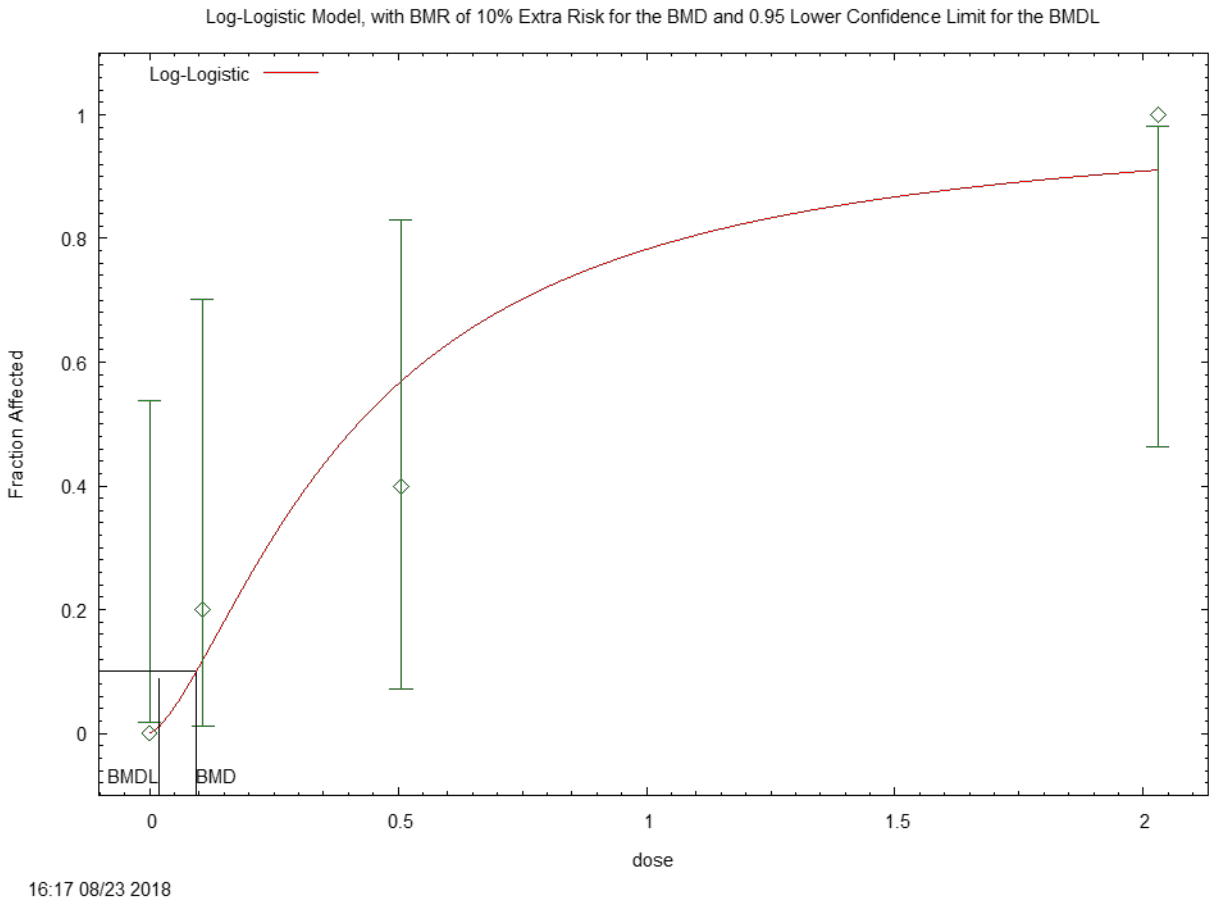


Figure C-7. Fit of LogLogistic Model to Data for Keratinizing Epithelial Hyperplasia in the Larynx of Female Albino Rats Exposed to *p*-α,α,α-Tetrachlorotoluene by Inhalation 6 Hours/Day, 5 Days/Week for 30 Days (Rose et al., 1984) (BMR = 10% Extra Risk)

BMD Model Output for Figure C-7:

```
================================================================
        Logistic Model. (Version: 2.15; Date: 3/20/2017)
        Input Data File: E:/lnl_karatinizingdax_Lnl-BMR10-Restrict.(d)
        Gnuplot Plotting File:  E:/lnl_karatinizingdax_Lnl-BMR10-Restrict.plt
                                          Thu Aug 23 16:17:18 2018
 ================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 4
```

```
   Total number of records with missing values = 0
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =           0
                      intercept =     1.13901
                          slope =     1.27298


           Asymptotic Correlation Matrix of Parameter Estimates

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

              intercept        slope

 intercept            1         0.64

     slope         0.64            1



                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background                0              NA
      intercept          1.27968         0.880893           -0.446836
3.0062
          slope          1.46505         0.701627           0.0898864
2.84021

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



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -5.86707         4
   Fitted model         -6.7585         2       1.78286      2          0.4101
  Reduced model        -13.4602         1       15.1863      3        0.001664

           AIC:          17.517


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000       5.000        0.000
```

```
    0.1070     0.1198         0.599     1.000       5.000        0.553
    0.5060     0.5700         2.850     2.000       5.000       -0.768
    2.0300     0.9103         4.551     5.000       5.000        0.702

 Chi^2 = 1.39      d.f. = 2        P-value = 0.4997


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =      0.0931788

            BMDL =      0.0182161

            BMDU =        1.62682
```

Increased Incidence of Unossified Sternebrae in CD (SD) BR Rat Fetuses Gestationally Exposed to *p*-α,α,α-Tetrachlorotoluene Vapors on GDs 6–19

The modeling procedure outlined above for nested dichotomous data was applied to the individual animal data for increased incidence of unossified sternebrae in fetuses from pregnant rats exposed to *p*-α,α,α-tetrachlorotoluene vapor by inhalation on Gestation Days (GDs) 6−19 (Edwards et al., 1985). The individual animal data modeled are shown in Table C-10. The NLogistic model was run using a BMR of 5% extra risk and was fit with and without the number of implantations as a litter-specific covariate, which is the preferred choice of covariate when dosing begins after implantation has taken place (U.S. EPA, 2018b). Each model was also fit with and without taking account of intralitter correlations. Modeling results are shown in Table C-11. Models not accounting for intralitter correlation did not provide adequate fit to the data. All models including intralitter correlation provided adequate fit. Among all models, the best fit (lowest AIC) was for the NLogistic model including number of implantations as a covariate and accounting for intralitter correlation. BMCLs for the NCTR, and Rai and Van Ryzin models with adequate fits were very small in relation to the corresponding BMCs (>10-fold difference) and were, therefore, considered unreliable. The NLogistic model with covariate and intralitter correlation was selected. Figure C-8 shows the fit of the selected NLogistic model to the data, using a BMR of 5% extra risk. Based on HECs, the BMC_{05} and $BMCL_{05}$ for increased unossified sternebrae in gestationally exposed fetuses were 1.38 and 0.385 mg/m^3, respectively.

Table C-10. Input Data of Unossified Sternebrae in CD (SD) BR Rat Fetuses Gestationally Exposed to *p*-α,α,α-Tetrachlorotoluene Vapors on GDs 6–19[a]

Exposure Concentration (HEC_{ER}) (mg/m^3)	Count of Dams within Each Exposure Group	Experimental Dam Number	Number of Fetuses Examined	Number of Examined Fetuses with Unossified Sternebrae	Number of Implants
0	1	1	6	6	12
0	2	4	5	3	14
0	3	5	4	3	8
0	4	6	4	1	10
0	5	7	6	2	12
0	6	8	6	2	12
0	7	10	6	4	14
0	8	11	6	2	14
0	9	12	5	1	12
0	10	13	7	3	14
0	11	14	4	2	9
0	12	15	7	1	15
0	13	16	5	4	13
0	14	18	6	4	13
0	15	19	7	4	14
0	16	20	5	5	13
0	17	21	6	3	13
0	18	23	7	4	13
0	19	24	5	1	12
1.0	1	26	5	4	15
1.0	2	27	5	4	11
1.0	3	28	6	6	12
1.0	4	29	5	4	11

Table C-10. Input Data of Unossified Sternebrae in CD (SD) BR Rat Fetuses Gestationally Exposed to *p*-α,α,α-Tetrachlorotoluene Vapors on GDs 6–19[a]

Exposure Concentration (HEC_{ER}) (mg/m^3)	Count of Dams within Each Exposure Group	Experimental Dam Number	Number of Fetuses Examined	Number of Examined Fetuses with Unossified Sternebrae	Number of Implants
1.0	5	34	6	2	13
1.0	6	35	7	7	13
1.0	7	36	6	4	15
1.0	8	37	6	3	13
1.0	9	38	4	1	11
1.0	10	39	5	3	10
1.0	11	40	7	4	15
1.0	12	41	6	6	15
1.0	13	42	7	4	14
1.0	14	43	5	4	10
1.0	15	44	5	5	14
1.0	16	45	6	6	13
1.0	17	47	8	4	15
1.0	18	48	5	2	13
1.0	19	49	7	1	14
2.6	1	51	6	3	13
2.6	2	52	6	6	15
2.6	3	54	6	6	14
2.6	4	55	1	1	1
2.6	5	56	7	4	14
2.6	6	57	7	4	14
2.6	7	58	6	4	14
2.6	8	59	6	3	12

Table C-10. Input Data of Unossified Sternebrae in CD (SD) BR Rat Fetuses Gestationally Exposed to *p*-α,α,α-Tetrachlorotoluene Vapors on GDs 6–19[a]

Exposure Concentration (HEC_{ER}) (mg/m^3)	Count of Dams within Each Exposure Group	Experimental Dam Number	Number of Fetuses Examined	Number of Examined Fetuses with Unossified Sternebrae	Number of Implants
2.6	9	60	6	5	14
2.6	10	61	4	2	10
2.6	11	62	6	3	13
2.6	12	63	7	5	14
2.6	13	64	7	4	14
2.6	14	66	7	6	14
2.6	15	67	7	7	14
2.6	16	68	5	5	13
2.6	17	69	6	2	13
2.6	18	70	6	4	14
2.6	19	73	6	3	12
2.6	20	74	5	0	12
2.6	21	75	6	3	13
6.3	1	76	6	6	14
6.3	2	77	7	6	14
6.3	3	78	6	6	12
6.3	4	79	7	7	13
6.3	5	80	6	5	12
6.3	6	82	7	6	15
6.3	7	83	7	7	13
6.3	8	84	6	6	14
6.3	9	86	6	4	13
6.3	10	87	7	6	13

Table C-10. Input Data of Unossified Sternebrae in CD (SD) BR Rat Fetuses Gestationally Exposed to *p*-α,α,α-Tetrachlorotoluene Vapors on GDs 6–19[a]

Exposure Concentration (HEC_{ER}) (mg/m^3)	Count of Dams within Each Exposure Group	Experimental Dam Number	Number of Fetuses Examined	Number of Examined Fetuses with Unossified Sternebrae	Number of Implants
6.3	11	88	5	5	11
6.3	12	90	6	5	13
6.3	13	91	2	1	5
6.3	14	92	7	7	14
6.3	15	93	5	5	11
6.3	16	94	6	4	12
6.3	17	95	5	4	10
6.3	18	97	5	4	11
6.3	19	98	6	6	14
6.3	20	99	5	3	9
6.3	21	100	4	2	11

[a]Edwards et al. (1985); individual litter data used for nested dichotomous modeling.

ER = extrarespiratory; GD = gestation day; HEC = human equivalent concentration.

Table C-11. BMC Modeling Results for Increased Incidence of Unossified Sternebrae in Fetuses of Pregnant CD (SD) BR Rats Exposed to *p*-α,α,α-Tetrachlorotoluene Vapors on GDs 6–19[a]

Nested Model	χ^2 Goodness-of-Fit *p*-Value[b]	AIC	Status of θ and Φ Coefficients	Average Scaled Residual for Dose Group Nearest the BMC	BMC (HEC) (mg/m^3)	BMCL (HEC) (mg/m^3)
Without number of implantations as a covariate, without intralitter correlation (BMR = 5% Extra Risk)						
NLogistic[c]	0.0030	553.93	θs and Φs set = 0	2.04	0.86	0.125
NCTR[c]	0.0030	553.09	θs and Φs set = 0	−0.57	0.42	0.034
Rai and Van Ryzin[c]	0.0030	553.09	θs and Φs set = 0	−0.57	0.42	0.034
With number of implantations as a covariate, without intralitter correlation (BMR = 5% Extra Risk)						
NLogistic[c]	0.0233	546.54	θs estimated nonzero; Φs set = 0	2.13	1.35	0.448
NCTR[c]	0.0083	552.84	θs estimated nonzero; Φs set = 0	2.07	0.65	0.333
Rai and Van Ryzin[c]	0.0047	554.81	θs estimated nonzero; Φs set = 0	−0.59	0.350	0.346
Without number of implantations as a covariate, with intralitter correlation (BMR = 5% Extra Risk)						
NLogistic[c]	0.4363	547.37	θs set = 0; Φs estimated nonzero	1.42	0.98	0.112
NCTR[c]	0.4340	546.90	θs set = 0; Φs estimated nonzero	1.40	0.51	0.032
Rai and Van Ryzin[c]	0.4340	546.90	θs set = 0; Φs estimated nonzero	1.40	0.51	0.032
With number of implantations as a covariate, with intralitter correlation (BMR = 5% Extra Risk)						
NLogistic[c, d]	**0.6150**	**541.99**	**θs and Φs estimated nonzero**	**1.48**	**1.38**	**0.3852**

[a]Edwards et al. (1985); individual litter data used for nested dichotomous modeling.
[b]Goodness-of-fit *p*-value combined from three bootstrap runs (adequate fit = $p > 0.1$).
[c]Power restricted ≥1.
[d]Selected model.

AIC = Akaike's information criterion; BMC = benchmark concentration (i.e., maximum likelihood estimates of the concentration associated with the selected BMR); BMCL = 95% lower confidence limit on the BMC; BMR = benchmark response; GD = gestation day; HEC = human equivalent concentration.

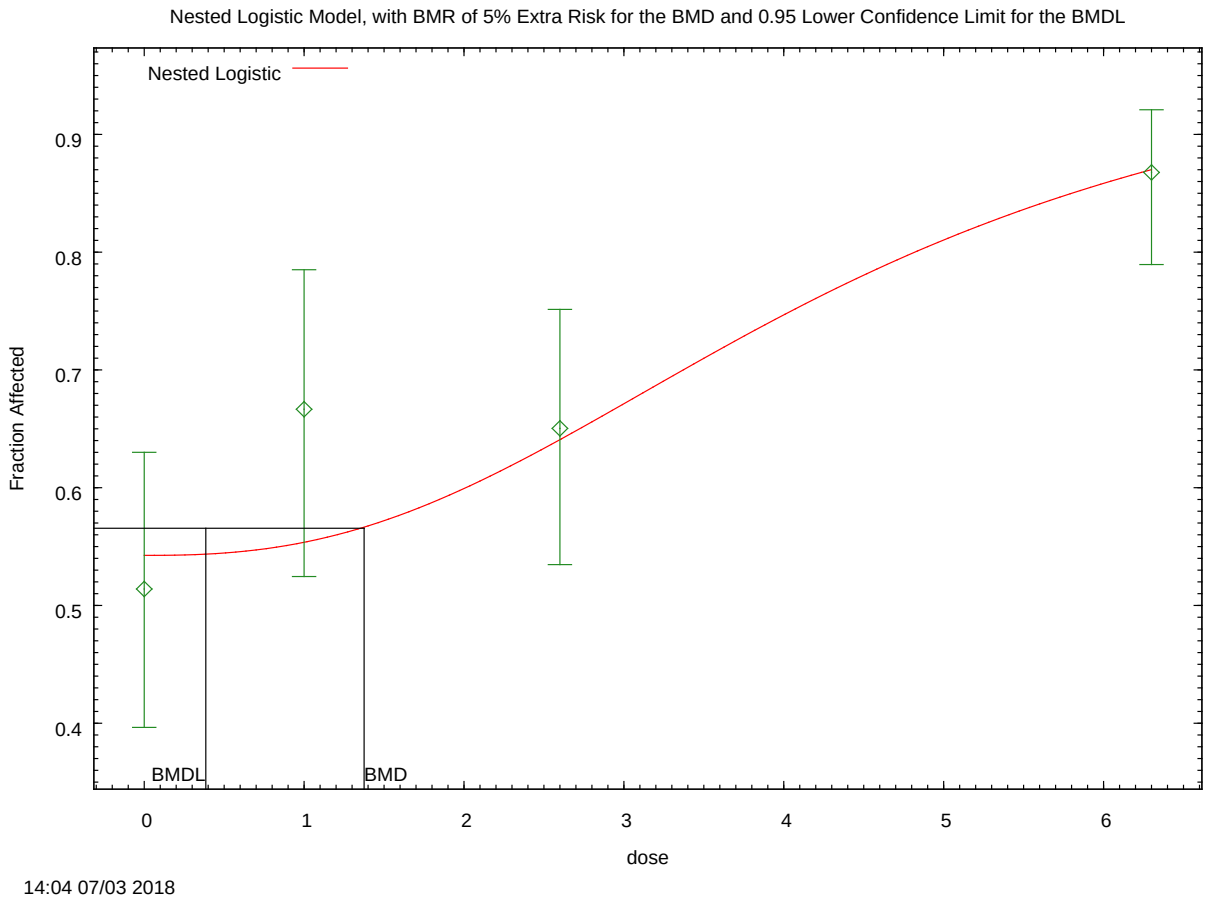


Figure C-8. Fit of the NLogistic Model to Data for Increased Incidence of Unossified Sternebrae in CD (SD) BR Rat Fetuses Gestationally Exposed to *p*-α,α,α-Tetrachlorotoluene Vapors on GDs 6–19 (Edwards et al., 1985) (BMR = 5% Extra Risk)

BMD Model Output for Figure C-8:

```
 ======================================================================
        NLogistic Model. (Version: 2.20; Date: 04/27/2015)
        Input Data File: //Esc-server1/ncea_eh028/TO3+5 PTV lit search and
develop/p-a,a,a-Tetrachlorotoluene_5216-25-1/Working Toxicologist
folder/Revisions_07_02_18/Edwards_BMD/nln_unossimplantrevised7_3_18_Nln-BMR05-Restrict
.(d)
                                                Tue Jul 03 14:04:28 2018
 ======================================================================
 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

 The probability function is:

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

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

          where Rij is the litter specific covariate.
```

```
Restrict Power rho >= 1.

Total number of observations = 80
Total number of records with missing values = 0
Total number of parameters in model = 9
Total number of specified parameters = 0

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
Number of Bootstrap Iterations per run: 1000
Bootstrap Seed:  1530641068

                 Default Initial Parameter Values
                         alpha =     0.559308
                          beta =      -2.9069
                        theta1 =            0
                        theta2 =            0
                           rho =      2.01147
                          phi1 =    0.0873332
                          phi2 =     0.227117
                          phi3 =      0.11692
                          phi4 =            0

                              Parameter Estimates

      Variable           Estimate            Std. Err.
         alpha           0.695632            0.269444
          beta            -13.046             4.76798
        theta1          -0.0122555           0.0865844
        theta2           0.745807            0.328334
           rho            2.50645            0.883357
          phi1           0.0791273           0.0893591
          phi2            0.236125             0.14086
          phi3           0.0587824           0.0861943
          phi4                   0             Bounded

Log-likelihood: -262.994   AIC: 541.989

                            Litter Data

          Lit.-Spec.              Litter                          Scaled
   Dose       Cov.     Est._Prob.   Size    Expected   Observed   Residual
-------------------------------------------------------------------------
   0.0000    8.0000      0.598         4       2.390         3      0.5588
   0.0000    9.0000      0.585         4       2.341         2     -0.3114
   0.0000   10.0000      0.573         4       2.292         1     -1.1744
   0.0000   12.0000      0.549         6       3.291         6      1.8809
   0.0000   12.0000      0.549         6       3.291         2     -0.8968
   0.0000   12.0000      0.549         5       2.743         1     -1.3650
   0.0000   12.0000      0.549         6       3.291         2     -0.8968
   0.0000   12.0000      0.549         5       2.743         1     -1.3650
   0.0000   13.0000      0.536         6       3.218         3     -0.1510
   0.0000   13.0000      0.536         5       2.682         4      1.0305
   0.0000   13.0000      0.536         5       2.682         5      1.8121
   0.0000   13.0000      0.536         7       3.754         4      0.1534
   0.0000   13.0000      0.536         6       3.218         4      0.5420
   0.0000   14.0000      0.524         6       3.144         4      0.5921
   0.0000   14.0000      0.524         6       3.144         2     -0.7918
   0.0000   14.0000      0.524         5       2.620         3      0.2964
   0.0000   14.0000      0.524         7       3.668         4      0.2067
   0.0000   14.0000      0.524         7       3.668         3     -0.4165
   0.0000   15.0000      0.512         7       3.583         1     -1.6080
```

1.0000	10.0000	0.575	5	2.873	3	0.0822
1.0000	10.0000	0.575	5	2.873	4	0.7309
1.0000	11.0000	0.564	4	2.257	1	-0.9698
1.0000	11.0000	0.564	5	2.821	4	0.7624
1.0000	11.0000	0.564	5	2.821	4	0.7624
1.0000	12.0000	0.556	6	3.336	6	1.4825
1.0000	13.0000	0.552	6	3.312	3	-0.1735
1.0000	13.0000	0.552	6	3.312	2	-0.7295
1.0000	13.0000	0.552	6	3.312	6	1.4943
1.0000	13.0000	0.552	5	2.760	2	-0.4902
1.0000	13.0000	0.552	7	3.864	7	1.5332
1.0000	14.0000	0.557	7	3.898	1	-1.4182
1.0000	14.0000	0.557	5	2.784	5	1.4306
1.0000	14.0000	0.557	7	3.898	4	0.0501
1.0000	15.0000	0.578	7	4.043	4	-0.0213
1.0000	15.0000	0.578	6	3.466	4	0.2990
1.0000	15.0000	0.578	5	2.888	4	0.7219
1.0000	15.0000	0.578	6	3.466	6	1.4184
1.0000	15.0000	0.578	8	4.621	4	-0.2729
2.6000	1.0000	0.683	1	0.683	1	0.6807
2.6000	10.0000	0.590	4	2.360	2	-0.3371
2.6000	12.0000	0.618	5	3.091	0	-2.5603
2.6000	12.0000	0.618	6	3.709	3	-0.5240
2.6000	12.0000	0.618	6	3.709	3	-0.5240
2.6000	13.0000	0.665	5	3.326	5	1.4277
2.6000	13.0000	0.665	6	3.991	3	-0.7533
2.6000	13.0000	0.665	6	3.991	2	-1.5138
2.6000	13.0000	0.665	6	3.991	3	-0.7533
2.6000	13.0000	0.665	6	3.991	3	-0.7533
2.6000	14.0000	0.737	6	4.423	4	-0.3448
2.6000	14.0000	0.737	7	5.160	7	1.3584
2.6000	14.0000	0.737	7	5.160	6	0.6201
2.6000	14.0000	0.737	7	5.160	4	-0.8565
2.6000	14.0000	0.737	7	5.160	5	-0.1182
2.6000	14.0000	0.737	6	4.423	5	0.4705
2.6000	14.0000	0.737	6	4.423	4	-0.3448
2.6000	14.0000	0.737	7	5.160	4	-0.8565
2.6000	14.0000	0.737	7	5.160	4	-0.8565
2.6000	14.0000	0.737	6	4.423	6	1.2859
2.6000	15.0000	0.820	6	4.919	6	1.0096
6.3000	5.0000	0.638	2	1.275	1	-0.4049
6.3000	9.0000	0.648	5	3.241	3	-0.2261
6.3000	10.0000	0.690	5	3.450	4	0.5317
6.3000	11.0000	0.755	4	3.022	2	-1.1882
6.3000	11.0000	0.755	5	3.777	4	0.2321
6.3000	11.0000	0.755	5	3.777	5	1.2725
6.3000	11.0000	0.755	5	3.777	5	1.2725
6.3000	12.0000	0.831	6	4.988	6	1.1032
6.3000	12.0000	0.831	6	4.988	4	-1.0773
6.3000	12.0000	0.831	6	4.988	5	0.0130
6.3000	13.0000	0.898	7	6.284	7	0.8929
6.3000	13.0000	0.898	6	5.387	5	-0.5208
6.3000	13.0000	0.898	7	6.284	6	-0.3546
6.3000	13.0000	0.898	6	5.387	4	-1.8683
6.3000	13.0000	0.898	7	6.284	7	0.8929
6.3000	14.0000	0.944	7	6.606	6	-0.9933
6.3000	14.0000	0.944	6	5.662	6	0.5984
6.3000	14.0000	0.944	6	5.662	6	0.5984
6.3000	14.0000	0.944	7	6.606	7	0.6463
6.3000	14.0000	0.944	6	5.662	6	0.5984
6.3000	15.0000	0.971	7	6.795	6	-1.7853

```
Scaled Residual(s) for Dose Group Nearest the BMD
-----------------------------
Minimum scaled residual for dose group nearest the BMD =         1.4825
Minimum ABS(scaled residual) for dose group nearest the BMD =    1.4825
Average scaled residual for dose group nearest the BMD =         1.4825
Average ABS(scaled residual) for dose group nearest the BMD =    1.4825
Maximum scaled residual for dose group nearest the BMD =         1.4825
Maximum ABS(scaled residual) for dose group nearest the BMD =    1.4825
Number of litters used for scaled residual for dose group nearest the BMD = 1

 Observed Chi-square =    76.2170

               Bootstrapping Results

Number of Bootstrap Iterations per run: 1000

                  Bootstrap Chi-square Percentiles
 Bootstrap
    Run        P-value    50th     90th     95th     99th
-----------------------------------------------------------
     1          0.6130  79.0982  95.0855  100.2383  111.9835
     2          0.6070  78.9837  94.8173  100.5251  111.7723
     3          0.6250  79.7000  94.1364  99.4197  113.7194
-----------------------------------------------------------
 Combined       0.6150  79.1795  94.8401  100.3218  112.2275

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


To calculate the BMD and BMDL, the litter specific covariate is fixed
 at the mean litter specific covariate of control group: 12.473684

   Benchmark Dose Computation

Specified effect =           0.05

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        1.37525

            BMDL =      0.385229
```

BMD MODELING TO IDENTIFY POTENTIAL PODs FOR THE DERIVATION OF A PROVISIONAL ORAL SLOPE FACTOR

Significant dose-related trends were found for increases in lung adenocarcinoma and multiple adenoma, forestomach squamous cell carcinoma and carcinoma in situ, thymomas, malignant lymphomas, and skin squamous cell carcinomas in female ICR mice treated with p-α,α,α-tetrachlorotoluene by gavage twice per week for 17.5 weeks (Fukuda et al., 1980, 1979). MS_Combo multiple-tumor BMD modeling was used to combine the tumor incidence data for all of these tumor types. For each tumor type, the best-fitting Multistage model (i.e., the degree

of Poly setting) was maintained in the MS_Combo model run. The calculated combined tumor $BMDL_{10}$ (HED) based on the MS_Combo model is 0.015 mg/kg-day. This $BMDL_{10}$ (HED) is used as the POD to derive the provisional oral slope factor (p-OSF). Summaries of modeling approaches and results for each data set follow.

Lung Adenocarcinomas in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks

The modeling procedure described above for cancer incidence data was applied to the incidence data for lung adenocarcinomas in female ICR mice treated with *p*-α,α,α-tetrachlorotoluene by gavage twice per week for 17.5 weeks (Fukuda et al., 1980, 1979). The data are shown in Table A-8 in the "Derivation of Provisional Cancer Potency Values" section in Appendix A. Table C-12 summarizes the BMD modeling results. No model provided adequate fit to the full data set. After dropping the highest dose group, the 1-degree Multistage model provided adequate fit to the data. The higher degree polynomial models took the form of the 1-degree model. Figure C-9 shows the fit of the 1-degree Multistage model to the data. Based on HEDs, the BMD_{10} and $BMDL_{10}$ for lung adenocarcinoma in female mice were 0.047 and 0.033 mg/kg-day, respectively.

Table C-12. BMD Modeling Results for Lung Adenocarcinoma in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks[a]

Model	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{10} (HED) (mg/kg-d)	$BMDL_{10}$ (HED) (mg/kg-d)
All doses					
Multistage (1-degree)[c]	0	NA	172.92	NA	NA
Multistage (2-degree)[c]	0	NA	172.92	NA	NA
Multistage (3-degree)[c]	0	NA	172.92	NA	NA
Multistage (4-degree)[c]	0	NA	172.92	NA	NA
Highest dose group dropped					
Multistage (1-degree)[c, d]	**0.14**	**0.823**	**129.37**	**0.047**	**0.033**
Multistage (2-degree)[c]	0.14	0.823	129.37	0.047	0.033
Multistage (3-degree)[c]	0.14	0.823	129.37	0.047	0.033

[a]Fukuda et al. (1980); Fukuda et al. (1979)
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Coefficients restricted to be positive.
[d]Selected model; all higher-order dose coefficients are zero.

AIC = Akaike's information criterion; BMD = benchmark dose (i.e., maximum likelihood estimates of the dose associated with the selected BMR); BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; HED = human equivalent dose; NA = not applicable (computation failed).

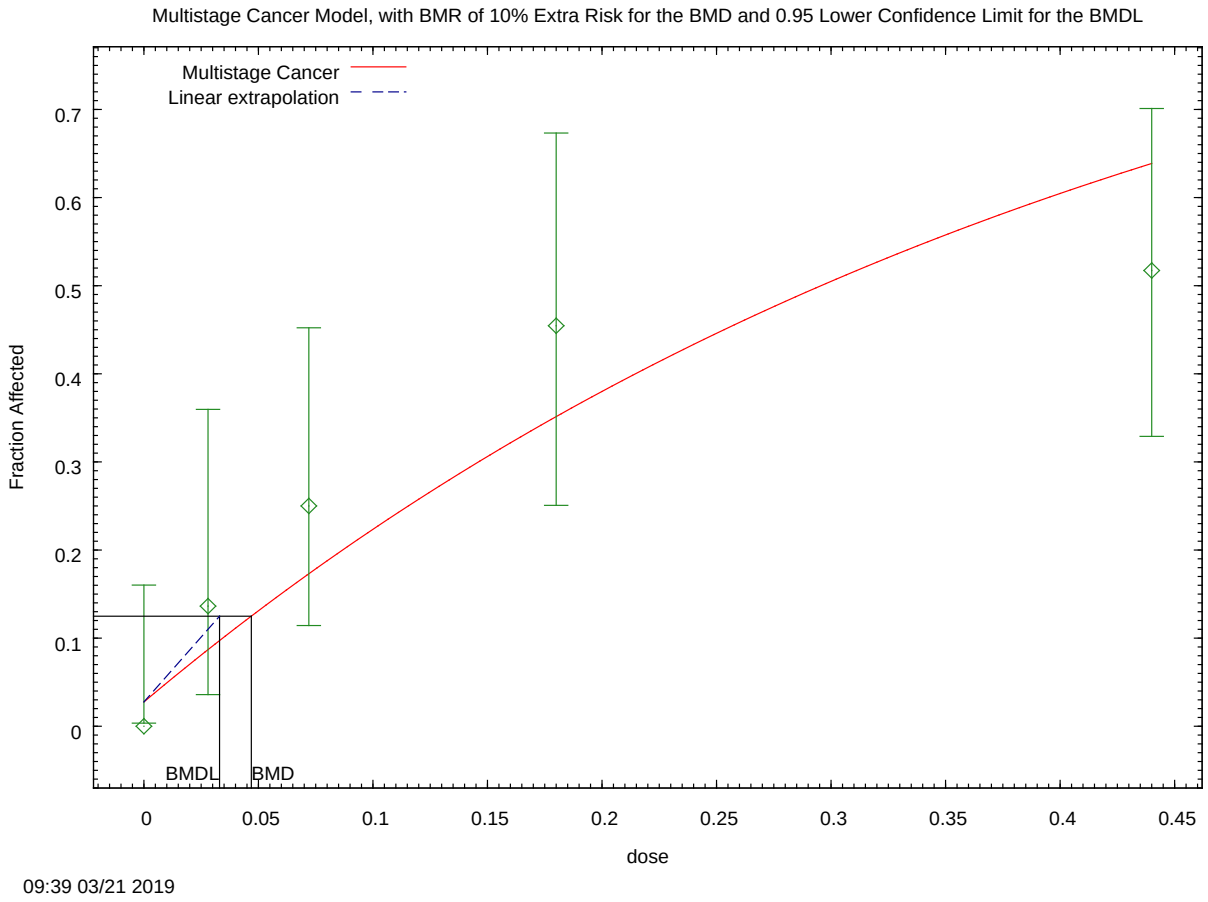


Figure C-9. Fit of the Multistage (1-Degree) Model to Data for Lung Adenocarcinoma in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks (Fukuda et al., 1980, 1979) (Highest Dose Group Dropped)

BMD Model Output for Figure C-9:

```
================================================================
        Multistage Model. (Version: 3.4;  Date: 05/02/2014)
        Input Data File:
C:/Users/JSWART/Desktop/BMDS/BMDS26/Data/msc_Fukuda_lung_adenocarcinoma_Opt.(d)
        Gnuplot Plotting File:
C:/Users/JSWART/Desktop/BMDS/BMDS26/Data/msc_Fukuda_lung_adenocarcinoma_Opt.plt
                                          Thu Mar 21 09:39:11 2019
 ================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive
```

```
  Dependent variable = Effect
  Independent variable = Dose

 Total number of observations = 5
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                    Background =     0.121569
                       Beta(1) =      1.55634


          Asymptotic Correlation Matrix of Parameter Estimates

            Background      Beta(1)

Background            1        -0.67

   Beta(1)        -0.67            1


                               Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background        0.0276431        0.0524855          -0.0752265
0.130513
        Beta(1)          2.24651         0.570266             1.12881
3.36422


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -59.7504         5
   Fitted model        -62.6831         2       5.86545      3          0.1183
  Reduced model          -74.77         1       30.0393      4         <.0001

          AIC:         129.366


                               Goodness  of  Fit
                                                                    Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
    0.0000     0.0276         0.719     0.000      26.000       -0.860
    0.0280     0.0869         1.912     3.000      22.000        0.823
    0.0720     0.1729         4.840     7.000      28.000        1.079
    0.1800     0.3511         7.723    10.000      22.000        1.017
```

```
    0.4400     0.6381        18.506    15.000      29.000       -1.355

 Chi^2 = 5.45      d.f. = 3        P-value = 0.1415


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =      0.0468995

             BMDL =      0.0330362

             BMDU =      0.0764043

Taken together, (0.0330362, 0.0764043) is a 90     % two-sided confidence
interval for the BMD

Cancer Slope Factor =       3.02698
```

Lung Multiple Adenomas in Female ICR Mice Orally Exposed to p-α,α,α-Tetrachlorotoluene for 17.5 Weeks

The modeling procedure described above for cancer incidence data was applied to the incidence data for multiple lung adenomas in female ICR mice treated with *p*-α,α,α-tetrachlorotoluene by gavage twice per week for 17.5 weeks (Fukuda et al., 1980, 1979). The data are shown in Table A-8 in the "Derivation of Provisional Cancer Potency Values" section in Appendix A. Table C-13 summarizes the BMD modeling results. The 1-degree Multistage model provided adequate fit to the data. The higher degree polynomial models took the form of the 1-degree model. Figure C-10 shows the fit of the 1-degree Multistage model to the data. Based on HEDs, the BMD_{10} and $BMDL_{10}$ for multiple lung adenomas in female mice were 0.127 and 0.092 mg/kg-day, respectively.

Table C-13. BMD Modeling Results for Lung Multiple Adenoma in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks[a]

Model	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{10} (HED) (mg/kg-d)	$BMDL_{10}$ (HED) (mg/kg-d)
Multistage (1-degree)[c, d]	**0.55**	**−1.11**	**140.21**	**0.127**	**0.092**
Multistage (2-degree)[c]	0.55	−1.11	140.21	0.127	0.092
Multistage (3-degree)[c]	0.55	−1.11	140.21	0.127	0.092
Multistage (4-degree)[c]	0.55	−1.11	140.21	0.127	0.092

[a]Fukuda et al. (1980); Fukuda et al. (1979).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Coefficients restricted to be positive.
[d]Selected model; all higher-order dose coefficients are zero.

AIC = Akaike's information criterion; BMD = benchmark dose (i.e., maximum likelihood estimates of the dose associated with the selected BMR); BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; HED = human equivalent dose.

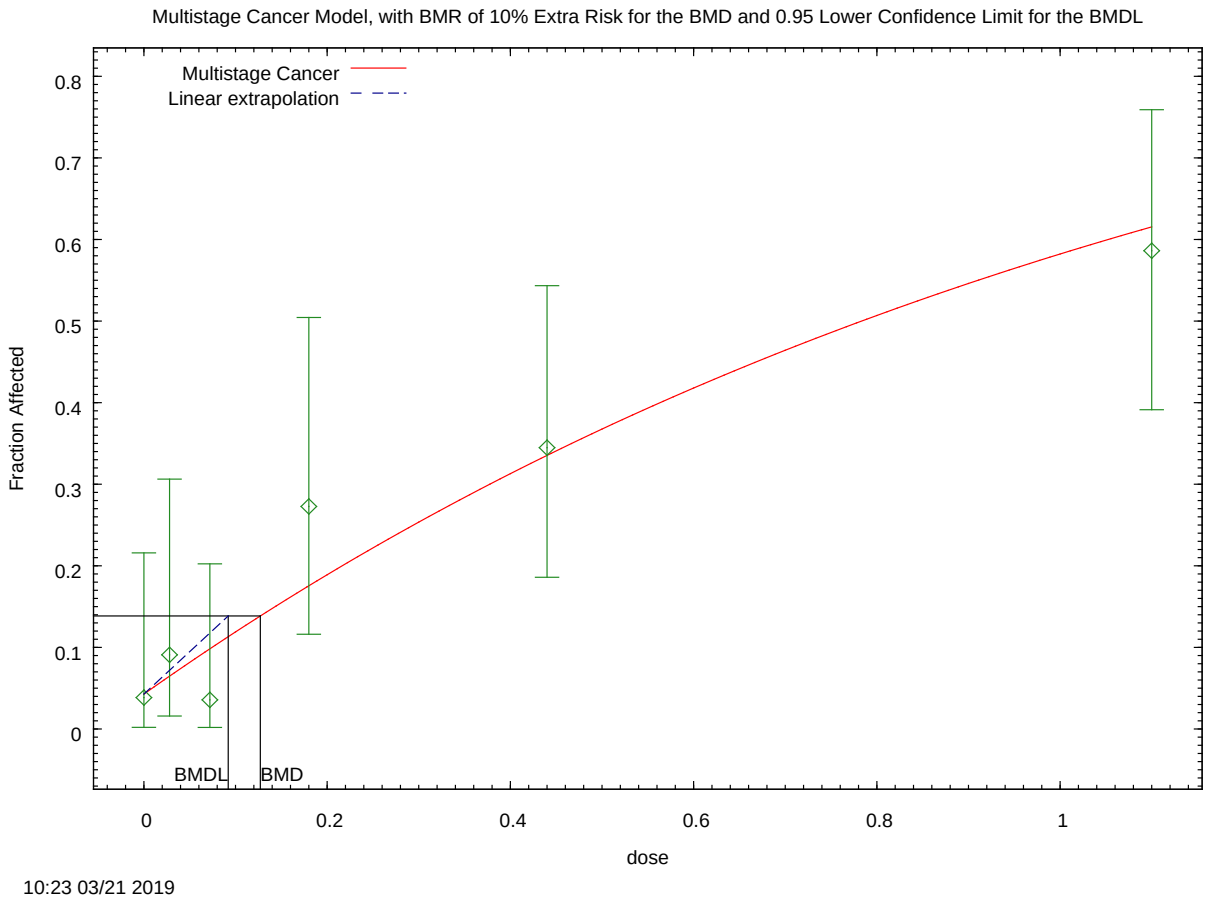


Figure C-10. Fit of the Multistage (1-Degree) Model to Data for Lung Multiple Adenoma in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks (Fukuda et al., 1980, 1979)

BMD Model Output for Figure C-10:

```
================================================================
        Multistage Model. (Version: 3.4;  Date: 05/02/2014)
        Input Data File:
C:/Users/JSWART/Desktop/BMDS/BMDS26/Data/msc_Fukuda_lung_mulitple_adenoma_Opt.(d)
        Gnuplot Plotting File:
C:/Users/JSWART/Desktop/BMDS/BMDS26/Data/msc_Fukuda_lung_mulitple_adenoma_Opt.plt
                                          Thu Mar 21 10:23:15 2019
 ================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive
```

```
  Dependent variable = Effect
  Independent variable = Dose

Total number of observations = 6
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1


Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                    Background =    0.0667116
                       Beta(1) =     0.758435


          Asymptotic Correlation Matrix of Parameter Estimates

            Background      Beta(1)

Background            1        -0.42

   Beta(1)        -0.42            1


                                Parameter Estimates

                                                      95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background        0.0428386        0.0292427          -0.0144759
0.100153
        Beta(1)         0.829035         0.177674            0.480799
1.17727



                      Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -66.4952         6
   Fitted model        -68.1064         2       3.22244      4          0.5213
  Reduced model        -85.4579         1       37.9254      5         <.0001

          AIC:         140.213


                                Goodness  of  Fit
                                                                      Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.0428         1.114     1.000      26.000       -0.110
    0.0280     0.0648         1.426     2.000      22.000        0.497
    0.0720     0.0983         2.752     1.000      28.000       -1.112
    0.1800     0.1755         3.862     6.000      22.000        1.198
    0.4400     0.3354         9.726    10.000      29.000        0.108
    1.1000     0.6155        17.848    17.000      29.000       -0.324
```

```
 Chi^2 = 3.05      d.f. = 4        P-value = 0.5495


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.127088

            BMDL =      0.0920397

            BMDU =       0.189035

Taken together, (0.0920397, 0.189035) is a 90     % two-sided confidence
interval for the BMD

Cancer Slope Factor =       1.08649
```

Thymomas in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks

The modeling procedure described above for cancer incidence data was applied to the incidence data for thymomas in female ICR mice treated with *p*-α,α,α-tetrachlorotoluene by gavage twice per week for 17.5 weeks (Fukuda et al., 1980, 1979). The data are shown in Table A-8 in the "Derivation of Provisional Cancer Potency Values" section in Appendix A. Table C-14 summarizes the BMD modeling results. The 1-degree Multistage model provided adequate fit to the data. The higher degree polynomial models took the form of the 1-degree model. Figure C-11 shows the fit of the 1-degree Multistage model to the data. Based on HEDs, the BMD_{10} and $BMDL_{10}$ for thymoma in female mice were 0.402 and 0.258 mg/kg-day, respectively.

Table C-14. BMD Modeling Results for Thymoma in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks[a]

Model	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{10} (HED) (mg/kg-d)	$BMDL_{10}$ (HED) (mg/kg-d)
Multistage (1-degree)[c, d]	**0.83**	**0.50**	**63.22**	**0.402**	**0.258**
Multistage (2-degree)[c]	0.83	0.50	63.22	0.402	0.258
Multistage (3-degree)[c]	0.83	0.50	63.22	0.402	0.258
Multistage (4-degree)[c]	0.83	0.50	63.22	0.402	0.258
Multistage (5-degree)[c]	0.83	0.50	63.22	0.402	0.258

[a]Fukuda et al. (1980); Fukuda et al. (1979).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Coefficients restricted to be positive.
[d]Selected model; all higher-order dose coefficients are zero.

AIC = Akaike's information criterion; BMD = benchmark dose (i.e., maximum likelihood estimates of the dose associated with the selected BMR); BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; HED = human equivalent dose.

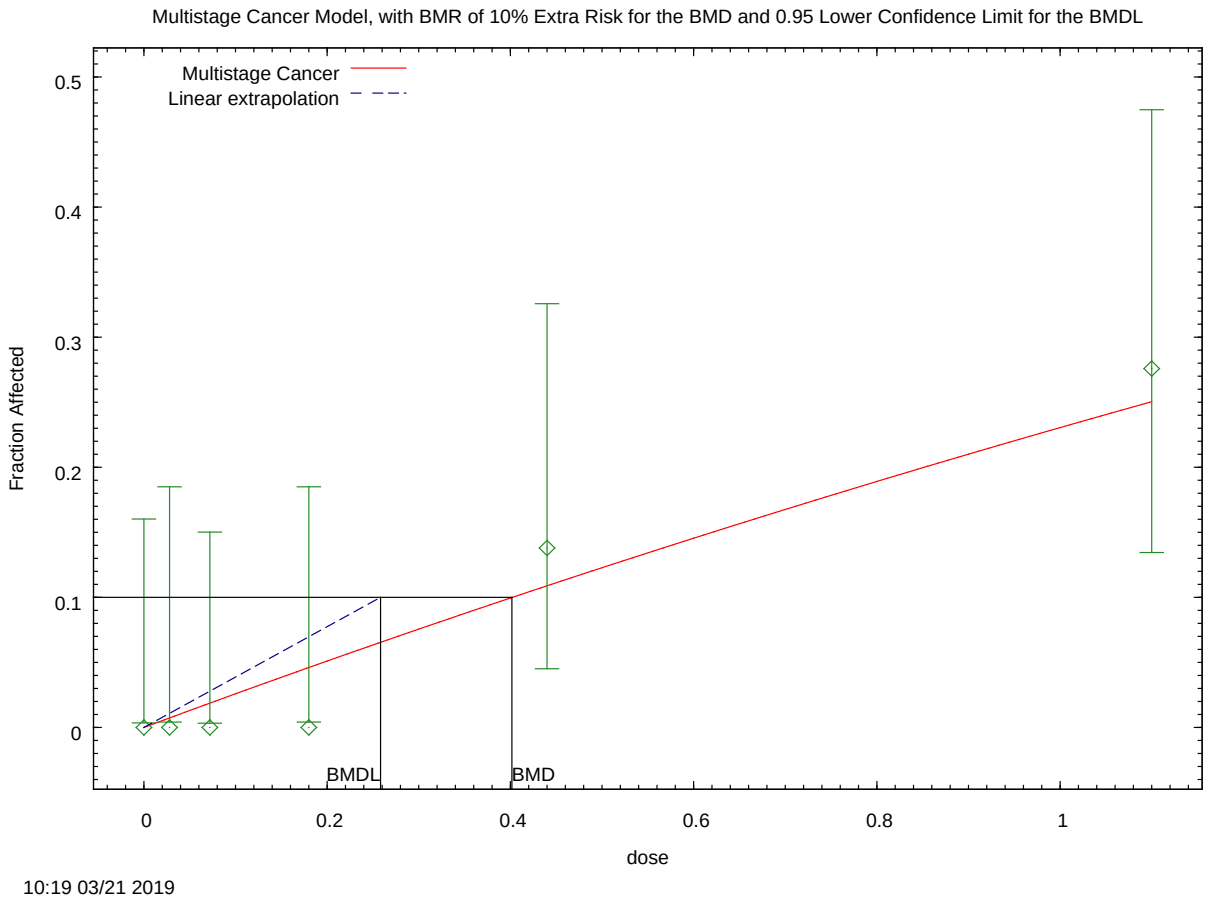


Figure C-11. Fit of the Multistage (1-Degree) Model to Data for Thymoma in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks (Fukuda et al., 1980, 1979)

BMD Model Output for Figure C-11:

```
=================================================================
        Multistage Model. (Version: 3.4;  Date: 05/02/2014)
        Input Data File:
C:/Users/JSWART/Desktop/BMDS/BMDS26/Data/msc_Fukuda_thymoma_Opt.(d)
        Gnuplot Plotting File:
C:/Users/JSWART/Desktop/BMDS/BMDS26/Data/msc_Fukuda_thymoma_Opt.plt
                                          Thu Mar 21 10:19:56 2019
 =================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive
```

```
  Dependent variable = Effect
  Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                    Background =            0
                       Beta(1) =      0.31175


          Asymptotic Correlation Matrix of Parameter Estimates

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

               Beta(1)

   Beta(1)           1



                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0              NA
        Beta(1)          0.26233       0.0759173            0.113535
0.411125

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



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -28.7156         6
   Fitted model        -30.6091         1       3.78712      5          0.5805
  Reduced model        -42.3055         1       27.1799      5         <.0001

          AIC:         63.2183


                                Goodness  of  Fit
                                                                    Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ------------------------------------------------------------------------
```

```
    0.0000     0.0000         0.000     0.000      26.000        0.000
    0.0280     0.0073         0.161     0.000      22.000       -0.403
    0.0720     0.0187         0.524     0.000      28.000       -0.731
    0.1800     0.0461         1.015     0.000      22.000       -1.031
    0.4400     0.1090         3.161     4.000      29.000        0.500
    1.1000     0.2507         7.269     8.000      29.000        0.313

 Chi^2 = 2.11      d.f. = 5        P-value = 0.8341


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =       0.401633

             BMDL =       0.258298

             BMDU =       0.673248

Taken together, (0.258298, 0.673248) is a 90     % two-sided confidence
interval for the BMD

Cancer Slope Factor =       0.38715
```

Malignant Lymphoma in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks

The modeling procedure described above for cancer incidence data was applied to the incidence data for malignant lymphoma in female ICR mice treated with *p*-α,α,α-tetrachlorotoluene by gavage twice per week for 17.5 weeks (Fukuda et al., 1980, 1979). The data are shown in Table A-8 in the "Derivation of Provisional Cancer Potency Values" section in Appendix A. Table C-15 summarizes the BMD modeling results. All models provided adequate fit to the data. The model with the lowest AIC was selected (4-degree Multistage). Figure C-12 shows the fit of the 4-degree Multistage model to the data. Based on HEDs, the BMD_{10} and $BMDL_{10}$ for malignant lymphoma in female mice were 0.979 and 0.727 mg/kg-day, respectively.

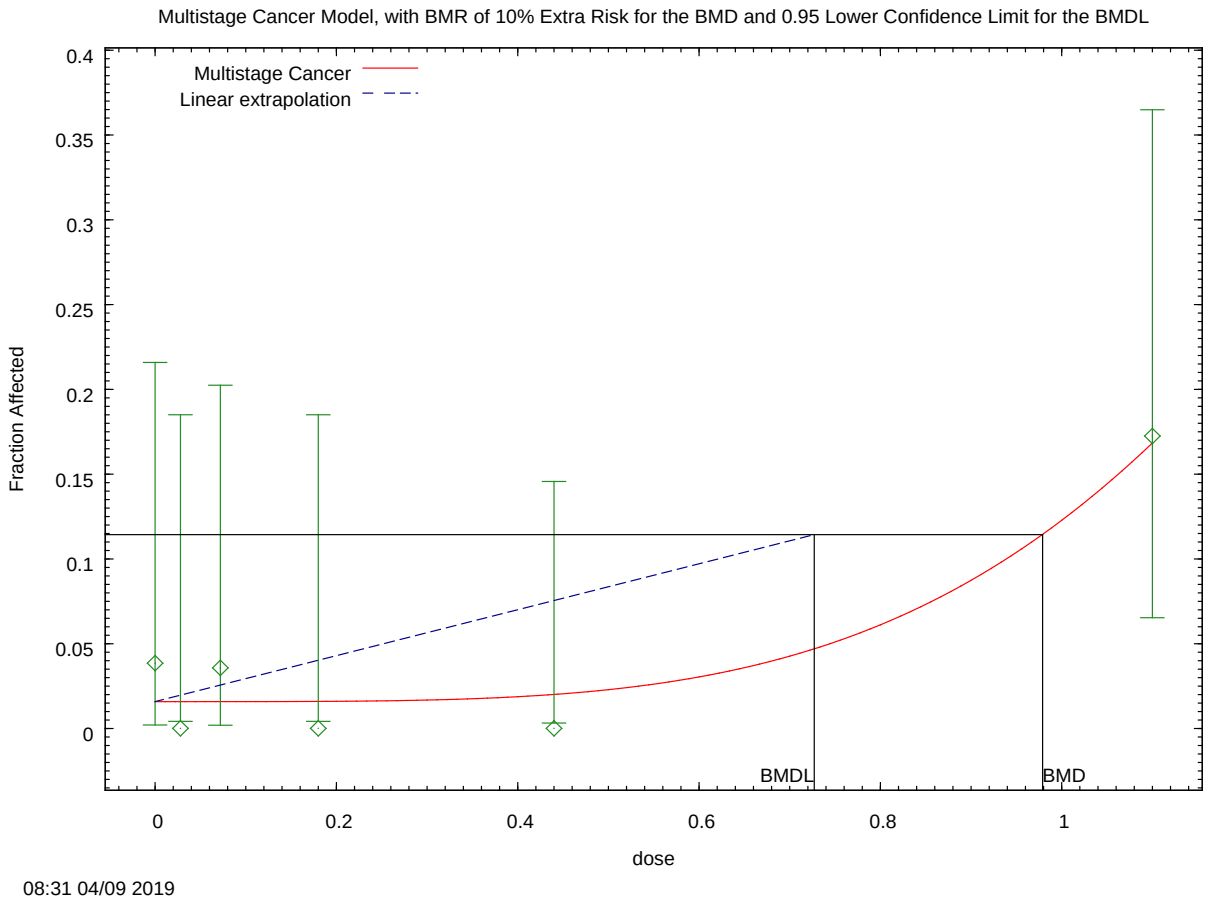


Figure C-12. Fit of the Multistage (4-Degree) Model to Data for Malignant Lymphomas in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks (Fukuda et al., 1980, 1979)

BMD Model Output for Figure C-12:

```
=================================================================
        Multistage Model. (Version: 3.4;  Date: 05/02/2014)
        Input Data File:
C:/Users/JSWART/Desktop/BMDS/BMDS26/Data/msc_Fukuda_malignant_lynphoma_Opt.(d)
        Gnuplot Plotting File:
C:/Users/JSWART/Desktop/BMDS/BMDS26/Data/msc_Fukuda_malignant_lynphoma_Opt.plt
                                          Wed Mar 27 14:05:55 2019
 =================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive
```

```
  Dependent variable = Effect
  Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                    Background =   0.00968251
                       Beta(1) =            0
                       Beta(2) =     0.143174


          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 )

            Background      Beta(2)

Background            1        -0.17

   Beta(2)        -0.17            1



                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background        0.0161135        0.0115327         -0.00649009
0.0387171
        Beta(1)                0              NA
        Beta(2)         0.117586        0.0595605         0.000849759
0.234323

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



                      Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -21.8838         6
   Fitted model        -24.4176         2       5.06757      4          0.2804
  Reduced model        -28.5682         1       13.3686      5         0.02016

          AIC:         52.8353
```

```
                                Goodness  of  Fit
                                                                    Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
    0.0000     0.0161         0.419     1.000      26.000        0.905
    0.0280     0.0162         0.356     0.000      22.000       -0.602
    0.0720     0.0167         0.468     1.000      28.000        0.784
    0.1800     0.0199         0.437     0.000      22.000       -0.668
    0.4400     0.0383         1.109     0.000      29.000       -1.074
    1.1000     0.1466         4.251     5.000      29.000        0.393

 Chi^2 = 3.55      d.f. = 4        P-value = 0.4703


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =       0.946587

             BMDL =       0.657968

             BMDU =        1.65402

Taken together, (0.657968, 1.65402) is a 90     % two-sided confidence
interval for the BMD

Cancer Slope Factor =      0.151983
```

Forestomach Carcinoma In Situ in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks

The modeling procedure described above for cancer incidence data was applied to the incidence data for forestomach carcinoma in situ in female ICR mice treated with *p*-α,α,α-tetrachlorotoluene by gavage twice per week for 17.5 weeks (Fukuda et al., 1980, 1979). The data are shown in Table A-8 in the "Derivation of Provisional Cancer Potency Values" section in Appendix A. Table C-16 summarizes the BMD modeling results. The 1-degree Multistage model provided adequate fit to the data. The higher degree polynomial models took the form of the 1-degree model. Figure C-13 shows the fit of the 1-degree Multistage model to the data. Based on HEDs, the BMD_{10} and $BMDL_{10}$ for forestomach carcinoma in situ in female mice were 0.640 and 0.376 mg/kg-day, respectively.

Table C-16. BMD Modeling Results for Forestomach Carcinoma In Situ in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks[a]

Model	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{10} (HED) (mg/kg-d)	$BMDL_{10}$ (HED) (mg/kg-d)
Multistage (1-degree)[c, d]	**0.62**	**1.44**	**56.29**	**0.640**	**0.376**
Multistage (2-degree)[c]	0.62	1.44	56.29	0.640	0.376
Multistage (3-degree)[c]	0.62	1.44	56.29	0.640	0.376
Multistage (4-degree)[c]	0.62	1.44	56.29	0.640	0.376
Multistage (5-degree)[c]	0.62	1.44	56.29	0.640	0.376

[a]Fukuda et al. (1980); Fukuda et al. (1979).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Coefficients restricted to be positive.
[d]Selected model; all higher-order dose coefficients are zero.

AIC = Akaike's information criterion; BMD = benchmark dose (i.e., maximum likelihood estimates of the dose associated with the selected BMR); BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; HED = human equivalent dose.

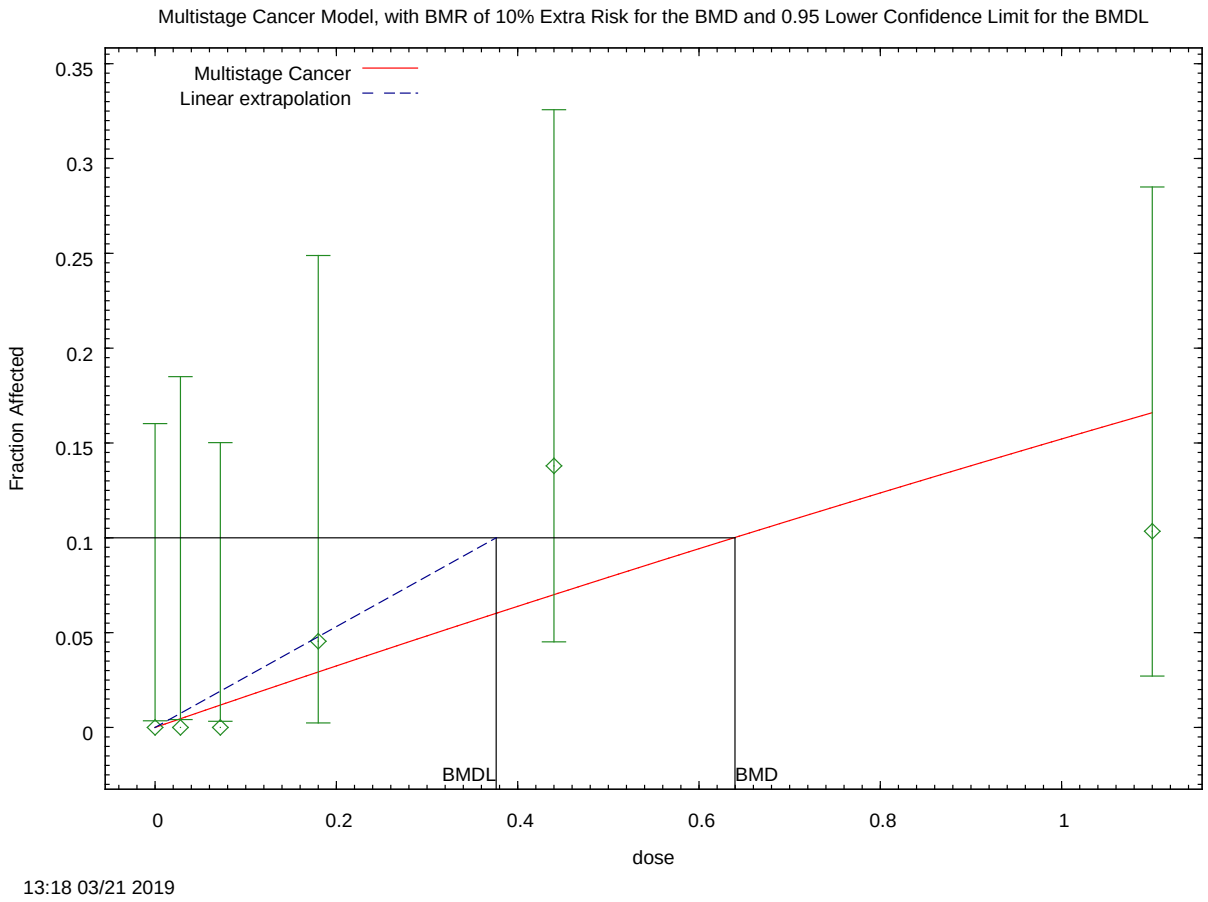


Figure C-13. Fit of the Multistage (1-Degree) Model to Data for Forestomach Carcinoma In Situ in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks (Fukuda et al., 1980, 1979)

BMD Model Output for Figure C-13:

```
================================================================
        Multistage Model. (Version: 3.4;  Date: 05/02/2014)
        Input Data File:
C:/Users/JSWART/Desktop/BMDS/BMDS26/Data/msc_Fukuda_forestomach_carcinoma_in_situ_Opt.
(d)
        Gnuplot Plotting File:
C:/Users/JSWART/Desktop/BMDS/BMDS26/Data/msc_Fukuda_forestomach_carcinoma_in_situ_Opt.
plt
                                              Thu Mar 21 13:18:06 2019
 ================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive
```

```
  Dependent variable = Effect
  Independent variable = Dose

Total number of observations = 6
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1


Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                    Background =    0.0159495
                       Beta(1) =     0.114105


          Asymptotic Correlation Matrix of Parameter Estimates

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

               Beta(1)

   Beta(1)            1



                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0               NA
        Beta(1)         0.164707        0.0582692           0.0505014
0.278912

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



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -25.3477         6
   Fitted model         -27.1465         1       3.59761      5          0.6087
  Reduced model         -31.5546         1       12.4138      5         0.02954

          AIC:          56.293


                                Goodness  of  Fit
                                                      Scaled
```

```
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000      26.000        0.000
    0.0280     0.0046         0.101     0.000      22.000       -0.319
    0.0720     0.0118         0.330     0.000      28.000       -0.578
    0.1800     0.0292         0.643     1.000      22.000        0.452
    0.4400     0.0699         2.027     4.000      29.000        1.437
    1.1000     0.1657         4.806     3.000      29.000       -0.902

 Chi^2 = 3.52      d.f. = 5        P-value = 0.6208


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =       0.639685

             BMDL =       0.376269

             BMDU =        1.33515

Taken together, (0.376269, 1.33515) is a 90     % two-sided confidence
interval for the BMD

Cancer Slope Factor =      0.265768
```

Forestomach Squamous Cell Carcinoma in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks

The modeling procedure described above for cancer incidence data was applied to the incidence data for forestomach squamous cell carcinoma in female ICR mice treated with *p*-α,α,α-tetrachlorotoluene by gavage twice per week for 17.5 weeks (Fukuda et al., 1980, 1979). The data are shown in Table A-8 in the "Derivation of Provisional Cancer Potency Values" section in Appendix A. Table C-17 summarizes the BMD modeling results. The 1-degree Multistage model provided adequate fit to the data. The higher degree polynomial models took the form of the 1-degree model. Figure C-14 shows the fit of the 1-degree Multistage model to the data. Based on HEDs, the BMD_{10} and $BMDL_{10}$ for forestomach squamous cell carcinoma in female mice were 0.372 and 0.243 mg/kg-day, respectively.

Table C-17. BMD Modeling Results for Forestomach Squamous Cell Carcinoma in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks[a]

Model	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{10} (HED) (mg/kg-d)	$BMDL_{10}$ (HED) (mg/kg-d)
Multistage (1-degree)[c, d]	**0.51**	**1.50**	**69.36**	**0.372**	**0.243**
Multistage (2-degree)[c]	0.51	1.50	69.36	0.372	0.243
Multistage (3-degree)[c]	0.51	1.50	69.36	0.372	0.243
Multistage (4-degree)[c]	0.51	1.50	69.36	0.372	0.243
Multistage (5-degree)[c]	0.51	1.50	69.36	0.372	0.243

[a]Fukuda et al. (1980); Fukuda et al. (1979).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Coefficients restricted to be positive.
[d]Selected model; all higher-order dose coefficients are zero.

AIC = Akaike's information criterion; BMD = benchmark dose (i.e., maximum likelihood estimates of the dose associated with the selected BMR); BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; HED = human equivalent dose.

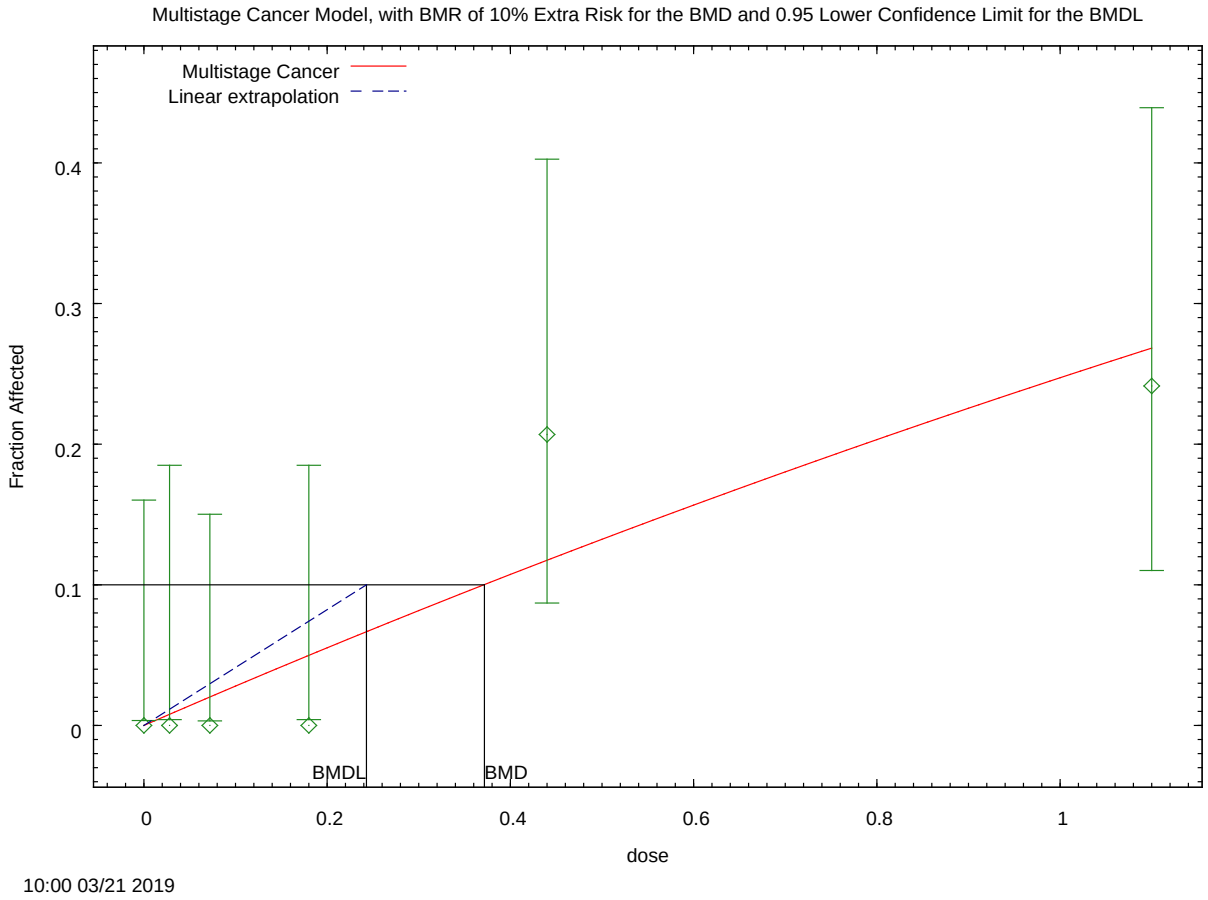


Figure C-14. Fit of the Multistage (1-Degree) Model to Data for Forestomach Squamous Cell Carcinoma in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks (Fukuda et al., 1980, 1979)

BMD Model Output for Figure C-14:

```
================================================================
        Multistage Model. (Version: 3.4;  Date: 05/02/2014)
        Input Data File:
C:/Users/JSWART/Desktop/BMDS/BMDS26/Data/msc_Fukuda_forestomach_squamous_cell_carcinom
a_Opt.(d)
        Gnuplot Plotting File:
C:/Users/JSWART/Desktop/BMDS/BMDS26/Data/msc_Fukuda_forestomach_squamous_cell_carcinom
a_Opt.plt
                                          Thu Mar 21 10:22:18 2019
 ================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive
```

```
  Dependent variable = Effect
  Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                    Background =            0
                       Beta(1) =     0.282909


          Asymptotic Correlation Matrix of Parameter Estimates

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

               Beta(1)

   Beta(1)           1



                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0              NA
        Beta(1)         0.283505         0.078825             0.12901
0.437999

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



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -30.8119         6
   Fitted model        -33.6778         1       5.73172      5          0.3332
  Reduced model        -44.7464         1        27.869      5         <.0001

          AIC:         69.3556


                                Goodness  of  Fit
                                                      Scaled
```

```
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000      26.000        0.000
    0.0280     0.0079         0.174     0.000      22.000       -0.419
    0.0720     0.0202         0.566     0.000      28.000       -0.760
    0.1800     0.0498         1.095     0.000      22.000       -1.073
    0.4400     0.1173         3.401     6.000      29.000        1.500
    1.1000     0.2679         7.769     7.000      29.000       -0.323

 Chi^2 = 4.26      d.f. = 5        P-value = 0.5128


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =       0.371636

             BMDL =       0.242891

             BMDU =       0.609459

Taken together, (0.242891, 0.609459) is a 90     % two-sided confidence
interval for the BMD

Cancer Slope Factor =      0.411707
```

Skin Squamous Cell Carcinoma in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks

The modeling procedure described above for cancer incidence data was applied to the incidence data for skin squamous cell carcinoma in female ICR mice treated with *p*-α,α,α-tetrachlorotoluene by gavage twice per week for 17.5 weeks (Fukuda et al., 1980, 1979). The data are shown in Table A-8 in the "Derivation of Provisional Cancer Potency Values" section in Appendix A. Table C-18 summarizes the BMD modeling results. All models provided adequate fit to the data. The model with the lowest AIC was selected (4-degree Multistage). Figure C-15 shows the fit of the 4-degree Multistage model to the data. Based on HEDs, the BMD_{10} and $BMDL_{10}$ for skin squamous cell carcinoma in female mice were 0.957 and 0.721 mg/kg-day, respectively.

Table C-18. BMD Modeling Results for Skin Squamous Cell Carcinoma in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks[a]

Model	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{10} (HED) (mg/kg-d)	$BMDL_{10}$ (HED) (mg/kg-d)
Multistage (1-degree)[c]	0.65	1.13	37.76	1.02	0.530
Multistage (2-degree)[c]	0.96	0.45	30.51	0.900	0.649
Multistage (3-degree)[c]	1.00	0.16	29.38	0.927	0.696
Multistage (4-degree)[c, d]	**1.00**	**0.06**	**28.95**	**0.957**	**0.721**

[a]Fukuda et al. (1980); Fukuda et al. (1979).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Coefficients restricted to be positive.
[d]Selected model, based on lowest AIC for models with all dose coefficients >0.

AIC = Akaike's information criterion; BMD = benchmark dose (i.e., maximum likelihood estimates of the dose associated with the selected BMR); BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; HED = human equivalent dose.

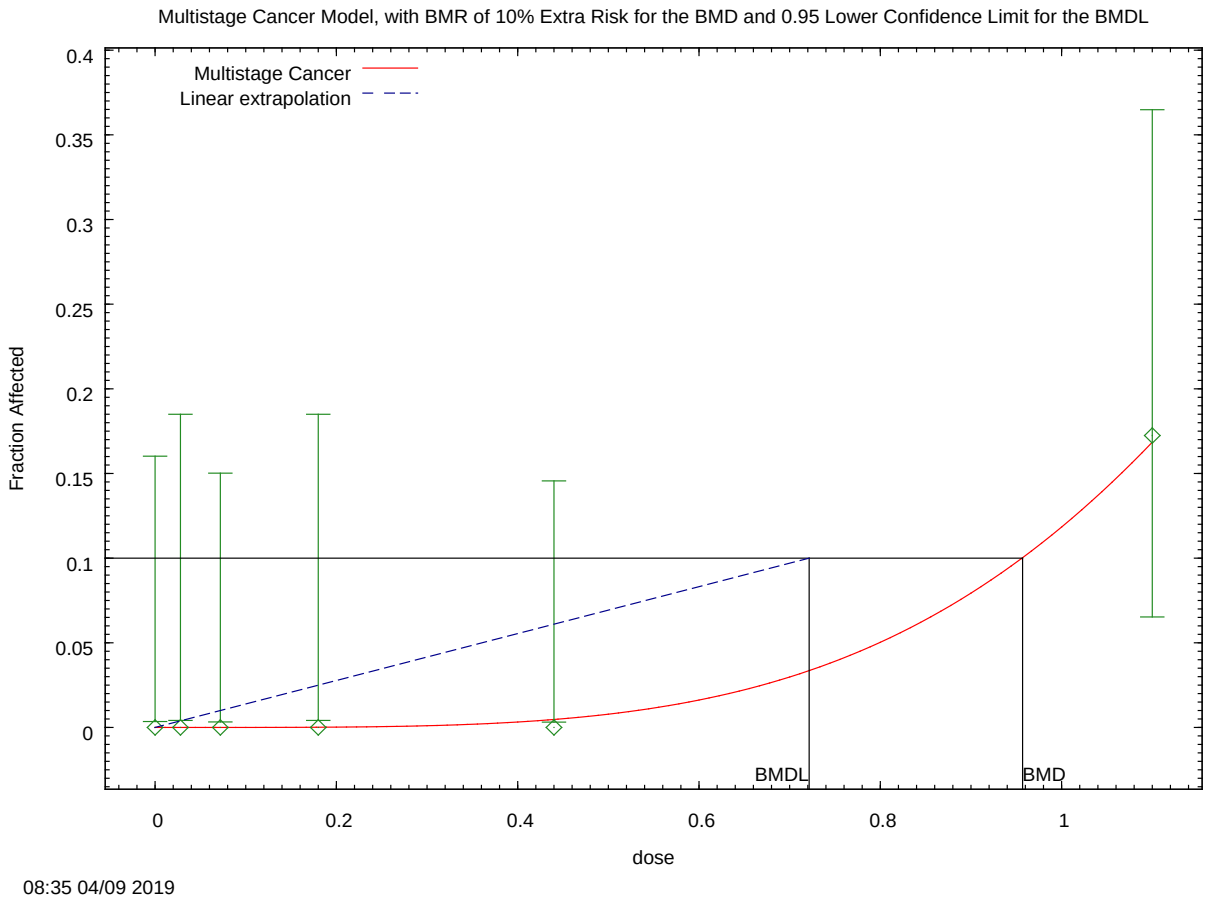


Figure C-15. Fit of the Multistage (4-Degree) Model to Data for Skin Squamous Cell Carcinoma in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks (Fukuda et al., 1980, 1979)

BMD Model Output for Figure C-15:

```
================================================================
        Multistage Model. (Version: 3.4;  Date: 05/02/2014)
        Input Data File:
C:/Users/JSWART/Desktop/BMDS/BMDS26/Data/msc_Fukuda_skin_squamous_cell_carcinoma_Opt.(
d)
        Gnuplot Plotting File:
C:/Users/JSWART/Desktop/BMDS/BMDS26/Data/msc_Fukuda_skin_squamous_cell_carcinoma_Opt.p
lt
                                                Wed Mar 27 14:11:28 2019
 ================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive
```

```
   Dependent variable = Effect
   Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =     0.158724


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                Beta(2)

   Beta(2)            1



                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0              NA
        Beta(1)                0              NA
        Beta(2)         0.129953       0.0581768           0.0159289
0.243978

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



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -13.3311         6
   Fitted model        -14.2549         1        1.8477      5          0.8698
  Reduced model        -22.1211         1         17.58      5        0.003522

           AIC:         30.5099
```

```
                                Goodness  of  Fit
                                                                    Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000      26.000        0.000
    0.0280     0.0001         0.002     0.000      22.000       -0.047
    0.0720     0.0007         0.019     0.000      28.000       -0.137
    0.1800     0.0042         0.092     0.000      22.000       -0.305
    0.4400     0.0248         0.721     0.000      29.000       -0.860
    1.1000     0.1455         4.220     5.000      29.000        0.411

 Chi^2 = 1.02      d.f. = 5        P-value = 0.9608


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        0.90042

             BMDL =         0.6485

             BMDU =        1.36941

Taken together, (0.6485 , 1.36941) is a 90     % two-sided confidence
interval for the BMD

Cancer Slope Factor =      0.154202
```

Forestomach Multiple Papillomas in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks

The modeling procedure described above for cancer incidence data was applied to the incidence data for forestomach multiple papillomas in female ICR mice treated with *p*-α,α,α-tetrachlorotoluene by gavage twice per week for 17.5 weeks (Fukuda et al., 1980, 1979). The data are shown in Table A-8 in the "Derivation of Provisional Cancer Potency Values" section in Appendix A. Table C-19 summarizes the BMD modeling results. No models provided an adequate fit to the data with the highest two doses included, at which the incidence was reduced. After dropping the highest two dose groups, the 1-degree Multistage model provided adequate fit to the data. The higher degree polynomial models took the form of the 1-degree model. Figure C-16 shows the fit of the 1-degree Multistage model to the data. Based on HEDs, the BMD_{10} and $BMDL_{10}$ for forestomach multiple papillomas in female mice were 0.0569 and 0.0359 mg/kg-day, respectively.

Table C-19. BMD Modeling Results for Forestomach Multiple Papillomas in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks[a]

Model	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{10} (HED) (mg/kg-d)	$BMDL_{10}$ (HED) (mg/kg-d)
Multistage (1-degree)[c, d]	**0.76**	**0.29**	**63.00**	**0.0569**	**0.0359**
Multistage (2-degree)[c]	0.76	0.29	63.00	0.0569	0.0359
Multistage (3-degree)[c]	0.76	0.29	63.00	0.0569	0.0359

[a]Fukuda et al. (1980); Fukuda et al. (1979).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Coefficients restricted to be positive.
[d]Selected model; all higher degree coefficients are zero.

AIC = Akaike's information criterion; BMD = benchmark dose (i.e., maximum likelihood estimates of the dose associated with the selected BMR); BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; HED = human equivalent dose.

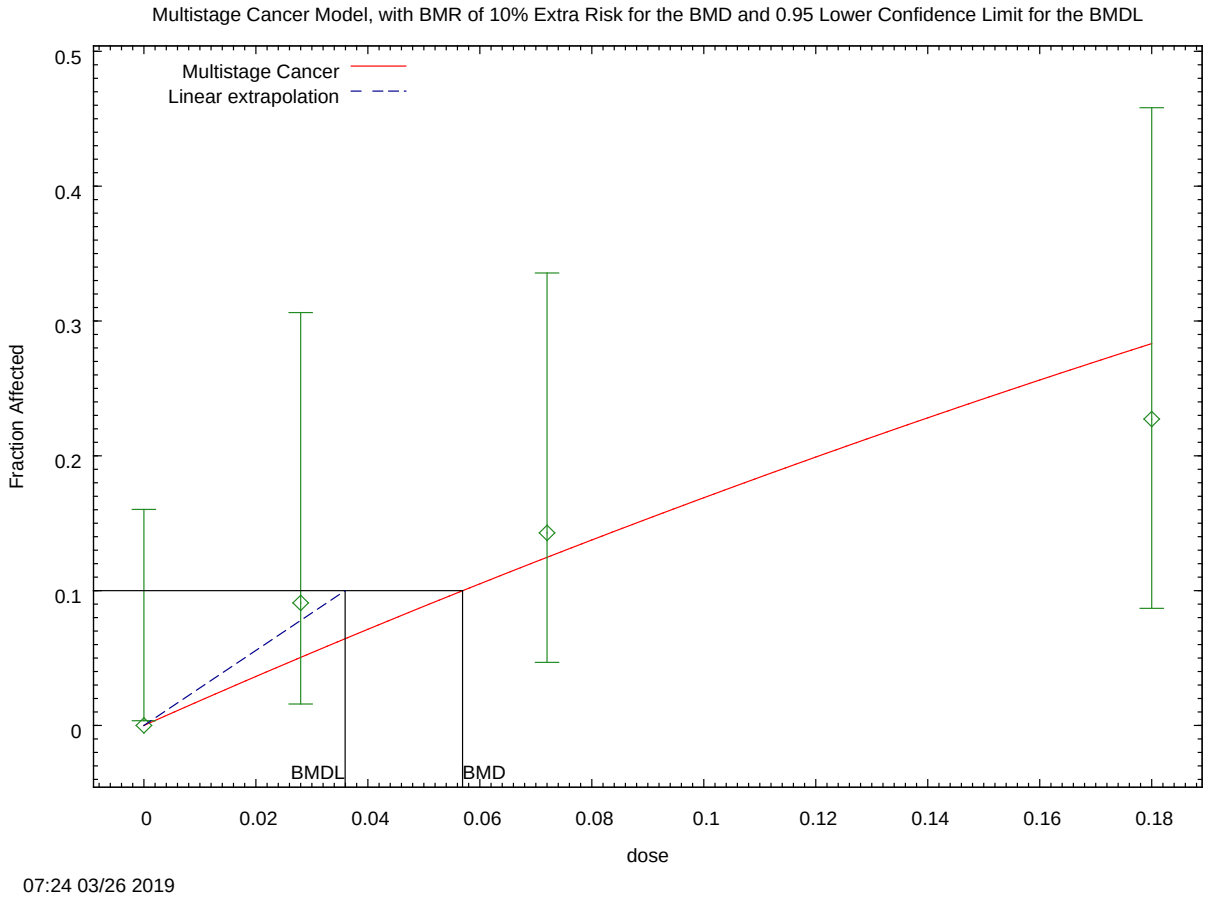


Figure C-16. Fit of the Multistage (1-Degree) Model to Data for Forestomach Multiple Papillomas in Female ICR Mice Orally Exposed to *p*-α,α,α-Tetrachlorotoluene for 17.5 Weeks (Fukuda et al., 1980, 1979)

BMD Model Output for Figure C-16:

```
=================================================================
        Multistage Model. (Version: 3.4;  Date: 05/02/2014)
        Input Data File:
C:/Users/JSWART/Desktop/BMDS/BMDS26/Data/msc_Fukuda_forestomach_multiple_papilloma_Opt
.(d)
        Gnuplot Plotting File:
C:/Users/JSWART/Desktop/BMDS/BMDS26/Data/msc_Fukuda_forestomach_multiple_papilloma_Opt
.plt
                                          Tue Mar 26 07:25:16 2019
 =================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive
```

```
  Dependent variable = Effect
  Independent variable = Dose

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1


Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                    Background =    0.0342233
                       Beta(1) =      1.31428


          Asymptotic Correlation Matrix of Parameter Estimates

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

               Beta(1)

   Beta(1)            1



                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0               NA
        Beta(1)          1.85135         0.559537            0.754678
2.94802

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



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -29.9764         4
   Fitted model         -30.5006         1       1.04855      3          0.7895
  Reduced model          -34.416         1       8.87918      3         0.03094

          AIC:         63.0013


                                Goodness  of  Fit
                                                      Scaled
```

```
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000      26.000        0.000
    0.0280     0.0505         1.111     2.000      22.000        0.865
    0.0720     0.1248         3.494     4.000      28.000        0.289
    0.1800     0.2834         6.235     5.000      22.000       -0.584

 Chi^2 = 1.17      d.f. = 3        P-value = 0.7594


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =      0.0569101

            BMDL =      0.0359441

            BMDU =       0.138961

Taken together, (0.0359441, 0.138961) is a 90     % two-sided confidence
interval for the BMD

Cancer Slope Factor =        2.7821
```

Screening p-OSF POD Selection Model: BMD Model Output for MS_Combo Model of All Tumors in Female ICR Mice Orally Exposed to p-α,α,α-Tetrachlorotoluene for 17.5 Weeks

```
================================================================
         MS_COMBO. (Version: 1.9;  Date: 05/20/2014)
         Input Data File:
C:\Users\JSWART\Desktop\BMDS\BMDS26\Data\SessionFiles\Fukuda_8_ms5.(d)
         Gnuplot Plotting File:
C:\Users\JSWART\Desktop\BMDS\BMDS26\Data\SessionFiles\Fukuda_8_ms5.plt
                                          Wed Mar 27 14:02:35 2019
 ================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose
   Data file name = Fukuda_lung_adenocarcinoma.dax

 Total number of observations = 5
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1
```

```
 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                     Background =     0.121569
                        Beta(1) =      1.55634


          Asymptotic Correlation Matrix of Parameter Estimates

            Background      Beta(1)

Background            1         -0.7

   Beta(1)         -0.7            1


                               Parameter Estimates

                                                     95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background        0.0276432            *                *                   *
        Beta(1)          2.24652            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -59.7504         5
   Fitted model        -62.6831         2       5.86545      3          0.1183
  Reduced model          -74.77         1       30.0393      4         <.0001

           AIC:         129.366

 Log-likelihood Constant             52.870081256733542


                               Goodness  of  Fit
                                                                    Scaled
    Dose     Est._Prob.    Expected    Observed     Size        Residual
  ----------------------------------------------------------------------
    0.0000     0.0276         0.719     0.000      26.000       -0.860
    0.0280     0.0869         1.912     3.000      22.000        0.823
    0.0720     0.1729         4.840     7.000      28.000        1.079
    0.1800     0.3511         7.723    10.000      22.000        1.017
    0.4400     0.6381        18.506    15.000      29.000       -1.355

 Chi^2 = 5.45      d.f. = 3        P-value = 0.1415


   Benchmark Dose Computation

Specified effect =           0.1
```

```
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =      0.0468995

            BMDL =      0.0330362

            BMDU =      0.0764043

Taken together, (0.0330362, 0.0764043) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =       3.02698



 ======================================================================
        MS_COMBO. (Version: 1.9;  Date: 05/20/2014)
        Input Data File:
C:\Users\JSWART\Desktop\BMDS\BMDS26\Data\SessionFiles\Fukuda_8_ms5.(d)
        Gnuplot Plotting File:
C:\Users\JSWART\Desktop\BMDS\BMDS26\Data\SessionFiles\Fukuda_8_ms5.plt
                                                Wed Mar 27 14:02:35 2019
 ======================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose
   Data file name = Fukuda_lung_mulitple_adenoma.dax

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0667116
                        Beta(1) =     0.758435


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)
```

```
Background            1        -0.59

   Beta(1)        -0.59            1


                              Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background        0.0428386            *                *                  *
        Beta(1)         0.829035            *                *                  *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -66.4952         6
   Fitted model        -68.1064         2       3.22244      4          0.5213
  Reduced model        -85.4579         1       37.9254      5         <.0001

           AIC:         140.213

 Log-likelihood Constant            57.830282020725626


                                 Goodness  of  Fit
                                                                      Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.0428         1.114     1.000      26.000       -0.110
    0.0280     0.0648         1.426     2.000      22.000        0.497
    0.0720     0.0983         2.752     1.000      28.000       -1.112
    0.1800     0.1755         3.862     6.000      22.000        1.198
    0.4400     0.3354         9.726    10.000      29.000        0.108
    1.1000     0.6155        17.848    17.000      29.000       -0.324

 Chi^2 = 3.05      d.f. = 4        P-value = 0.5495


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =       0.127088

            BMDL =      0.0920397

            BMDU =       0.189035

Taken together, (0.0920397, 0.189035) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =       1.08649
```

```
 ================================================================
        MS_COMBO. (Version: 1.9;  Date: 05/20/2014)
        Input Data File:
C:\Users\JSWART\Desktop\BMDS\BMDS26\Data\SessionFiles\Fukuda_8_ms5.(d)
        Gnuplot Plotting File:
C:\Users\JSWART\Desktop\BMDS\BMDS26\Data\SessionFiles\Fukuda_8_ms5.plt
                                              Wed Mar 27 14:02:35 2019
 ================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose
   Data file name = Fukuda_malignant_lynphoma.dax

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =   0.00968251
                        Beta(1) =            0
                        Beta(2) =     0.143174


           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 )

             Background      Beta(2)

Background            1        -0.45

   Beta(2)        -0.45            1



                               Parameter Estimates

                                                       95.0% Wald Confidence
Interval
```

Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
Background	0.0161135	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0.117586	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-21.8838	6			
Fitted model	-24.4176	2	5.06757	4	0.2804
Reduced model	-28.5682	1	13.3686	5	0.02016

AIC: 52.8353

Log-likelihood Constant 18.275118874470813

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0161	0.419	1.000	26.000	0.905
0.0280	0.0162	0.356	0.000	22.000	-0.602
0.0720	0.0167	0.468	1.000	28.000	0.784
0.1800	0.0199	0.437	0.000	22.000	-0.668
0.4400	0.0383	1.109	0.000	29.000	-1.074
1.1000	0.1466	4.251	5.000	29.000	0.393

Chi^2 = 3.55 d.f. = 4 P-value = 0.4703

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.946587

BMDL = 0.657968

BMDU = 1.65402

Taken together, (0.657968, 1.65402) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.151983

==========

MS_COMBO. (Version: 1.9; Date: 05/20/2014)
Input Data File:
C:\Users\JSWART\Desktop\BMDS\BMDS26\Data\SessionFiles\Fukuda_8_ms5.(d)
Gnuplot Plotting File:
C:\Users\JSWART\Desktop\BMDS\BMDS26\Data\SessionFiles\Fukuda_8_ms5.plt
Wed Mar 27 14:02:35 2019

```
 ================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose
   Data file name = Fukuda_thymoma.dax

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =      0.31175


           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(1)

   Beta(1)            1



                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0            *                *                   *
        Beta(1)          0.26233            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
```

```
     Full model        -28.7156         6
   Fitted model        -30.6091         1       3.78712      5          0.5805
  Reduced model        -42.3055         1       27.1799      5         <.0001

           AIC:         63.2183

 Log-likelihood Constant             25.347677079785861


                                 Goodness  of  Fit
                                                                      Scaled
    Dose      Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000      26.000        0.000
    0.0280     0.0073         0.161     0.000      22.000       -0.403
    0.0720     0.0187         0.524     0.000      28.000       -0.731
    0.1800     0.0461         1.015     0.000      22.000       -1.031
    0.4400     0.1090         3.161     4.000      29.000        0.500
    1.1000     0.2507         7.269     8.000      29.000        0.313

 Chi^2 = 2.11      d.f. = 5        P-value = 0.8341


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =       0.401633

             BMDL =       0.258298

             BMDU =       0.673248

Taken together, (0.258298, 0.673248) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =       0.38715



 ======================================================================
         MS_COMBO. (Version: 1.9;  Date: 05/20/2014)
         Input Data File:
C:\Users\JSWART\Desktop\BMDS\BMDS26\Data\SessionFiles\Fukuda_8_ms5.(d)
         Gnuplot Plotting File:
C:\Users\JSWART\Desktop\BMDS\BMDS26\Data\SessionFiles\Fukuda_8_ms5.plt
                                            Wed Mar 27 14:02:35 2019
 ======================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive
```

```
  Dependent variable = Effect
  Independent variable = Dose
  Data file name = Fukuda_forestomach_squamous_cell_carcinoma.dax

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                    Background =            0
                       Beta(1) =     0.282909


          Asymptotic Correlation Matrix of Parameter Estimates

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

               Beta(1)

   Beta(1)           1



                               Parameter Estimates

                                                      95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0           *               *                   *
        Beta(1)         0.283505           *               *                   *

* - Indicates that this value is not calculated.



                       Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -30.8119         6
   Fitted model        -33.6778         1       5.73172      5          0.3332
  Reduced model        -44.7464         1        27.869      5         <.0001

          AIC:         69.3556

 Log-likelihood Constant             27.33180844166138


                                Goodness  of  Fit
                                                                  Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
```

```
    0.0000     0.0000         0.000     0.000      26.000        0.000
    0.0280     0.0079         0.174     0.000      22.000       -0.419
    0.0720     0.0202         0.566     0.000      28.000       -0.760
    0.1800     0.0498         1.095     0.000      22.000       -1.073
    0.4400     0.1173         3.401     6.000      29.000        1.500
    1.1000     0.2679         7.769     7.000      29.000       -0.323

 Chi^2 = 4.26      d.f. = 5        P-value = 0.5128


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.371636

            BMDL =       0.242891

            BMDU =       0.609459

Taken together, (0.242891, 0.609459) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =      0.411707



 ======================================================================
        MS_COMBO. (Version: 1.9;  Date: 05/20/2014)
        Input Data File:
C:\Users\JSWART\Desktop\BMDS\BMDS26\Data\SessionFiles\Fukuda_8_ms5.(d)
        Gnuplot Plotting File:
C:\Users\JSWART\Desktop\BMDS\BMDS26\Data\SessionFiles\Fukuda_8_ms5.plt
                                                Wed Mar 27 14:02:35 2019
 ======================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose
   Data file name = Fukuda_forestomach_carcinoma_in_situ.dax

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
```

```
 Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                     Background =    0.0159495
                        Beta(1) =     0.114105


           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(1)

   Beta(1)            1


                               Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0            *                *                   *
        Beta(1)         0.164707            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -25.3477         6
   Fitted model        -27.1465         1       3.59761      5          0.6087
  Reduced model        -31.5546         1       12.4138      5         0.02954

           AIC:          56.293

 Log-likelihood Constant            21.370000104136281


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
  ---------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000      26.000         0.000
    0.0280     0.0046         0.101     0.000      22.000        -0.319
    0.0720     0.0118         0.330     0.000      28.000        -0.578
    0.1800     0.0292         0.643     1.000      22.000         0.452
    0.4400     0.0699         2.027     4.000      29.000         1.437
    1.1000     0.1657         4.806     3.000      29.000        -0.902

 Chi^2 = 3.52      d.f. = 5        P-value = 0.6208


   Benchmark Dose Computation

Specified effect =           0.1
```

```
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.639685

            BMDL =       0.376269

            BMDU =        1.33515

Taken together, (0.376269, 1.33515) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =      0.265768



 ======================================================================
        MS_COMBO. (Version: 1.9;  Date: 05/20/2014)
        Input Data File:
C:\Users\JSWART\Desktop\BMDS\BMDS26\Data\SessionFiles\Fukuda_8_ms5.(d)
        Gnuplot Plotting File:
C:\Users\JSWART\Desktop\BMDS\BMDS26\Data\SessionFiles\Fukuda_8_ms5.plt
                                                Wed Mar 27 14:02:35 2019
 ======================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose
   Data file name = Fukuda_forestomach_multiple_papilloma.dax

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0342233
                        Beta(1) =      1.31428


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
```

```
                have been estimated at a boundary point, or have been specified by
the user,
                and do not appear in the correlation matrix )

               Beta(1)

   Beta(1)            1


                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0            *                *                   *
        Beta(1)          1.85135            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -29.9764         4
   Fitted model         -30.5006         1       1.04855      3          0.7895
  Reduced model          -34.416         1       8.87918      3         0.03094

           AIC:         63.0013

 Log-likelihood Constant            25.547993778159679


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000      26.000        0.000
    0.0280     0.0505         1.111     2.000      22.000        0.865
    0.0720     0.1248         3.494     4.000      28.000        0.289
    0.1800     0.2834         6.235     5.000      22.000       -0.584

 Chi^2 = 1.17      d.f. = 3        P-value = 0.7594


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =      0.0569101

            BMDL =      0.0359441

            BMDU =       0.138961

Taken together, (0.0359441, 0.138961) is a 90     % two-sided confidence
interval for the BMD
```

```
Multistage Cancer Slope Factor =        2.7821



 ================================================================
        MS_COMBO. (Version: 1.9;  Date: 05/20/2014)
        Input Data File:
C:\Users\JSWART\Desktop\BMDS\BMDS26\Data\SessionFiles\Fukuda_8_ms5.(d)
        Gnuplot Plotting File:
C:\Users\JSWART\Desktop\BMDS\BMDS26\Data\SessionFiles\Fukuda_8_ms5.plt
                                              Wed Mar 27 14:02:35 2019
 ================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose
   Data file name = Fukuda_skin_squamous_cell_carcinoma.dax

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =     0.158724


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                Beta(2)

   Beta(2)           1



                                Parameter Estimates

                                                      95.0% Wald Confidence
Interval
```

Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0.129953	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-13.3311	6			
Fitted model	-14.2549	1	1.8477	5	0.8698
Reduced model	-22.1211	1	17.58	5	0.003522

AIC: 30.5099

Log-likelihood Constant 11.684817826274118

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	26.000	0.000
0.0280	0.0001	0.002	0.000	22.000	-0.047
0.0720	0.0007	0.019	0.000	28.000	-0.137
0.1800	0.0042	0.092	0.000	22.000	-0.305
0.4400	0.0248	0.721	0.000	29.000	-0.860
1.1000	0.1455	4.220	5.000	29.000	0.411

Chi^2 = 1.02 d.f. = 5 P-value = 0.9608

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.90042

BMDL = 0.6485

BMDU = 1.36941

Taken together, (0.6485 , 1.36941) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.154202

**** Start of combined BMD and BMDL Calculations.****

Combined Log-Likelihood -291.39612823909221

Combined Log-likelihood Constant 240.2577793819473

```
   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =      0.0186741

            BMDL =      0.0148245

Multistage Cancer Slope Factor =       6.74558
```

APPENDIX D. REFERENCES

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