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Provisional Peer-Reviewed Toxicity Values for

p-Toluic Acid
(CASRN 99-94-5)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGER

Jon Reid, PhD, DABT
National Center for Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY

SRC, Inc.
7502 Round Pond Road
North Syracuse, NY 13212

PRIMARY INTERNAL REVIEWERS

Dan Petersen, PhD, DABT
National Center for Environmental Assessment, Cincinnati, OH

Suryanarayana V. Vulimiri, PhD
National Center for Environmental Assessment, Research Triangle Park, NC

This document was externally peer reviewed under contract to:

Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421-3136

Questions regarding the content of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

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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
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
NCEA	National Center for Environmental Assessment
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*-TOLUIC ACID (CASRN 99-94-5)

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 National Center for Environment Assessment (NCEA) 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.

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. Environmental Protection Agency (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 EPA Office of Research and Development's (ORD's) NCEA, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

p-Toluic acid, CASRN 99-94-5, is also known as crithminic acid, 4-methylbenzoic acid, *p*-carboxytoluene, *p*-methylbenzoic acid, *p*-toluylic acid, *p*-tolylcarboxylic acid, and 4-toluic acid. This compound belongs to the class of compounds known as carboxylic acids. It is used as an intermediate for antibiotic pharmaceuticals, photosensitive pigments, fluorescent dyes, and colorants (Maki and Takeda, 2012; OECD, 2008a). *p*-Toluic acid is listed on the U.S. EPA's Toxic Substances Control Act's public inventory (U.S. EPA, 2015), and was assessed under the joint U.S. EPA high production volume (HPV) chemical and Organisation for Economic Co-operation and Development Screening Information Data Set (OECD SIDS) programme (OECD, 2008a). It is not registered with Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) programme (ECHA, 2017).

Commercial production of *p*-toluic acid occurs primarily by the vapor-phase or nitric acid oxidation of *p*-xylene in the presence of a catalyst, such as cobalt naphthenate. It may also be isolated as a byproduct during the manufacture of terephthalic acid from *p*-xylene (Maki and Takeda, 2012; OECD, 2008a).

The empirical formula for *p*-toluic acid is $C_8H_8O_2$ (see Figure 1). Table 1 summarizes the physicochemical properties of *p*-toluic acid. *p*-Toluic acid is a white to yellow-brown crystalline solid at room temperature (OECD, 2008a). The acid dissociation constant (pKa) of *p*-toluic acid is 4.22, indicating that it will exist predominantly as an anion in the environment. *p*-Toluic acid's low vapor pressure indicates that it will exist in both the vapor and particulate phases in the atmosphere. The estimated half-life of vapor-phase *p*-toluic acid in air by reaction with photochemically produced hydroxyl radicals is 4.2 days. *p*-Toluic acid's low vapor pressure indicates that it is not likely to volatilize from dry soil surfaces. Volatilization is not expected from moist soil or water because this compound exists as an anion. The moderate water solubility and low soil adsorption coefficient for *p*-toluic acid indicate that it may leach to groundwater or undergo runoff after a rain event. *p*-Toluic acid may also undergo ready biodegradation in the environment, based on screening tests (OECD, 2008a).

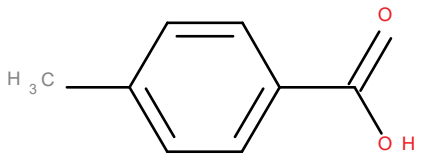

Figure 1. *p*-Toluic Acid Structure

Table 1. Physicochemical Properties of *p*-Toluic Acid (CASRN 99-94-5)

Property (unit)	Value
Physical state	Solid
Boiling point (°C)	273.9[a]
Melting point (°C)	179.6[b]
Density (g/cm^3 at 20°C)	1.23[c]
Vapor pressure (mm Hg at 25°C)	5.08×10^{-5} (extrapolated)[b]
pH (unitless)	3.6[a]
pKa (unitless)	4.22[a]
Solubility in water (mg/L at 25°C)	340[b]
Octanol-water partition coefficient (log K_{ow})	2.27[b]
Henry's law constant (atm-m^3/mol at 25°C)	1.2×10^{-7} (estimated)[b]
Soil adsorption coefficient K_{oc} (L/kg)	27 (estimated)[b]
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	2.5×10^{-12} (estimated)[b]
Atmospheric half-life (d)	4.2 (estimated)[b]
Relative vapor density (air = 1)	NA
Molecular weight (g/mol)	136[b]
Flash point (°C)	181[c]

[a]OECD (2008a).
[b]U.S. EPA (2012c).
[c]Maki and Takeda (2012).

NA = not applicable.

No toxicity values for *p*-toluic acid from EPA or other agencies/organizations were located (see Table 2).

Table 2. Summary of Available Toxicity Values for *p*-Toluic Acid (CASRN 99-94-5)

Source[a]	Value	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2017)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
ATSDR	NV	NA	ATSDR (2017)
IPCS	NV	NA	IPCS (2017); WHO (2017)
Cal/EPA	NV	NA	Cal/EPA (2014); Cal/EPA (2017a); Cal/EPA (2017b)
OSHA	NV	NA	OSHA (2006); OSHA (2011)
NIOSH	NV	NA	NIOSH (2016)
ACGIH	NV	NA	ACGIH (2016)
Cancer			
IRIS	NV	NA	U.S. EPA (2017)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
NTP	NV	NA	NTP (2014)
IARC	NV	NA	IARC (2017)
Cal/EPA	NV	NA	Cal/EPA (2011); Cal/EPA (2017a); Cal/EPA (2017b)
ACGIH	NV	NA	ACGIH (2016)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; 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.

NA = not applicable; NV = not available.

Non-date-limited literature searches were conducted in December 2015 and updated in August 2017 for studies relevant to the derivation of provisional toxicity values for *p*-toluic acid (CASRN 99-94-5). 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 data: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (Cal/EPA), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), European Chemicals Agency (ECHA), U.S. EPA Health Effects Assessment Summary Tables (HEAST), U.S. EPA HPV, U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Office of Water (OW), U.S. EPA TSCATS2, U.S. EPA TSCATS4/8d/8e/FYI, 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), OECD HPV, OECD International Uniform Chemical Information Database (IUCLID), OECD SIDS, 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*-toluic acid 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.

Table 3A. Summary of Potentially Relevant Noncancer Data for *p*-Toluic Acid (CASRN 99-94-5)							
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	5 M/5 F, S-D Crj:CD(SD) rat, gavage in sodium carboxymethyl-cellulose, 7 d/wk, 28 d; 0, 100, 300, 1,000 mg/kg-d	0, 100, 300, 1,000	Increased AST; decreased RBC counts, Hb, and Hct (end of recovery period)	300	1,000	Shirota et al. (2008)	PR
R/D	**13 M/13 F, S-D Crj:CD(SD) rat, gavage in sodium carboxymethyl-cellulose, ~6 wk (2 wk premating and during mating in both sexes, and continuing thereafter for a total of 42 d in males and throughout gestation and until LD 4 in females); 0, 100, 300, 1,000 mg/kg-d**	**ADD: 0, 100, 300, 1,000**	**Parental males: Decreased absolute and relative epididymis weights; increased incidence of animals with fewer numbers of spermatozoa** **Parental females: Decreased gestational body-weight gain** **R/D: Decreased implantation index; decreased number of pups born; decreased number of live pups on LD 0 and 4**	**300** **100** **100**	**1,000** **300** **300**	**Shirota et al. (2008)**	**PR, PS**

Table 3A. Summary of Potentially Relevant Noncancer Data for *p*-Toluic Acid (CASRN 99-94-5)							
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)							
ND							

[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 animals); and chronic = repeated exposure for >10% lifespan for humans (more than approximately 90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002).
[b]Dosimetry: Doses are presented as an ADD (mg/kg-day) for oral noncancer effects.
[c]Notes: PR = peer reviewed; PS = principal study.

ADD = adjusted daily dose; AST = aspartate aminotransferase; F = female(s); Hb = hemoglobin; Hct = hematocrit; LD = lactation day; LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; RBC = red blood cell; R/D = reproductive/developmental; S-D = Sprague-Dawley.

Table 3B. Summary of Potentially Relevant Cancer Data for *p*-Toluic Acid (CASRN 99-94-5)							
Category	**Number of Male/Female, Strain, Species, Study Type, Study Duration, Reported Doses**	**Dosimetry**	**Critical Effects**	**NOAEL**	**LOAEL**	**Reference (comments)**	**Notes**
Human							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
ND							
Animal							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
ND							

LOAEL = lowest-observed-adverse-effect level; ND = no data; NOAEL = no-observed-adverse-effect level.

HUMAN STUDIES

Oral Exposures

No studies have been identified.

Inhalation Exposures

No studies have been identified.

ANIMAL STUDIES

Oral Exposures

Short-Term-Duration Studies

Shirota et al. (2008)

In a 28-day study, *p*-toluic acid (purity 98.95%) was administered to Sprague-Dawley (S-D) Crj:CD(SD) rats (five/sex/group), daily by gavage (sodium carboxymethyl-cellulose was used as a vehicle) at doses of 0, 100, 300, or 1,000 mg/kg-day. Rats were 5 weeks old at the start of dosing. The control group received the vehicle only. Additional animals (five/sex/group) were included in the control and high-dose groups for assessment of recovery during a 14-day post-treatment observation period. Animals were observed for mortality and clinical signs daily, and detailed clinical observations were recorded weekly. Body weights were measured three times during Week 1 and twice weekly thereafter. Food consumption was determined weekly. A four-item neurobehavioral auditory and visual function assessment (parameters not reported) was performed during Week 4. Urine was collected in a metabolic cage during the final week of the treatment and recovery periods, and evaluated for color, turbidity, sediments, pH, occult blood, protein ketone bodies, urobilinogen, bilirubin, volume, weight, and specific gravity. On the last day of treatment, the animals were fasted for 18−24 hours. Blood was collected for hematological and clinical chemistry measurements on the day following the last day of treatment or recovery. All surviving animals were sacrificed and subjected to a complete gross necropsy. Hematological parameters included red blood cell (RBC) count, hemoglobin (Hb) concentration, hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), leukocyte count, and differential leukocyte (neutrophils, eosinophils, basophils, monocytes, and lymphocytes) counts. Clinical chemistry parameters included total protein (TP), albumin, albumin:globulin (A:G) ratio, blood urea nitrogen (BUN), creatinine, glucose, total cholesterol, triglycerides, total bilirubin, inorganic phosphorus, calcium, sodium, potassium, chloride, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and *gamma*-glutamyl transpeptidase (γ-GTP). Organ weights were determined for the brain, thymus, heart, liver, kidneys, spleen, adrenals, testes, and epididymides of all animals, and relative organ weights were calculated. All weighed organs, as well as the following organs and tissues, were examined microscopically for histopathological abnormalities: spinal cord, lungs, bronchi, stomach, ileum, colon, seminal vesicles, ovaries, uterus, vagina, urinary bladder, thyroid gland, femoral marrow, mesenteric lymph nodes, mandibular lymph nodes, and ischiadic nerves. Statistical analyses included the Fisher's direct probability test, Mann-Whitney U test, χ^2-square test, Student's *t*-test, Aspin-Welch's *t*-test, analysis of variance (ANOVA), Kruskal-Wallis rank test, Bartlett's test, and Dunnett's test.

No deaths were reported. Slight, statistically significant increases in mean food consumption were observed in high-dose females on Days 7−8. Clinical signs during exposure were confined to temporary, postdosing salivation, a common finding in gavage studies, in a few

high-dose animals (incidence was not reported). No treatment-related effects on body-weight gain, absolute and relative organ weights, gross necropsy, or histopathology were observed (data not shown). Hematological changes were restricted to high-dose males and included a statistically significant decrease in the differential eosinophil count at the end of treatment on Day 42 (1% at 0 mg/kg-day and 0% at 1,000 mg/kg-day as percent of leukocytes), and slight, yet statistically significant, decreases relative to controls (−4%) in RBC count, Hb, and Hct at the end of the recovery period (see Table B-1). Changes in blood chemistry parameters included a statistically significant decrease (−11%) in TP concentration and an increase (36%) in AST concentration in high-dose females at the end of treatment (see Table B-1). Changes in urinalysis parameters were observed in mid- and high-dose males and females and included statistically significant decreases in specific gravity (−1% at 300 and 1,000 mg/kg-day) and increases in urinary volume (34% and 53% for males and 11% and 89% for females) at the end of treatment (see Table B-1). At Day 9 of the recovery period, urine volumes were not statistically significant but were increased (33% for males and 38% for females) (see Table B-1). The increase in urine volume was preceded by an increase in water consumption.

A lowest-observed-adverse-effect level (LOAEL) of 1,000 mg/kg-day and a no-observed-adverse-effect level (NOAEL) of 300 mg/kg-day are identified for increased AST levels in female rats.

Reproductive/Developmental Studies

Shirota et al. (2008)

In a reproductive/developmental (R/D) toxicity screening study, groups of 26 S-D Crj:CD(SD) rats (13/sex/group) at 10 weeks of age received daily doses of *p*-toluic acid (purity 98.95%) at 0, 100, 300, or 1,000 mg/kg-day via gavage in sodium carboxymethyl-cellulose for 2 weeks prior to mating. Females continued exposure throughout mating, gestation, and lactation, until Lactation Day (LD) 4; males continued to receive daily gavage exposures throughout mating and postmating, for a total of 42 consecutive days of exposure. Rats were observed daily for survival and clinical signs. Male body weights and food consumption were recorded weekly. Female body weights were recorded weekly until mating and then on Gestation Days (GDs) 0, 7, 14, and 20 and LDs 0 and 4. Food consumption was measured weekly in females until mating and then on GDs 0−1, 7−8, 14−15, and 20−21 and LDs 3−4. The estrous cycle was monitored daily until copulation. Reproductive endpoints evaluated included pairing days until copulation (precoital interval), estrus cycles until copulation; birth, and F1 viability indices; number of corpora lutea, implantation sites, pups born, and live and dead pups; gestation length; sex ratio; and F1 body weight. Live F1 animals were examined daily during the postnatal period for external morphology and general condition. On LD 4, all surviving dams and offspring were weighed and sacrificed. F0 animals were subjected to a complete gross necropsy, and organ weights including testes and epididymides for males were recorded at terminal sacrifice. Histopathology of the reproductive organs was performed at terminal sacrifice of F0 animals and included the testes, epididymides, prostate, seminal vesicles, coagulating glands, ovaries, uterus, and vagina. Pups were examined for external and visceral abnormalities at terminal sacrifice on LD 4. Statistical analyses included the Fisher's direct probability test, Mann-Whitney U test, Student's *t*-test, Aspin-Welch's *t*-test, F-test, ANOVA, Kruskal-Wallis rank test, Bartlett's test, and Dunnett's test. It is not evident whether the data were analyzed on a litter/dam basis. While the study was conducted according to a standard guideline (OECD Test Guideline 421) (OECD, 1995), the version of the test guideline followed in this study did not require that analyses be performed using litter/dam as the

experimental unit of analysis, which is a requirement of the revised version (OECD, 2016) of the test guideline.

No deaths were reported. Food consumption in the females was statistically significantly increased in the 1,000 mg/kg-day group during GDs 14−15, but was significantly decreased during Days 3−4 of lactation (data not shown). In male rats, however, there were no measurable effects on feed intake or body-weight changes. Postdosing salivation was temporarily observed in high-dose animals (incidence not reported), but this is a common finding in gavage studies. It is noted that data from this study used body weights which were split into weekly changes. No effects on body weight or body-weight gain were observed in males. In females, no effects on body weight were observed during the premating or gestation periods (see Table B-2). However, female mean body weights were statistically significantly increased on LD 0 at the mid- and high-dose levels relative to controls (13% for both groups, estimated from Figure 5A of the study report; see Table B-2). On LD 4, no significant treatment-related effects on female mean body weights were observed. Female mean body-weight gains were not significantly different compared to controls during the premating period, but were statistically significantly decreased during GDs 14−20 at the mid- and high doses (−17 and −25%, respectively; estimated from Figure 5B of the study report; see Table B-2) and during LDs 0−4 at the high dose (−73%; estimated from Figure 5B of the study report; see Table B-2). A decrease in female mean body-weight gain relative to controls (−43%) was also observed in mid-dose females during LDs 0−4, but the decrease was not statistically significant.

Reproductive parameters are shown in Table B-3. No treatment-related effects were observed on estrous cyclicity, ovulation, mating, gestation length, or delivery index. Although all females that had copulated in the control and low-dose groups became pregnant (i.e., 13/13 for both groups), one and four such females in the mid- and high-dose groups (i.e., 1/13 and 4/13, respectively) did not become pregnant. A statistically significant decrease in the fertility index (pregnant females/copulated pairs) was observed at the high dose relative to controls (−31%). There was no effect on the number of corpora lutea, but the number of implantation sites was decreased insignificantly at the mid and high doses (−13 and −24%, respectively), leading to statistically significant decreases in implantation index (number of implantation sites/number of corpora lutea) at the mid and high doses relative to controls (−13 and −23%, respectively). Related findings were statistically significant decreases in the number of pups born in the mid- and high-dose groups relative to controls (−18 and −33%, respectively) and decreases in the number of pups alive on LD 0 (−14 and −30%, respectively) and LD 4 (−14 and −32%, respectively) (statistically significant only in the high-dose group). Examination of pup morphology, behavior, and body weight during the postnatal period showed no treatment-related effects. Temporary cyanosis at birth and dilatation of the renal pelvis at necropsy were observed in one high-dose pup. No other effects on mating, fertility, pregnancy, or pup parameters were observed.

Adult male reproductive organ weights and histopathology are shown in Tables B-4 and B-5. Absolute and relative epididymis weights were statistically significantly decreased (−12 and −13%, respectively) in high-dose animals (see Table B-4). The decreases in absolute and relative epididymis weights in high-dose males were accompanied by an increased incidence (0/13 at 0, 100, and 300 mg/kg-day; 13/13 at 1,000 mg/kg-day) of animals with fewer numbers of spermatozoa in the cauda epididymis (see Tables B-4 and B-5). This effect (graded as very slight or slight; see Table B-5) was localized to the cauda epididymis and was not present in the

caput epididymis of any animal. The incidence of animals with cell debris in the cauda epididymal lumen was increased, but not significantly, at the highest dose relative to the control group (graded as very slight; 5/13 vs. 1/13, respectively; see Tables B-4 and B-5). The uterus of the mid-dose female that failed to become pregnant showed ballooning and accumulation of cloudy fluid, and histopathology revealed lumen dilatation and cellular infiltration of neutrophils in the epithelium and endometrial stroma, with edema present in the endometrial stroma. A moderate increase in atretic follicles was observed in one high-dose female. No other abnormalities in male or female reproductive organs were reported.

Parental male NOAEL and LOAEL values of 300 and 1,000 mg/kg-day, respectively, are identified, based on statistically significant decreases in absolute and relative epididymis weights, and a significant increase in the incidence of animals with reduced numbers of spermatozoa. Parental female NOAEL and LOAEL values of 100 and 300 mg/kg-day, respectively, were identified, based on a significant decrease in gestational body-weight gain. R/D NOAEL and LOAEL values of 100 and 300 mg/kg-day, respectively, were identified based on statistically significant decreases in implantation index and number of pups born. Reduced fertility in females could be related to effects on the male reproductive system at this dose (e.g., decreased epididymal weight and number of luminal sperm) and/or other treatment-related reproductive effects in both sexes. Reduced fertility in females is also among the potential causes for increased preimplantation loss (i.e., decreased implantation index) observed in this study at the high and mid doses. The decreases in the number of pups born and the number of pups alive on LDs 0 and 4 appear to be sequelae of preimplantation loss. The decrease in maternal body-weight gain at the mid and high doses during the latter part of gestation (i.e., GDs 14−20) is attributed to the small litter size, resulting from the reduced number of implantations, rather than to a direct, test substance-related effect on maternal body weight. This was also the conclusion of the study authors.

Inhalation Exposures

No studies examining the effects of *p*-toluic acid in animals exposed via inhalation have been identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Acute and Short-Term Tests (Oral and Dermal)

Oral median lethal dose (LD_{50}) values for *p*-toluic acid in rodents were 1,130−3,113 mg/kg (rats) and 2,340−2,484 mg/kg (mice) (OECD, 2008a; Hazelton Lab, 1986, 1984). Clinical signs observed following immediately or by Day 2 of oral exposure in the acute toxicity studies in rats and mice included respiratory arrest, tremors, sedation, ataxia, decreased locomotor activity, absent pain reflex, decreased grasping reflex, limb weakness, impaired use of front limbs, loss of righting reflex, abasia, prostration, ptosis, bradypnea, loss of reflexes, subnormal temperature, and temporary reductions in body-weight gain. Hemorrhages in the stomach mucosa and small intestine and petechial hemorrhages in the thymus were observed in animals that died during the study (OECD, 2008a). Reduced locomotor activity was observed at two daily doses of 500 mg/kg-day and higher, while prone position was observed at two daily doses of 2,000 mg/kg-day.

p-Toluic acid induced strong dermal reactions upon initial challenge in adult human volunteers and was a potent dermal sensitizer (Emmett and Suskind, 1973). Simultaneous and repeated application of *p*-toluic acid (50% in polystyrene) and *o*-toluic acid to different sites on

the upper back produced severe dermal reactions in 4/10 subjects. Challenge application induced sensitization reactions in 5/10 subjects. The five subjects that displayed sensitization reactions also showed cross-sensitization to *p*-, *o*-, and *m*-toluic acids (Emmett and Suskind, 1973).

Genotoxicity

p-Toluic acid has been tested in in vitro (positive and negative results) and in vivo (negative results) studies (see Table 4). Although English-language peer-reviewed study reports are not available, these studies were summarized in the OECD (2008a) dossier for *p*-toluic acid. In a bacterial mutation test, *p*-toluic acid was negative (both with and without exogenous metabolic activation) for reverse mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and in *Escherichia coli* strain WP2 uvrA/pKM101 (OECD, 2008a). Doses were 313, 625, 1,250, 2,500, and 5,000 µg/plate without activation and 156, 313, 625, 1,250, 2,500, and 5,000 µg/plate with activation. In clastogenicity tests, *p*-toluic acid induced chromosomal aberrations (CAs) in Chinese hamster lung (CHL) cells in the absence and presence of S9 metabolic activation (OECD, 2008a), but was negative for induction of micronuclei (MN) in vivo in male CD-1 mice following two daily gavage exposures (OECD, 2008a).

Metabolism/Toxicokinetic Studies

Evidence of toxic effects from animal studies indicates that *p*-toluic acid can be absorbed through the gastrointestinal (GI) tract (Shirota et al., 2008), but no data are available regarding the rate or extent of absorption. An in vitro dermal absorption study demonstrated that *p*-toluic acid penetrated skin samples from pigs and rodents (Dyer and Aziza, 1989). The study authors reported a partition coefficient (K_m) of 0.47−0.51 for penetration of *p*-toluic acid from aqueous solution to pig or rodent skin, and a self-diffusion permeation rate coefficient (D) of $0.57-1.3 \times 10^{-10}$ m^2/sec for diffusion of *p*-toluic acid through pig or rodent skin (Dyer and Aziza, 1989).

Table 4. Summary of *p*-Toluic Acid Genotoxicity

Endpoint	Test System	Dose/Concentration	Results without Activation[a]	Results with Activation[a]	Comments	References
Genotoxicity studies in prokaryotic organisms						
Mutation	*Salmonella typhimurium* strain TA98, TA100, TA1535, TA1537; *Escherichia coli* strain WP2 uvrA/pKM101	0, 313, 625, 1,250, 2,500, 5,000 µg/plate in DMSO (−S9); 0, 156, 313, 625, 1,250, 2,500, 5,000 µg/plate in DMSO (+S9)	−	−	Toxicity was observed in all strains at 5,000 µg/plate with S9 mix.	OECD (2008a); Mori et al. (1980)
Genotoxicity studies in mammalian cells—in vitro						
CAs	CHL cells; DNA damage assessed at 6 or 24 hr after treatment	0, 500, 1,000, 1,250, 1,400, 1,500, 1,600, 1,800, 2,000, 2,500, 5,000 (6 hr, −S9); 0, 250, 500, 1,000, 1,250, 1,500, 2,000, 2,500, 3,000, 5,000 (24 hr, −S9); 0, 250, 500, 1,000, 1,200, 1,250, 1,400, 1,500, 2,500, 5,000 (6 hr, +S9)	+	+	In the presence of metabolic activation, the number of cells with structural CAs was increased at concentrations of ≥1,000 µg/mL in the absence of metabolic activation and at ≥1,200 µg/mL in the presence of metabolic activation. Toxicity was observed at concentrations ≥1,500 µg/mL in the absence of metabolic activation and at ≥3,000 µg/mL in the presence of metabolic activation.	OECD (2008a)
Genotoxicity studies—in vivo						
Micronucleus test	Male CD-1 mice (five/group); gavage in sodium carboxymethyl-cellulose; twice with 24-hr interval; DNA damage assessed 24 hr after the second dose	0, 500, 1,000, 2,000 mg/kg-d (24 hr)	−	NA	No significant increase in the frequency of micronucleated polychromatic erythrocytes. There was no indication of cytotoxicity, as evidenced by no increase in the frequency of polychromatic erythrocytes in total erythrocytes. No deaths occurred. Clinical signs included reduced locomotor activity at 500 mg/kg-d and prone position at 2,000 mg/kg-d.	Taningher et al. (1993)

[a]+ = positive; − = negative

CA = chromosomal aberration; CHL = Chinese hamster lung; DMSO = dimethyl sulfoxide; DNA = deoxyribonucleic acid; NA = not applicable.

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present summaries of noncancer and cancer reference values, respectively.

Table 5. Summary of Noncancer Reference Values for *p*-Toluic Acid (CASRN 99-94-5)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD (HED)	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	Rat/F	Decreased implantation index	5×10^{-2}	$BMDL_{1SD}$	13.5	300	Shirota et al. (2008)
Chronic p-RfD (mg/kg-d)	Rat/F	Decreased implantation index	5×10^{-3}	$BMDL_{1SD}$	13.5	3,000	Shirota et al. (2008)
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

BMDL = benchmark dose lower confidence limit; F = female(s); HED = human equivalent dose; M = male(s); NDr = not determined; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; SD = standard deviation; UF_C = composite uncertainty factor.

Table 6. Summary of Cancer Reference Values for *p*-Toluic Acid (CASRN 99-94-5)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF $(mg/kg\text{-}d)^{-1}$	NDr			
p-IUR $(mg/m^3)^{-1}$	NDr			

NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

DERIVATION OF ORAL REFERENCE DOSES

Derivation of a Subchronic Provisional Reference Dose

No data were located on the effects of oral exposure to *p*-toluic acid in humans. There is only one 28-day study in rats (Shirota et al., 2008) and one reproductive developmental toxicity screening test in rats [also reported in Shirota et al. (2008)] available for consideration for derivation of a subchronic provisional reference dose. The R/D toxicity study (Shirota et al., 2008) is selected as the principal study and decreased implantation index is identified as the critical effect; the rationale for selecting the principal study and critical effect are discussed below.

Justification for the Principal Study

The 28-day study in rats exposed to *p*-toluic acid by gavage (Shirota et al., 2008) is considered to be of acceptable quality. Effects observed in this study include significantly increased urine volume in males (≥300 mg/kg-day) and females (1,000 mg/kg-day). Urine specific gravity was statistically significantly reduced for males at ≥300 mg/kg-day. Total protein was significantly decreased and the levels of AST were significantly increased in the

blood of female rats, both at 1,000 mg/kg-day. Eosinophils were decreased in males at 1,000 mg/kg-day. Levels of RBCs, Hb, and Hct were all significantly decreased in males at 1,000 mg/kg-day at the end of the recovery period. The biological relevance of these effects is questionable and therefore were not considered for subchronic p-RfD derivation. Furthermore, except for decreased urine volume in males, these effects occurred at higher doses than the reproductive effects observed in the R/D toxicity study conducted by Shirota et al. (2008). Therefore, the 28-day study in rats was not selected as the principal study for the subchronic p-RfD derivation.

The R/D toxicity study by Shirota et al. (2008) is also of acceptable quality and was designed and performed according to standard protocols in rodents, included in *OECD Guidelines for the Testing of Chemicals, Section 4,* "Test No. 421: Reproduction/Developmental Toxicity Screening Test" adopted 29 July 2016, and "Test No. 407: Repeated Dose 28-day Oral Toxicity Study in Rodents" adopted on 3 October 2008 (OECD, 2016, 2008b). All potential *p*-toluic acid-induced effects observed in the R/D toxicity study conducted by Shirota et al. (2008) were evaluated to determine the most sensitive response. The most sensitive endpoints (i.e., those at the LOAEL of 300 mg/kg-day) included decreased maternal body-weight gain (gestational), decreased implantation index, and decreased number of pups born. Data sets for sensitive R/D endpoints in Shirota et al. (2008) were considered to derive potential points of departure (PODs) via benchmark dose (BMD) modeling (see Table 7 and Appendix B). Other reproductive endpoints (e.g., decreased number of live pups on LDs 0 and 4, decreased fertility index [nonpregnant females/copulated pairs], and decreased absolute and relative epididymis weights) observed at ≥300 mg/kg-day were significant at the high dose only. These effects were suggestive of a dose response and were, therefore, also modeled.

Table 7. R/D Endpoints in S-D Crj:CD(SD) Rats Exposed via Gavage to *p*-Toluic Acid during Premating, Mating, Gestation, and Lactation Considered for Benchmark Dose Modeling[a, b]

Endpoint	Dose, mg/kg-d			
	0	100	300	1,000
Number of pregnant animals	13	13	11	9
Fertility index (number of nonpregnant females/copulated pairs)	0	0	1	4*, †
Implantation index (%)	99.1 ± 2.2	98.2 ± 3.5	86.5 ± 12.6**	75.9 ± 32.6*
Number of pups born	15.2 ± 1.4	14.1 ± 1.8	12.5 ± 2.1**	10.2 ± 5.1**
Number of live pups on LD 0	14.3 ± 1.7	14.1 ± 1.8	12.3 ± 2.2	10.0 ± 5.0*
Number of live pups on LD 4	14.3 ± 1.7	13.9 ± 1.8	12.3 ± 2.2	9.7 ± 5.3*
Absolute epididymis weight (g)[b]	1.28 ± 0.08	1.27 ± 0.08 (−0.8%)	1.24 ± 0.07 (−3%)	1.13 ± 0.09* (−12%)
Relative epididymis weight (g/100 g)[b]	0.24 ± 0.03	0.23 ± 0.02 (−4%)	0.23 ± 0.01 (−4%)	0.21 ± 0.02* (−13%)
Few number of sperm, lumen, bilateral	0/13 (0%)	0/13 (0%)	0/13 (0%)	13/13* (100%)

[a]Shirota et al. (2008).
[b]Values expressed as mean ± SD.
*Significantly different from controls ($p < 0.05$) as presented by study authors.
**Significantly different from controls ($p < 0.01$) as presented by study authors.
[†]The data for the fertility index were presented by the study authors as number of pregnant females/copulated pairs with a negative dose-response. Because BMDS cannot model negative quantal data, the data were converted to number of nonpregnant females/copulated pairs with a positive dose-response.

BMDS = Benchmark Dose Software; LD = lactation day; R/D = reproductive/developmental; S-D = Sprague-Dawley; SD = standard deviation.

Dosimetric Adjustments

No dosimetric adjustments for duration are made because continual dosing occurred during the exposure portion of the R/D toxicity study. In *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), the Agency endorses a hierarchy of approaches to derive human equivalent oral exposures from data on laboratory animal species, with the preferred approach being physiologically based toxicokinetic modeling. Other approaches may include using some chemical-specific information, without a complete physiologically based toxicokinetic model. In the absence of chemical-specific models or data to inform the derivation of human equivalent oral exposures, the EPA endorses body-weight scaling to the 3/4 power (i.e., $BW^{3/4}$) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an oral reference dose (RfD) under certain exposure conditions. More specifically, the use of $BW^{3/4}$ scaling for deriving an RfD is recommended when the observed effects are associated with the parent compound or a stable metabolite but not for portal-of-entry effects.

A validated human physiologically based toxicokinetic model for *p*-toluic acid is not available for use in dose extrapolation from animals to humans. Furthermore, the R/D endpoints are not portal-of-entry effects. Therefore, scaling by $BW^{3/4}$ is relevant for deriving human equivalent doses (HEDs) for this effect.

Doses provided in the study in mg/kg-day were converted to HEDs according to U.S. EPA (2011b) guidance.

$$DAF = (BW_a^{1/4} \div BW_h^{1/4})$$

where

DAF = dosimetric adjustment factor
BW_a = animal body weight
BW_h = human body weight; 70 kg

Table 8 shows animal doses converted to HEDs.

Table 8. Time-Adjusted Body Weights (DAF and HED)[a]

Dose Level from Principal Study (mg/kg-d)	Time-Weighted Body Weight (F) (kg)	DAF (F/M)[b]	HED (F/M) (mg/kg-d)
0	0.2925	0.25/0.25	0/0
100	0.2950	0.25/0.25	25.0/25.0
300	0.2998	0.26/0.25	78.0/75.0
1,000	0.2986	0.26/0.25	260.0/250.0

[a]Shirota et al. (2008).
[b]Male default weight 0.267 kg for S-D male rats following subchronic-duration exposure (U.S. EPA, 1988), female weight is time weighted.

DAF = dosimetric adjustment factor; F = female(s); HED = human equivalent dose; M = male(s); S-D = Sprague-Dawley.

Approach for Deriving the Subchronic p-RfD

All available continuous-variable models in the Benchmark Dose Software (BMDS, Version 2.5) were fit to the four R/D endpoints from Shirota et al. (2008) that were amenable to BMD modeling. Dichotomous models were fit to the decreased fertility index data. Reduced fertility in females could be related to effects on the male reproductive system (e.g., decreased epididymal weight and number of luminal sperm) and/or other treatment-related reproductive effects in both sexes, therefore, these data were modeled using dosimetry for both male and female rats. Appendix C presents the modeling results, with benchmark dose lower confidence limits (BMDLs), for the five BMD modeled data sets: (1) decreased implantation index (see Table C-1), (2) decreased number of pups born (see Table C-2), (3) decreased number of live pups on LDs 0 and 4 (see Tables C-3 and C-4, respectively), (4) reduced fertility index for female and male rats (see Tables C-5 and C-6, respectively), and (5) decreased absolute and relative epididymis weights in male rats (see Tables C-7 and C-8, respectively). BMDs (HEDs) and BMDLs (HEDs) from the best fitting models are presented in Table 9.

Table 9. BMD and BMDL Values from Best Fitting Models for Selected R/D Endpoints in Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation[a, b]

Endpoint	Best Fitting Model	BMD_{1SD} (HED) mg/kg-d[c]	$BMDL_{1SD}$ (HED) mg/kg-d[c]
Implantation index	Linear[d]	BMD_{1SD} = 22.3	$BMDL_{1SD}$ = 13.5
Number of pups born	Exponential (models 2 and 3)	BMD_{1SD} = 49.7	$BMDL_{1SD}$ = 29.9
Number of live pups on LD 0	Exponential (model 2)	BMD_{1SD} = 73.6	$BMDL_{1SD}$ = 42.7
Number of live pups on LD 4	Exponential (model 2)	BMD_{1SD} = 69.4	$BMDL_{1SD}$ = 40.6
Fertility Index	Male and female: LogProbit	Male: BMD_{10} = 105 Female: BMD_{10} = 109	Male: $BMDL_{10}$ = 65.3 Female: $BMDL_{10}$ = 67.8
Decreased absolute epididymis weight	Linear	BMD_{1SD} = 127	$BMDL_{1SD}$ = 94.6

[a]Data sets from Shirota et al. (2008).
[b]Modeling results are described in more detail in Appendix C.
[c]HEDs were calculated using the species-specific DAF based on the animal:human $BW^{1/4}$ ratio recommended by U.S. EPA (2011b).
[d]Best fitting model for this endpoint is for a reduced data set with the high-dose group dropped.

BMD = benchmark dose; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; $BMDL_{1SD}$ = benchmark dose 95th lower confidence limit based on 1 SD from the mean of the data; BW = body weight; DAF = dosimetric adjustment factor; HED = human equivalent dose; LD = lactation day; R/D = reproductive/developmental; SD = standard deviation.

Among the available candidate endpoints (see Table 10), decreased implantation index represents the most sensitive (i.e., lowest) candidate POD for deriving a subchronic p-RfD. Therefore, the $BMDL_{1SD}$ (HED) for decreased implantation index in female rats exposed to *p*-toluic acid during premating, mating, gestation, and lactation (13.5 mg/kg-day) is selected as the POD for derivation of the subchronic p-RfD.

Table 10. Candidate PODs for Derivation of the Subchronic p-RfD[a, b]

Endpoint	Male				Female				Comments
	NOAEL (HED) mg/kg-d	**LOAEL (HED) mg/kg-d**	**BMDL (HED) mg/kg-d[e]**	**POD**	**NOAEL (HED) mg/kg-d**	**LOAEL (HED) mg/kg-d**	**BMDL (HED) mg/kg-d[e]**	**POD**	
Fertility Index	75.0	250.0	65.3	$BMDL_{10}$ (HED)	78.0	260.0	67.8	$BMDL_{10}$ (HED)	NA
Implantation index	**NDr**	**NDr**	**NDr**	**NDr**	**25.0**	**78.0**	**13.5[f]**	**$BMDL_{1SD}$ (HED)**	**Most sensitive endpoint**
Number of pups born[c]	NDr	NDr	NDr	NDr	25.0	78.0	29.9	$BMDL_{1SD}$ (HED)	NA
Number of live pups on LD 0[c]	NDr	NDr	NDr	NDr	78.0	260.0	42.7	$BMDL_{1SD}$ (HED)	NA
Number of live pups on LD 4[c]	NDr	NDr	NDr	NDr	78.0	260.0	40.6	$BMDL_{1SD}$ (HED)	NA
Decreased gestational body-weight gain[c]	NDr	NDr	NDr	NDr	25.0	78.0	DUB	NOAEL (HED)	BMD modeling was not possible because variances were not reported
Decreased absolute epididymis weight[d]	75.0	250.0	94.6	$BMDL_{1SD}$ (HED)	NDr	NDr	NDr	NDr	NA

Table 10. Candidate PODs for Derivation of the Subchronic p-RfD[a, b]

Endpoint	Male				Female				Comments
	NOAEL (HED) mg/kg-d	LOAEL (HED) mg/kg-d	BMDL (HED) mg/kg-d[e]	POD	NOAEL (HED) mg/kg-d	LOAEL (HED) mg/kg-d	BMDL (HED) mg/kg-d[e]	POD	
Decreased relative epididymis weight[d]	75.0	250.0	DUB	NOAEL (HED)	NDr	NDr	NDr	NDr	BMD modeling failed
Increased incidence of animals with fewer numbers of spermatozoa[d]	75.0	250.0	DUB	NOAEL (HED)	NDr	NDr	NDr	NDr	BMD modeling was not attempted due to the lack of dose-response

[a]Shirota et al. (2008).
[b]Following U.S. EPA (2011b) guidance, animal doses from candidate principal studies were converted to HEDs through the application of a DAF. DAFs for each dose are 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. For all DAF calculations, a reference human body weight (BW_h) of 70 kg (U.S. EPA, 1988) was used.
[c]DAFs were calculated using study-specific time-weighted body weights (BW_a) data for female rats during premating and gestation from Shirota et al. (2008).
[d]DAFs were calculated using reference body weights (BW_a) for S-D male rats following subchronic-duration exposure (U.S. EPA, 1988).
[e]All modeling was conducted using U.S. EPA BMDS (Version 2.5). BMD analysis details are available in Appendix C.
[f]An adequate fit was achieved when the high-dose group was dropped.

BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; BMDS = Benchmark Dose Software; BW = body weight; DAF = dosimetric adjustment factor; DUB = data unamenable to BMDS; HED = human equivalent dose; LD = lactation day; LOAEL = lowest-observed-adverse-effect level; NA = not applicable; NDr = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; S-D = Sprague-Dawley; SD = standard deviation.

The subchronic p-RfD for *p*-toluic acid, based on a $BMDL_{1SD}$ (HED) of 13.5 mg/kg-day (see Table 9 and 10) for decreased implantation index in female rats and composite uncertainty factor (UF_C), is derived as follows:

$$\begin{aligned} \textbf{Subchronic p-RfD} &= BMDL_{1SD}\text{ (HED)} \div UF_C \\ &= 13.5\text{ mg/kg-day} \div 300 \\ &= \mathbf{5 \times 10^{-2}\text{ mg/kg-day}} \end{aligned}$$

Table 11 summarizes the uncertainty factors for the subchronic p-RfD for *p*-toluic acid.

Table 11. Uncertainty Factors for the Subchronic p-RfD for *p*-Toluic Acid

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rats and humans following oral *p*-toluic exposure. The toxicokinetic uncertainty has been accounted for by calculating a HED through application of a DAF as outlined in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b).
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. The database is limited to a 28-d repeated-dose study and a R/D toxicity screening study in rats (Shirota et al., 2008). The R/D screening study indicates that R/D endpoints are sensitive targets of *p*-toluic acid following oral exposure, but was not a definitive study of reproductive or developmental effects. The database is lacking subchronic-duration, two-generation reproduction, and comprehensive developmental toxicity studies.
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*-toluic acid 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 is based on a R/D toxicity study wherein parental rats were exposed for 6 wk.
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; POD = point of departure; p-RfD = provisional reference dose; R/D = reproductive/developmental; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies variability uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

The confidence in the subchronic p-RfD for *p*-toluic acid is low, as described in Table 12.

Table 12. Confidence Descriptors for the Subchronic p-RfD for *p*-Toluic Acid

Confidence Categories	Designation	Discussion
Confidence in study	M	Confidence in the principal study (Shirota et al., 2008) is medium. The principal study is a peer-reviewed, R/D toxicity screening study. The study was conducted according to OECD guidelines (OECD Test Guideline 421), with an adequate number of dose groups and dose spacing, group sizes, and quantitation of results to describe dose-response relationships for effects. The study identified sensitive R/D effects and identified NOAEL and LOAEL values. Confidence is not considered high because some details were not provided in the report (i.e., variances for maternal body-weight gain; whether analyses were conducted using litters/dams as the experimental unit).
Confidence in database	L	Confidence in the database is low. The database is limited to a 28-d repeated-dose study that found no clear evidence of treatment-related effects and a R/D toxicity screening study (Shirota et al., 2008) that identified R/D effects. No subchronic-duration, two-generation reproductive, or comprehensive developmental toxicity studies are available.
Confidence in subchronic p-RfD[a]	L	The overall confidence in the subchronic p-RfD is low.

[a]The overall confidence cannot be greater than the lowest entry in the table (low).

L = low; LOAEL = lowest-observed-adverse-effect level; M = medium; NOAEL = no-observed-adverse-effect level; OECD = Organisation for Economic Co-operation and Development; p-RfD = provisional reference dose; R/D = reproductive/developmental.

Derivation of a Chronic Provisional Reference Dose

There are no chronic-duration studies of humans or animals orally exposed to *p*-toluic acid. In the absence of additional data, the subchronic p-RfD based on decreased implantation index in female rats exposed to *p*-toluic acid in a R/D toxicity study (Shirota et al., 2008) is used as the basis for deriving a chronic p-RfD.

The chronic p-RfD for *p*-toluic acid, based on a $BMDL_{1SD}$ (HED) of 13.5 mg/kg-day (see Table 9 and 10) for decreased implantation index in female rats and UF_C is derived as follows:

$$\textbf{Chronic p-RfD} = BMDL_{1SD}\ (HED) \div UF_C$$
$$= 13.5\ \text{mg/kg-day} \div 3{,}000$$
$$= \mathbf{5 \times 10^{-3}\ mg/kg\text{-}day}$$

Table 13 summarizes the uncertainty factors for the chronic p-RfD for *p*-toluic acid.

Table 13. Uncertainty Factors for the Chronic p-RfD for *p*-Toluic Acid

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rats and humans following oral *p*-toluic exposure. The toxicokinetic uncertainty has been accounted for by calculating a HED through application of a DAF as outlined in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b).
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. The database is limited to a 28-d repeated-dose study and a R/D toxicity screening study in rats (Shirota et al., 2008). The R/D study indicates that R/D endpoints are sensitive targets of *p*-toluic acid following oral exposure, but was not a definitive study of reproductive or developmental effects. The database is lacking chronic-duration, two-generation reproductive, and comprehensive developmental toxicity studies.
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*-toluic acid 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 to account for exposure for less than a complete reproductive cycle of a single generation in the R/D toxicity screening study used to identify the POD. Furthermore, the critical effect (i.e., decreased implantation index) was observed in female rats that were treated for 6 wk, which is less than chronic duration.
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; POD = point of departure; p-RfD = provisional reference dose; R/D = reproductive/developmental; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies variability uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

The confidence in the chronic p-RfD for *p*-toluic acid is low, as described in Table 14.

Table 14. Confidence Descriptors for the Chronic p-RfD for *p*-Toluic Acid

Confidence Categories	Designation	Discussion
Confidence in study	M	Confidence in the principal study (Shirota et al., 2008) is medium. The principal study is a peer-reviewed, R/D toxicity study. The study was conducted according to OECD guidelines (OECD Test Guideline 421), with an adequate number of dose groups and dose spacing, group sizes, and quantitation of results to describe dose-response relationships for critical effects. The study identified sensitive R/D effects and identified NOAEL and LOAEL values. Confidence is not considered high because some details were not provided in the report (i.e., variances for maternal body-weight gain, whether analyses were conducted using litters/dams as the experimental unit).
Confidence in database	L	Confidence in the database is low. No chronic-duration, two-generation reproductive, or comprehensive developmental toxicity studies are available. The R/D toxicity screening study included exposure for less than a complete reproductive cycle of a single generation.
Confidence in the chronic p-RfD[a]	L	The overall confidence in the chronic p-RfD is low.

[a]The overall confidence cannot be greater than the lowest entry in the table (low).

L = low; LOAEL = lowest-observed-adverse-effect level; M = medium; NOAEL = no-observed-adverse-effect level; OECD = Organisation for Economic Co-operation and Development; p-RfD = provisional reference dose; R/D = reproductive/developmental.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No studies have been identified regarding toxicity of *p*-toluic acid to humans or animals by inhalation; therefore, subchronic and chronic provisional reference concentrations (p-RfCs) are not derived.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

No relevant data are available. Under the U.S. EPA Cancer Guidelines (U.S. EPA, 2005), there is *"Inadequate Information to Assess Carcinogenic Potential"* of *p*-toluic acid (see Table 15).

Table 15. Cancer WOE Descriptor for *p*-Toluic Acid

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	There are no human data to support this.
"Likely to Be Carcinogenic to Humans"	NS	NA	There are no suitable animal studies to support this.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	There are no suitable animal studies to support this.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**This descriptor is selected due to the lack of any information on the carcinogenicity of *p*-toluic acid.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	There are no suitable animal studies to support this.

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

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

The lack of data on the carcinogenicity of *p*-toluic acid precludes deriving quantitative estimates for either oral (provisional oral slope factor [p-OSF]) or inhalation (provisional inhalation unit risk [p-IUR]) exposure.

APPENDIX A. SCREENING PROVISIONAL VALUES

No screening provisional values for *p*-toluic acid are derived.

APPENDIX B. DATA TABLES

Table B-1. Hematology, Clinical Chemistry, and Urinalysis Data for Rats Treated Orally with *p*-Toluic Acid in a Repeated-Dose 28-Day Oral Toxicity Study[a]

Effect	Males				Females				Males (end of recovery)		Females (end of recovery)	
Dose (mg/kg)	**0**	**100**	**300**	**1,000**	**0**	**100**	**300**	**1,000**	**0**	**1,000**	**0**	**1,000**
RBC (× 104/µL)	755 ± 53	780 ± 15	770 ± 27	755 ± 18	742 ± 19	771 ± 26	750 ± 25	751 ± 30	797 ± 13	766 ± 22**	749 ± 25	766 ± 24
Hb (g/dL)	14.9 ± 0.6	15.2 ± 0.2	15.2 ± 0.3	15.0 ± 0.2	14.8 ± 0.3	15.1 ± 0.5	14.9 ± 0.3	14.7 ± 0.5	15.2 ± 0.1	14.6 ± 0.3**	14.5 ± 0.4	14.4 ± 0.7
Hct (%)	44.8 ± 2.9	46.0 ± 0.7	45.5 ± 1.1	45.2 ± 0.4	44.2 ± 1.0	44.9 ± 1.3	44.4 ± 0.7	43.6 ± 1.9	45.3 ± 0.8	43.5 ± 1.0**	42.6 ± 1.3	42.7 ± 1.9
Total protein (g/dL)	5.0 ± 0.2	5.2 ± 0.2	5.1 ± 0.1	5.0 ± 0.0	5.4 ± 0.3	5.3 ± 0.3	5.2 ± 0.3	4.8 ± 0.3**	5.6 ± 0.4	5.4 ± 0.1	5.5 ± 0.1	5.70 ± 0.3
AST (U/L)	72 ± 10	66 ± 11	67 ± 7	88 ± 24	69 ± 3	66 ± 5	69 ± 8	94 ± 16*	83 ± 14	66 ± 2	62 ± 3	66 ± 5
Eosinophil	1 ± 0	1 ± 0	1 ± 0	0 ± 0*	1 ± 0	1 ± 1	1 ± 0	1 ± 0	1 ± 0	1 ± 1	2 ± 1	1 ± 1
Urine volume on D 23 of treatment or D 9 of recovery (mL/24 hr)	15.6 ± 2.2	15.6 ± 2.1	20.9 ± 4.7*	23.8 ± 4.7**	11.7 ± 3.5	11.9 ± 3.4	13.0 ± 4.3	22.1 ± 7.5**	18.3 ± 4.7	24.3 ± 4.6	13.3 ± 2.8	18.3 ± 5.6
Specific Gravity	1.058 ± 0.0008	1.051 ± 0.0007	1.043 ± 0.011**	1.045 ± 0.006**	1.045 ± 0.012	1.046 ± 0.008	1.043 ± 0.007	1.038 ± 0.009	1.056 ± 0.009	1.038 ± 0.0006**	1.041 ± 0.010	1.044 ± 0.011

[a]Shirota et al. (2008).
*Significantly different from controls ($p < 0.05$) as presented by study authors.
**Significantly different from controls ($p < 0.01$) as presented by study authors.

AST = aspartate transaminase (also known as SGOT); Hb = hemoglobin; Hct = hematocrit; RBC = red blood cell; SGOT = glutamic oxaloacetic transaminase.

Table B-2. Body Weights and Body-Weight Gains in Female S-D Crj:CD(SD) Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation[a, b]

Endpoint	Exposure Group, mg/kg-d			
	0	100	300	1,000
Body weight, g[c]				
Premating				
D 1	236.2	244.7 (+4%)	242.4 (+3%)	242.4 (+3%)
D 7	246.8	250.6 (+2%)	249.1 (+1%)	248.3 (+1%)
D 14	258.1	260.4 (+1%)	264.3 (+2%)	264.3 (+2%)
Gestation				
D 0	267.9	267.9 (0%)	275.6 (+3%)	277.2 (+3%)
D 7	304.2	304.9 (0%)	313.4 (+3%)	311.9 (+3%)
D 14	339.7	339.7 (0%)	350.5 (+3%)	350.5 (+3%)
D 20	416.8	413.7 (−1%)	415.3 (0%)	413.7 (−1%)
Lactation				
D 0	297.2	304.9 (+2%)	336.6* (+13%)	337.3* (+13%)
D 4	326.5	335.8 (+3%)	349.7 (+7%)	341.2 (+5%)
Body weight gain, g[c]				
Premating				
D 1−7	10.6	8.7 (−18%)	8.8 (−17%)	13.2 (+25%)
D 7−14	10.7	11.4 (+7%)	15.5 (+45%)	16.6 (+55%)
Gestation				
D 0−7	35.2	35.0 (−1%)	40.5 (+15%)	36.1 (+3%)
D 7−14	34.6	36.3 (+5%)	36.8 (+6%)	38.5 (+11%)
D 14−20	74.1	70.1 (−5%)	61.4* (−17%)	55.7** (−25%)
Lactation				
D 0−4	29.4	31.5 (+7%)	16.7 (−43%)	8.0** (−73%)

[a]Shirota et al. (2008).
[b]Mean body weight and relative body-weight values were estimated from Figure 5 of the study report with digitizing software (Softonic Grab It! XP2 software) because numerical values were not available. Variances were not provided.
[c]Mean body weight; value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from controls ($p < 0.05$), as reported by the study authors.
**Significantly different from controls ($p < 0.01$), as reported by the study authors.

S-D = Sprague-Dawley.

Table B-3. Selected Reproductive Parameters in S-D Crj:CD(SD) Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation[a]

Endpoint	Exposure Group, mg/kg-d			
	0	100	300	1,000
Mating performance				
Copulated pairs/cohoused pairs[b]	13/13 (100%)	13/13 (100%)	12/13 (92%)	13/13 (100%)
Pregnant females/copulated pairs[b]	13/13 (100%)	13/13 (100%)	11/12 (92%)	9/13* (69%)
Pairing days until copulation[c]	3.0 ± 3.4	2.4 ± 1.3 (−20%)	2.4 ± 1.3 (−20%)	3.2 ± 3.3 (+7%)
Estrus cycles until copulation[c]	1.0 ± 0.0	1.0 ± 0.0 (0%)	1.0 ± 0.0 (0%)	1.1 ± 0.3 (+10%)
Pregnancy data				
Pregnant females with live pups[b]	13/13 (100%)	13/13 (100%)	11/11 (100%)	9/9 (100%)
Gestation length in d[c]	22.3 ± 0.5	22.5 ± 0.5 (+1)	22.3 ± 0.5 (0%)	22.8 ± 0.4 (+2%)
Number of corpora lutea[c]	16.2 ± 1.3	15.7 ± 1.3 (−3%)	16.2 ± 1.5 (0%)	15.9 ± 1.3 (−2%)
Number of implantation sites[c]	16.0 ± 1.3	15.4 ± 1.0 (−4%)	14.0 ± 2.4 (−13%)	12.1 ± 5.3 (−24%)
Implantation index (%)[c, d]	99.1 ± 2.2	98.2 ± 3.5 (−1%)	86.5 ± 12.6** (−13%)	75.9 ± 32.6* (−23%)
LD 0				
Number of pups born[c]	15.2 ± 1.4	14.1 ± 1.8 (−7%)	12.5 ± 2.1** (−18%)	10.2 ± 5.1** (−33%)
Delivery index (%)[c, e]	94.7 ± 5.2	91.4 ± 8.5 (−3%)	90.1 ± 8.4 (−5%)	82.9 ± 19.5 (−12)
Number of live pups[c]	14.3 ± 1.7	14.1 ± 1.8 (−1%)	12.3 ± 2.2 (−14%)	10.0 ± 5.0* (−30%)
Birth index (%)[c, f]	89.7 ± 10.4	91.4 ± 8.5 (+2%)	88.0 ± 9.1 (−2%)	81.5 ± 19.8 (−9%)
Live birth index (%)[c, g]	94.8 ± 10.5	100.0 ± 0 (+5%)	97.6 ± 4.2 (+3%)	98.2 ± 3.7 (+4%)
Sex ratio, M:F (%)[c]	54.1 ± 14.3	51.9 ± 12.8 (−4%)	46.6 ± 13.8 (−14%)	59.8 ± 17.7 (+11%)

Table B-3. Selected Reproductive Parameters in S-D Crj:CD(SD) Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation[a]

Endpoint	Exposure Group, mg/kg-d			
	0	100	300	1,000
Pregnancy data, continued				
LD 4				
Number of live pups[c]	14.3 ± 1.7	13.9 ± 1.8 (−3%)	12.3 ± 2.2 (−14%)	9.7 ± 5.3* (−32%)
Viability index (%)[c, h]	100.0 ± 0	99.0 ± 3.7 (−1%)	100 ± 0 (0%)	88.1 ± 33.1 (−12%)[j]
Sex ratio (%)[c, i]	54.1 ± 14.3	52.3 ± 12.3 (−3%)	46.6 ± 13.8 (−14%)	54.4 ± 9.5 (+1%)

[a]Shirota et al. (2008).
[b]Number of animals/total in group; value in parentheses expressed as % of animals.
[c]Mean ± SD. Percent change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Defined as (number of implantation sites ÷ number of corpora lutea) × 100.
[e]Defined as (number of pups born ÷ number of implantation sites) × 100.
[f]Defined as (number of live pups on LD 0 ÷ number of implantation sites) × 100.
[g]Defined as (number of live pups on LD 0 ÷ number of pups born) × 100.
[h]Not defined by the study authors; interpreted by the reviewer as: (number of live pups on LD 4 ÷ number of live pups on LD 0) × 100.
[i]Defined as (number of live male pups ÷ number of live pups) × 100.
[j]Value (88.1%) as reported by the study authors appears to be an error. The calculated value was 97%.
*Significantly different from controls ($p < 0.05$), as reported by study authors.
**Significantly different from controls ($p < 0.01$), as reported by study authors.

F = female(s); LD = lactation day; M = male(s); S-D = Sprague-Dawley; SD = standard deviation.

Table B-4. Selected Effects on Reproductive Organ Weights and Histopathology in Male S-D Crj:CD(SD) Rats Exposed to *p*-Toluic Acid via Gavage for 42 Days[a]

Endpoint	Exposure Group, mg/kg-d			
	0	100	300	1,000
Animal data				
Number of animals	13	13	13	13
Terminal body weight (g)[b]	527.0 ± 37.8	549.9 ± 42.8 (+4%)	541.6 ± 26.6 (+3%)	542.4 ± 30.7 (+3%)
Organ weights				
Absolute testes weight (g)[b]	3.37 ± 0.24	3.29 ± 0.19 (−2%)	3.29 ± 0.22 (−2%)	3.31 ± 0.17 (−2%)
Relative testes weight (g/100 g)[b]	0.64 ± 0.07	0.60 ± 0.06 (−6%)	0.61 ± 0.04 (−5%)	0.61 ± 0.05 (−5%)
Absolute epididymis weight (g)[b]	1.28 ± 0.08	1.27 ± 0.08 (−1%)	1.24 ± 0.07 (−3%)	1.13 ± 0.09* (−12%)
Relative epididymis weight (g/100 g)[b]	0.24 ± 0.03	0.23 ± 0.02 (−4%)	0.23 ± 0.01 (−4%)	0.21 ± 0.02* (−13%)
Histopathology				
Testis, seminiferous tubule				
Atrophy, focal, bilateral[c]	1/13 (8%)	1/13 (8%)	0/13 (0%)	0/13 (0%)
Multinucleated giant cell[c]	0/13 (0%)	0/13 (0%)	0/13 (0%)	1/13 (8%)
Epididymis, cauda				
Few sperm, lumen, bilateral[c]	0/13 (0%)	0/13 (0%)	0/13 (0%)	13/13* (100%)
Cell debris, lumen, bilateral[c]	1/13 (8%)	0/13 (0%)	0/13 (0%)	5/13 (38%)
Spermatid granuloma, unilateral[c]	0/13 (0%)	0/13 (0%)	1/13 (8%)	0/13 (0%)

[a]Shirota et al. (2008).
[b]Mean ± SD. Percent change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[c]Number of animals ÷ total in group with lesion; value in parentheses expressed as % of animals.
*Significantly different from controls ($p < 0.01$), as reported by study authors.

S-D = Sprague-Dawley; SD = standard deviation.

Table B-5. Selected Non-neoplastic Lesions in Male S-D Crj:CD(SD) Rats Exposed to *p*-Toluic Acid via Gavage for 42 Days[a]

Endpoint	Exposure Group, mg/kg-d			
	0	100	300	1,000
Epididymidis, cauda[b]				
Few number of sperm, lumen, bilateral	0/13 (0%)	0/13 (0%)	0/13 (0%)	13/13* (100%)
Normal (−)	13/13 (100%)	13/13 (100%)	13/13 (100%)	0/13 (0%)
Very slight (±)	0/13 (0%)	0/13 (0%)	0/13 (0%)	11/13 (85%)
Slight (+)	0/13 (0%)	0/13 (0%)	0/13 (0%)	2/13 (15%)
Moderate (++)	0/13 (0%)	0/13 (0%)	0/13 (0%)	0/13 (0%)
Severe (+++)	0/13 (0%)	0/13 (0%)	0/13 (0%)	0/13 (0%)
Cell debris, lumen, bilateral	1/13 (8%)	0/13 (0%)	0/13 (0%)	5/13 (38%)
Normal (−)	12/13 (92%)	13/13 (100%)	13/13 (100%)	8/13 (62%)
Very slight (±)	1/13 (8%)	0/13 (0%)	0/13 (0%)	5/13 (38%)
Slight (+)	0/13 (0%)	0/13 (0%)	0/13 (0%)	0/13 (0%)
Moderate (++)	0/13 (0%)	0/13 (0%)	0/13 (0%)	0/13 (0%)
Severe (+++)	0/13 (0%)	0/13 (0%)	0/13 (0%)	0/13 (0%)
Spermatid granuloma, unilateral	0/13 (0%)	0/13 (0%)	1/13 (8%)	0/13 (0%)
Normal (−)	13/13 (100%)	13/13 (100%)	12/13 (92%)	13/13 (100%)
Very slight (±)	0/13 (0%)	0/13 (0%)	0/13 (0%)	0/13 (0%)
Slight (+)	0/13 (0%)	0/13 (0%)	1/13 (8%)	0/13 (0%)
Moderate (++)	0/13 (0%)	0/13 (0%)	0/13 (0%)	0/13 (0%)
Severe (+++)	0/13 (0%)	0/13 (0%)	0/13 (0%)	0/13 (0%)

[a]Shirota et al. (2008).
[b]Number of animals ÷ group with lesion; value in parentheses expressed as % of animals.
*Significantly different from controls ($p < 0.01$) for incidence and severity, respectively, as reported by study authors.

S-D = Sprague-Dawley.

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

MODELING PROCEDURE FOR CONTINUOUS DATA

Benchmark dose (BMD) modeling of continuous data is conducted with EPA's Benchmark Dose Software (BMDS, Version 2.5). All continuous models available within the software are fit using a default benchmark response (BMR) of 1 standard deviation (SD) relative risk unless a biologically determined BMR is available (e.g., BMR 10% relative deviation for body weight based on a biologically significant weight loss of 10%), as outlined in the *Benchmark Dose Technical Guidance* (U.S. EPA, 2012b). An adequate fit is judged based on the χ^2 goodness-of-fit *p*-value ($p > 0.1$), magnitude of the scaled residuals in the vicinity of the BMR, 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 ($p < 0.1$), 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; $p < 0.1$), the data set is considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest benchmark dose lower confidence limit/benchmark concentration lower confidence limit (BMDL/BMCL) is selected if the BMDL/BMCL estimates from different models vary >threefold; otherwise, the BMDL/BMCL from the model with the lowest Akaike's information criterion (AIC) is selected as a potential point of departure (POD) from which to derive the reference dose/reference concentration (RfD/RfC).

In addition, 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 is deemed reasonable.

MODELING PROCEDURE FOR DICHOTOMOUS DATA

The BMD modeling of dichotomous data was conducted with the EPA's BMDS (Version 2.2.2). For these data, all of the dichotomous models (i.e., Gamma, Multistage, Logistic, LogLogistic, Probit, LogProbit, and Weibull models) available within the software were fit using a default BMR of 10% extra risk based on the EPA's *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2012b). Adequacy of model fit was judged based on the goodness-of-fit *p*-value ($p > 0.1$), magnitude of scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. Among all models providing adequate fit, the lowest BMDL was selected if the BMDLs estimated from different models varied greater than threefold; otherwise, the BMDL from the model with the lowest AIC was selected as a potential POD from which to derive a p-RfD.

BMD MODELING TO IDENTIFY POTENTIAL PODs FOR DERIVING A PROVISIONAL REFERENCE DOSE

The data sets for sensitive reproductive/developmental (R/D) endpoints observed in the principal study of rats exposed orally to *p*-toluic acid during premating, mating, gestation, and lactation (Shirota et al., 2008) were selected to determine potential PODs for the provisional reference dose (p-RfD), using BMD analysis. Table 7 shows the data that were modeled. Summaries of modeling approaches and results (see Tables C-1 to C-8 and Figures C-1 to C-8) for each data set follow.

Decreased Implantation Index in Female Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation

The procedure outlined above was applied to the data for decreased implantation index in the R/D toxicity study in rats (Shirota et al., 2008) (see Table 7). Table C-1 summarizes the BMD modeling results. The constant variance model did not provide adequate fit to the variance data. Variance was modeled adequately using the power model in the BMDS, but none of the available models fit the means with the variance model applied. The high-dose group was dropped in an effort to model the data. Using the reduced data set, the constant variance model did not provide adequate fit to the variance data, but the nonconstant variance model did. With the nonconstant variance model applied, the only models that provided adequate fit were the Exponential models 2 and 4 and the linear model. BMDLs for models providing adequate fit were considered to be sufficiently close (i.e., differed by <two- to threefold), so the model with the lowest AIC was selected (Linear model).

Table C-1. Modeling Results for Implantation Index Data in Female Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation[a]

Model	Variance *p*-Value[b]	*p*-Value for Fit[b]	Scaled Residual for Dose Group[c]	AIC	BMD_{1SD}	$BMDL_{1SD}$
Exponential (model 2)[d, e]	0.1912	0.1259	1.138	154.7342	22.2487	13.116
Exponential (model 3)[d, e]	0.1912	NA	0.4058	154.0213	33.314	18.2503
Exponential (model 4)[d, e]	0.1912	0.1259	1.138	154.7342	22.2487	12.8216
Linear[d, e, f]	**0.2474**	**0.1102**	**1.15**	**154.572929**	**22.2766**	**13.4576**
Polynomial (2-degree)[d, e]	0.2474	NA	0.406	154.021294	33.7566	17.8553
Polynomial (3-degree)[d, e]	0.2474	NA	0.406	156.021294	35.6382	17.6413
Power[d, e]	0.1912	NA	0.406	154.021294	33.4727	18.1475

[a]Shirota et al. (2008).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[d]Coefficients restricted to be negative.
[e]Power restricted to ≥1.
[f]Selected model.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD; BMR = benchmark response; NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested); SD = standard deviation.

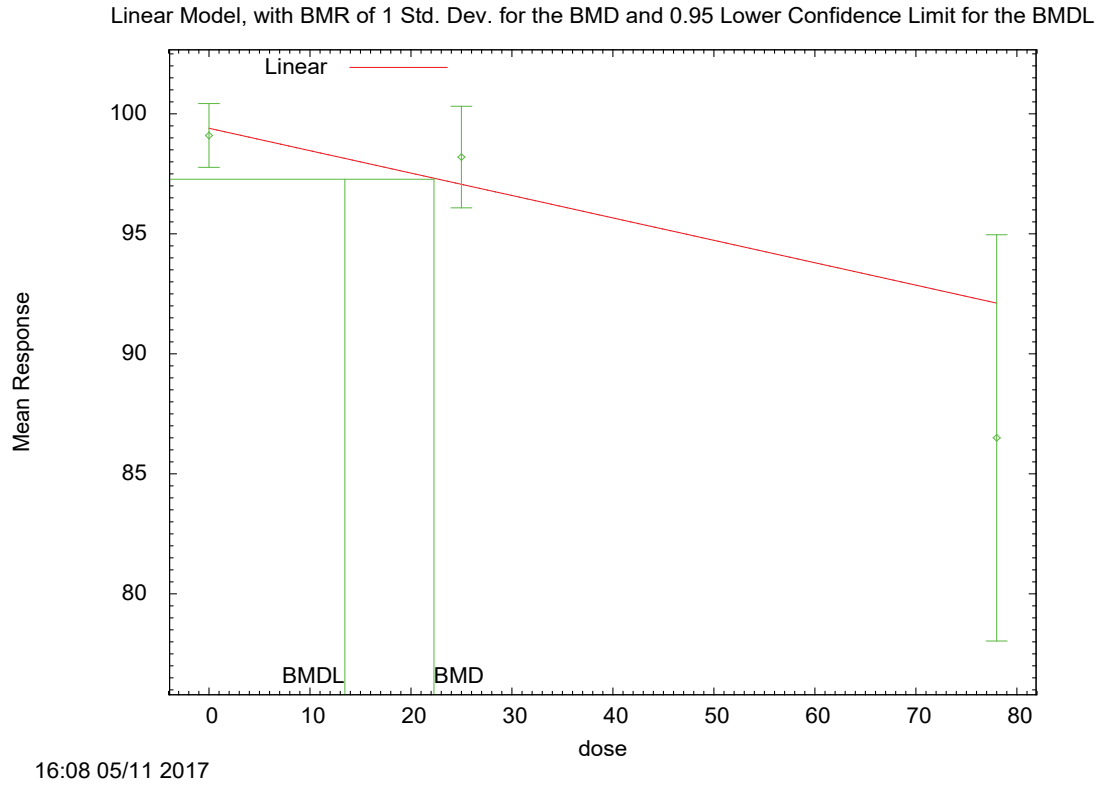

Figure C-1. Linear Model for Implantation Index Data (Reduced Data Set) in Female Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation (Shirota et al., 2008)

Text Output for Figure C-1:

```
================================================================================
        Polynomial Model. (Version: 2.17;  Date: 01/28/2013)
        Input Data File:
C:/Users/JKaiser/Desktop/BMDS240/Data/lin_Implantation_pta_nohd_Lin-ModelVariance-BMR1
Std.(d)
        Gnuplot Plotting File:
C:/Users/JKaiser/Desktop/BMDS240/Data/lin_Implantation_pta_nohd_Lin-ModelVariance-BMR1
Std.plt
                                                Tue May 16 10:56:35 2017
 ================================================================================

 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 = 3
```

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 =	3.96511
rho =	0
beta_0 =	100.463
beta_1 =	-0.170771

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	beta_0	beta_1
lalpha	1	-1	-0.18	0.35
rho	-1	1	0.18	-0.35
beta_0	-0.18	0.18	1	-0.52
beta_1	0.35	-0.35	-0.52	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	223.555	35.9332	153.127	293.983
rho	-48.2942	7.86667	-63.7126	-32.8758
beta_0	99.3548	0.58484	98.2086	100.501
beta_1	-0.093378	0.0429776	-0.177613	-0.0091435

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	13	99.1	99.4	2.2	2.08	-0.442
25	13	98.2	97	3.5	3.69	1.15
78	11	86.5	92.1	12.6	13.1	-1.41

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          -90.290158            4     188.580316
             A2          -71.341768            6     154.683536
             A3          -72.010647            5     154.021294
         fitted          -73.286465            4     154.572929
              R          -99.435945            2     202.871890


                   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              56.1884          4          <.0001
   Test 2              37.8968          2          <.0001
   Test 3              1.33776          1          0.2474
   Test 4              2.55164          1          0.1102

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 =        22.2766


             BMDL =        13.4576
```

Decreased Number of Pups Born for Female Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation

The procedure outlined above was applied to the data for decreased number of pups born in the R/D toxicity study in rats (Shirota et al., 2008) (see Table 7). Table C-2 summarizes the BMD modeling results. The constant variance model did not provide adequate fit to the variance data, but the nonconstant variance model did. With the nonconstant variance model applied, all models provided adequate fit to the means. BMDLs for models providing adequate fit were considered to be sufficiently close (differed by >two- to threefold, but <threefold), so the model with the lowest AIC was selected (Exponential models 2 and 3).

Table C-2. Modeling Results for Number of Pups Born Data for Female Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation[a]

Model	Variance *p*-Value[b]	*p*-Value for Fit[b]	Scaled Residual for Dose Group[c]	AIC	BMD_{1SD}	$BMDL_{1SD}$
Exponential (model 2)[d, e, f]	**0.7989**	**0.576**	**−0.3771**	**121.0425**	**49.7412**	**29.8647**
Exponential (model 3)[d, e, f]	**0.7989**	**0.6834**	**−0.3771**	**121.0425**	**49.7412**	**29.8647**
Exponential (model 4)[d, e]	0.7989	0.6834	−0.1834	122.1053	36.3464	18.5538
Exponential (model 5)[d, e]	0.7989	0.7306	−0.1834	122.1053	36.3464	18.5538
Hill[d, e]	0.7989	0.3263	−0.129	122.057565	35.0056	17.7975
Linear[d, e]	0.7989	0.3263	−0.881	122.179185	63.2159	39.8283
Polynomial (2-degree)[d, e]	0.7989	0.3263	−0.881	122.179185	63.2159	39.8283
Polynomial (3-degree)[d, e]	0.7989	0.3263	−0.881	122.179185	63.2159	39.8283
Power[d, e]	0.7989	0.3263	−0.881	122.179185	63.2159	39.8283

[a]Shirota et al. (2008).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[d]Coefficients restricted to be negative.
[e]Power restricted to ≥1.
[f]Selected model.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD; BMR = benchmark response; SD = standard deviation.

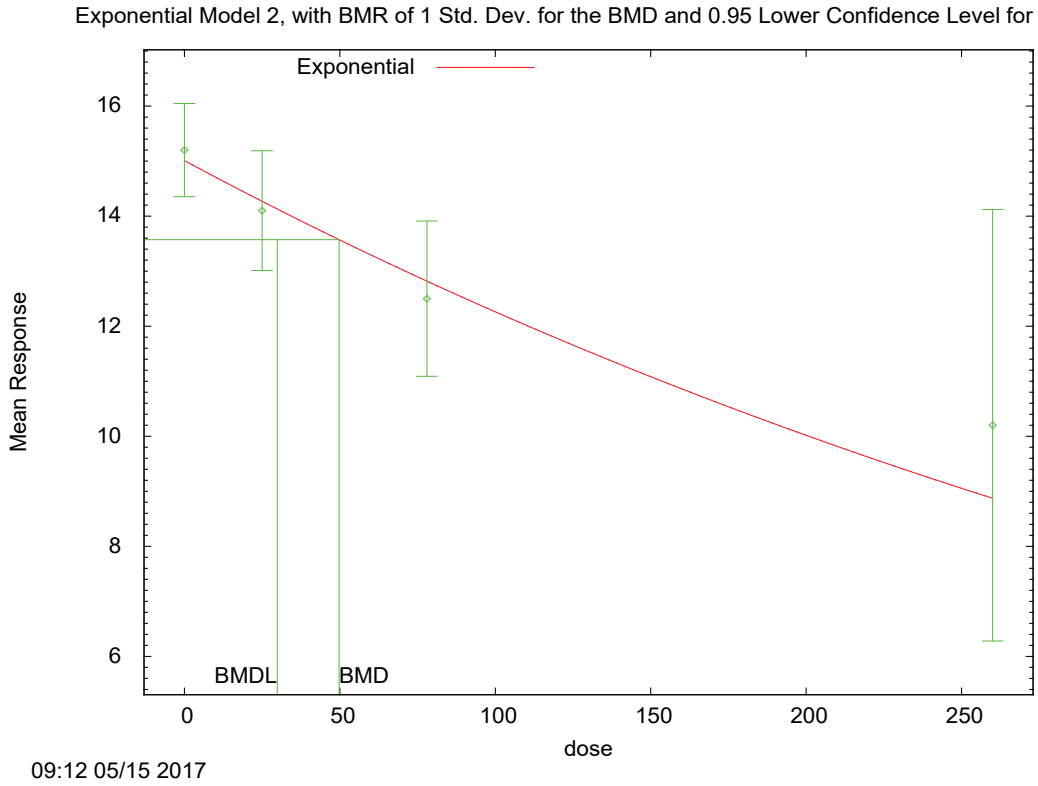

Figure C-2. Exponential Model 2 for Number of Pups Born Data for Female Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation (Shirota et al., 2008)

Text Output for Figure C-2:

```
================================================================
        Exponential Model. (Version: 1.9;  Date: 01/29/2013)
        Input Data File:
C:/Users/JKaiser/Desktop/BMDS240/Data/exp_pupsborn_pta_Exp-ModelVariance-BMR1Std-Down.
(d)
        Gnuplot Plotting File:
                                                Tue May 16 11:50:26 2017
 ================================================================

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

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

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

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

Total number of dose groups = 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 2
lnalpha	17.7989
rho	-6.32411
a	11.7294
b	0.00147751
c	0
d	1

Parameter Estimates

Variable	Model 2
lnalpha	13.5612
rho	-4.73947
a	15.009
b	0.00202169
c	0
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	13	15.2	1.4
25	13	14.1	1.8
78	11	12.5	2.1
260	9	10.2	5.1

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	15.01	1.436	0.4796
25	14.27	1.619	-0.3771
78	12.82	2.087	-0.5077
260	8.873	4.99	0.7978

```
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	-67.21973	5	144.4395
A2	-55.74506	8	127.4901
A3	-55.96952	6	123.939
R	-76.12408	2	156.2482
2	-56.52125	4	121.0425

Additive constant for all log-likelihoods = -42.27. 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 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	40.76	6	< 0.0001
Test 2	22.95	3	< 0.0001
Test 3	0.4489	2	0.7989
Test 4	1.103	2	0.576

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. Model 2 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 =      49.7412

            BMDL =      29.8647
```

Decreased Number of Live Pups on LD 0 for Female Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation

The procedure outlined above was applied to the data for decreased number of live pups on Lactation Day (LD) 0 in the R/D toxicity study in rats (Shirota et al., 2008) (see Table 7). Table C-3 summarizes the BMD modeling results. The constant variance model did not provide adequate fit to the variance data, but the nonconstant variance model did. With the nonconstant variance model applied, all models (except for the Exponential 5 and Hill models) provided adequate fit to the data. BMDLs for models providing adequate fit were considered to be sufficiently close (differed by <two- to threefold), so the model with the lowest AIC was selected (Exponential model 2).

Table C-3. Modeling Results for Number of Live Pups on LD 0 Data for Female Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation[a]

Model	Variance *p*-Value[b]	*p*-Value for Fit[b]	Scaled Residual for Dose Group[c]	AIC	BMD_{1SD}	$BMDL_{1SD}$
Exponential (model 2)[d, e, f]	**0.8357**	**0.761**	**−0.6057**	**126.1103**	**73.6269**	**42.7243**
Exponential (model 3)[d, e]	0.8357	0.4722	−0.5284	128.0809	74.0713	42.726
Exponential (model 4)[d, e]	0.8357	0.761	−0.6057	129.5641	69.7282	33.5638
Exponential (model 5)[d, e]	0.8357	NA	–0.2643	129.564135	72.7046	35.9164
Hill[d, e]	0.8357	NA	–0.264	126.34659	72.261	37.6492
Linear[d, e]	0.8357	0.6762	–0.805	126.34659	84.4452	52.2126
Polynomial (2-degree)[d, e]	0.8357	0.6762	–0.805	126.34659	84.4452	52.2126
Polynomial (3-degree)[d, e]	0.8357	0.6762	–0.805	126.34659	84.4453	52.2126
Power[d, e]	0.8357	0.6762	–0.805	126.34659	84.4452	52.2126

[a]Shirota et al. (2008).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[d]Coefficients restricted to be negative.
[e]Power restricted to ≥1.
[f]Selected model.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD; BMR = benchmark response; LD = lactation day; NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested); SD = standard deviation.

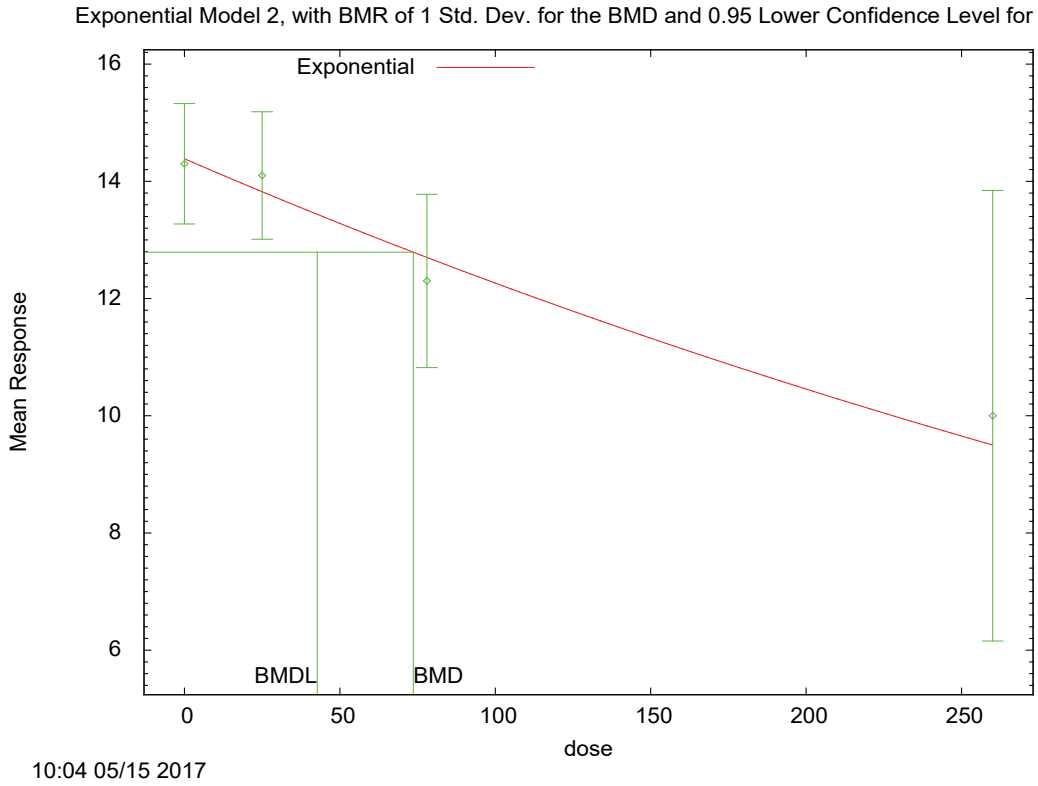

Figure C-3. Exponential Model 2 for Number of Live Pups on LD 0 Data for Female Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation (Shirota et al., 2008)

Text Output for Figure C-3:

```
================================================================================
        Exponential Model. (Version: 1.9;  Date: 01/29/2013)
        Input Data File: C:/Users/JKaiser/Desktop/BMDS240/Data/exp_live
pups0_Exp-ModelVariance-BMR1Std-Down.(d)
        Gnuplot Plotting File:
                                                  Tue May 16 15:59:58 2017
 ================================================================================

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

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

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

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

Total number of dose groups = 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 2
lnalpha	16.6717
rho	-5.89548
a	11.4991
b	0.00141022
c	0
d	1

Parameter Estimates

Variable	Model 2
lnalpha	14.7865
rho	-5.19603
a	14.3854
b	0.00159531
c	0
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	13	14.3	1.7
25	13	14.1	1.8
78	11	12.3	2.2
260	9	10	5

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	14.39	1.594	-0.1931
25	13.82	1.768	0.5649
78	12.7	2.203	-0.6057
260	9.501	4.683	0.3194

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	-67.75308	5	145.5062
A2	-58.60258	8	133.2052
A3	-58.78207	6	129.5641
R	-75.23743	2	154.4749
2	-59.05514	4	126.1103

Additive constant for all log-likelihoods = -42.27. 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 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	33.27	6	< 0.0001
Test 2	18.3	3	0.0003812
Test 3	0.359	2	0.8357
Test 4	0.5461	2	0.761

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. Model 2 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 =      73.6269

             BMDL =      42.7243
```

Decreased Number of Live Pups on LD 4 for Female Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation

The procedure outlined above was applied to the data for decreased number of live pups on LD 4 in the R/D toxicity study in rats (Shirota et al., 2008) (see Table 7). Table C-4 summarizes the BMD modeling results. The constant variance model did not provide adequate fit to the variance data, but the nonconstant variance model did. With the nonconstant variance model applied, all models (except for the Exponential 5 and Hill models) provided adequate fit to the data. BMDLs for models providing adequate fit were considered to be sufficiently close (differed by <two- to threefold), so the model with the lowest AIC was selected (Exponential model 2).

Table C-4. Modeling Results for Number of Live Pups on LD 4 Data for Female Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation[a]

Model	Variance *p*-Value[b]	*p*-Value for Fit[b]	Scaled Residual for Dose Group[c]	AIC	BMD_{1SD}	$BMDL_{1SD}$
Exponential (model 2)[d, e, f]	**0.8688**	**0.9155**	**−0.4143**	**126.717**	**69.4258**	**40.5548**
Exponential (model 3)[d, e]	0.8688	0.679	−0.4278	128.7098	70.349	40.5614
Exponential (model 4)[d, e]	0.8688	0.9155	−0.3823	128.7064	67.8377	32.5953
Exponential (model 5)[d, e]	0.8688	NA	−0.2314	130.5352	70.0084	33.3092
Hill[d, e]	0.8688	NA	−0.231	130.535192	69.7588	NA
Linear[d, e]	0.8688	0.8341	−0.618	126.898088	79.9491	49.9065
Polynomial (2-degree)[d, e]	0.8688	0.8341	−0.618	126.898088	79.9491	49.9065
Polynomial (3-degree)[d, e]	0.8688	0.8341	−0.618	126.898088	79.9491	49.9065
Power[d, e]	0.8688	0.8341	−0.618	126.898088	79.9491	49.9065

[a]Shirota et al. (2008).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[d]Coefficients restricted to be negative.
[e]Power restricted to ≥1.
[f]Selected model.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD; BMR = benchmark response; LD = lactation day; NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested); SD = standard deviation.

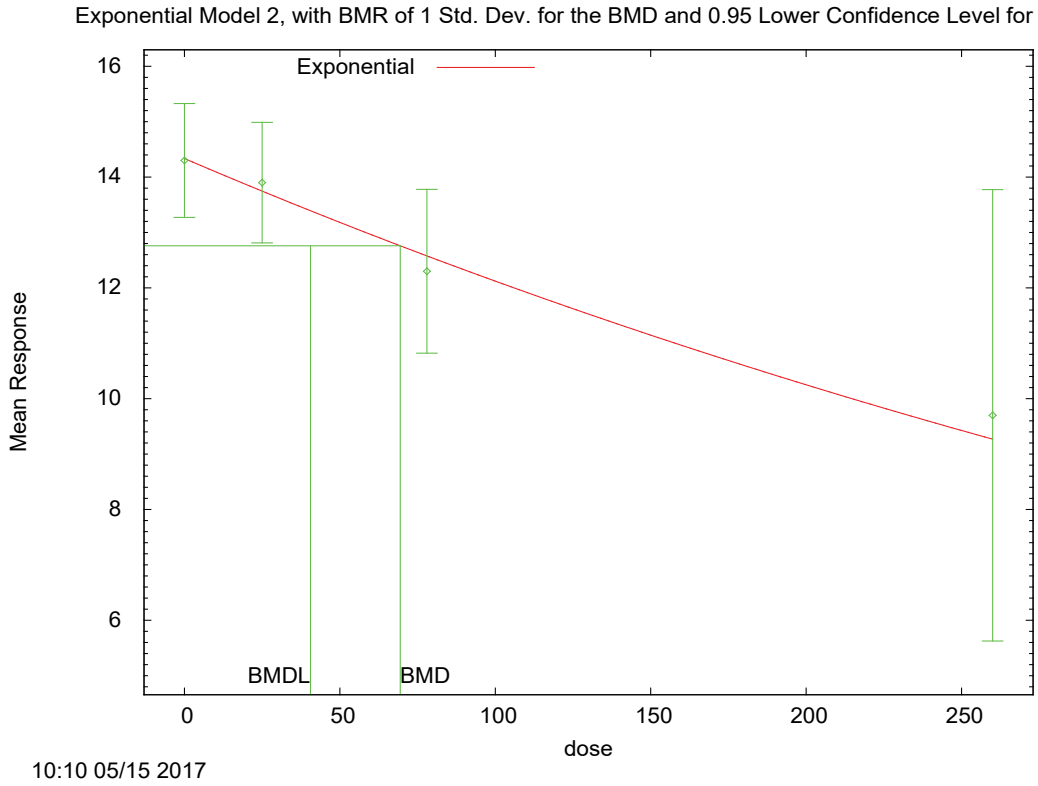

Figure C-4. Exponential Model 2 for Number of Live Pups on LD 4 Data for Female Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation (Shirota et al., 2008)

Text Output for Figure C-4:

```
================================================================
        Exponential Model. (Version: 1.9;  Date: 01/29/2013)
        Input Data File: C:/Users/JKaiser/Desktop/BMDS240/Data/exp_live
pups4_Exp-ModelVariance-BMR1Std-Down.(d)
        Gnuplot Plotting File:
                                                Wed May 17 08:21:52 2017
 ================================================================

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

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

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

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

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

Total number of dose groups = 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 2
lnalpha	16.6143
rho	-5.88729
a	11.2992
b	0.00150862
c	0
d	1

Parameter Estimates

Variable	Model 2
lnalpha	14.8352
rho	-5.23018
a	14.3345
b	0.00167692
c	0
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	13	14.3	1.7
25	13	13.9	1.8
78	11	12.3	2.2
260	9	9.7	5.3

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	14.33	1.575	-0.07906
25	13.75	1.758	0.3158
78	12.58	2.218	-0.4143
260	9.269	4.927	0.2625

```
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	-69.4545	5	148.909
A2	-59.127	8	134.254
A3	-59.2676	6	130.5352
R	-76.98125	2	157.9625
2	-59.35583	4	126.7117

Additive constant for all log-likelihoods = -42.27. 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 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	35.71	6	< 0.0001
Test 2	20.65	3	0.0001242
Test 3	0.2812	2	0.8688
Test 4	0.1765	2	0.9155

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. Model 2 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 =      69.4258

             BMDL =      40.5548
```

Decreased Fertility Index in Female Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation

The procedure outlined above was applied to the data for decreased fertility index (number of nonpregnant females/copulated pairs) in the R/D toxicity study in rats (Shirota et al., 2008) (see Table 7). Table C-5 summarizes the BMD dichotomous modeling results. All models provided adequate fit to the data. BMDLs for models providing adequate fit were considered to be sufficiently close (differed by <threefold), so the model with the lowest AIC was selected (LogProbit model).

Table C-5. Modeling Results for Fertility Index in Female Rats Exposed to *p*-Toluic Acid during Premating, Mating, and Gestation[a]

Model	*p*-Value[b]	Scaled Residuals[c]; Dose	Scaled Residuals[d]; Control	AIC	BMD_{10}	$BMDL_{10}$
Gamma	0.8833	0.334	0	27.2979	109.371	46.9343
Logistic	0.5674	0.842	−0.416	28.2967	164.134	111.606
LogLogistic	0.8882	0.311	0	27.2938	107.708	41.5267
LogProbit[e]	**0.9563**	**0.473**	**0**	**25.2593**	**109.22**	**67.7922**
Multistage	0.8464	0.384	0	27.4279	116.131	46.1995
Probit	0.6104	0.792	–0.366	28.1131	152.334	102.293
Weibull	0.8766	0.334	0	27.33	110.677	46.7493

[a]Shirota et al. (2008).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[d]Scaled residuals for control.
[e]Selected model.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD; BMR = benchmark response.

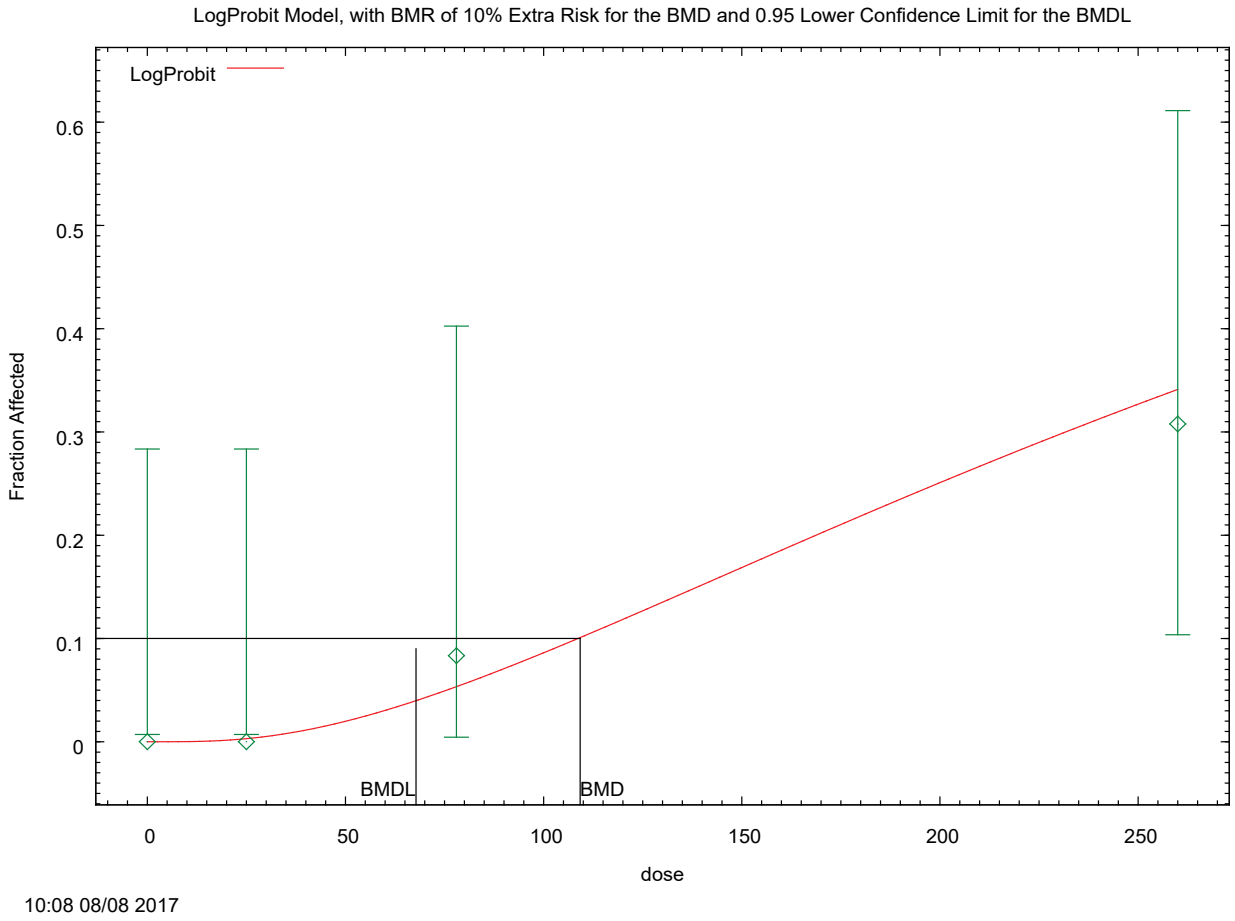

Figure C-5. LogProbit Model for Decreased Fertility Index in Female Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation (Shirota et al., 2008)

Text Output for Figure C-5:

```
Probit Model. (Version: 3.3;  Date: 2/28/2013)
        Input Data File:
C:/Users/JREID/Desktop/BMDS2601/lnp_PREGNANT_Lnp-BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/JREID/Desktop/BMDS2601/lnp_PREGNANT_Lnp-BMR10-Restrict.plt
                                                  Tue Aug 08 10:08:52 2017
 ================================================================

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

   The form of the probability function is:

   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function


   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 (and Specified) Parameter Values
                    background =            0
                     intercept =       -5.821
                         slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

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

              intercept

 intercept            1



                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background                0              NA
      intercept         -5.97491
0.300852            -6.56457            -5.38525
          slope                1              NA

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        -11.4662         4
   Fitted model        -11.6296         1      0.326916      3          0.9549
  Reduced model        -16.3584         1       9.78448      3         0.02049

           AIC:         25.2593


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

```
    0.0000     0.0000         0.000     0.000      13.000        0.000
   25.0000     0.0029         0.038     0.000      13.000       -0.195
   78.0000     0.0528         0.634     1.000      12.000        0.473
  260.0000     0.3394         4.412     4.000      13.000       -0.241

 Chi^2 = 0.32      d.f. = 3        P-value = 0.9563


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =         109.22

            BMDL =        67.7922
```

Decreased Fertility Index in Male Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation

The procedure outlined above was applied to the data for decreased fertility index (number of nonpregnant females/copulated pairs) in the R/D toxicity study in rats (Shirota et al., 2008) (see Table 7). Table C-6 summarizes the BMD dichotomous modeling results. All models provided adequate fit to the data. BMDLs for models providing adequate fit were considered to be sufficiently close (differed by <threefold), so the model with the lowest AIC was selected (LogProbit model).

Table C-6. Modeling Results for Fertility Index in Male Rats Exposed to *p*-Toluic Acid during Premating, Mating, and Gestation[a]

Model	*p*-Value[b]	Scaled Residuals; Dose[c]	Scaled Residuals; Control[c]	AIC	BMD_{10}	$BMDL_{10}$
Gamma	0.8778	0.344	0	27.315	105.607	45.3595
Logistic	0.5656	0.845	−0.415	28.3033	157.895	107.397
LogLogistic	0.8827	0.321	0	27.3112	104.03	40.2255
LogProbit[d]	**0.9552**	**0.475**	**0**	**25.2687**	**105.145**	**65.3087**
Multistage	0.8406	0.395	0	27.448	112.2	44.6475
Probit	0.6083	0.795	–0.365	28.1207	146.558	98.4465
Weibull	0.871	0.344	0	27.3477	106.895	45.1768

[a]Shirota et al. (2008).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also for control.
[d]Selected model.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD; BMR = benchmark response.

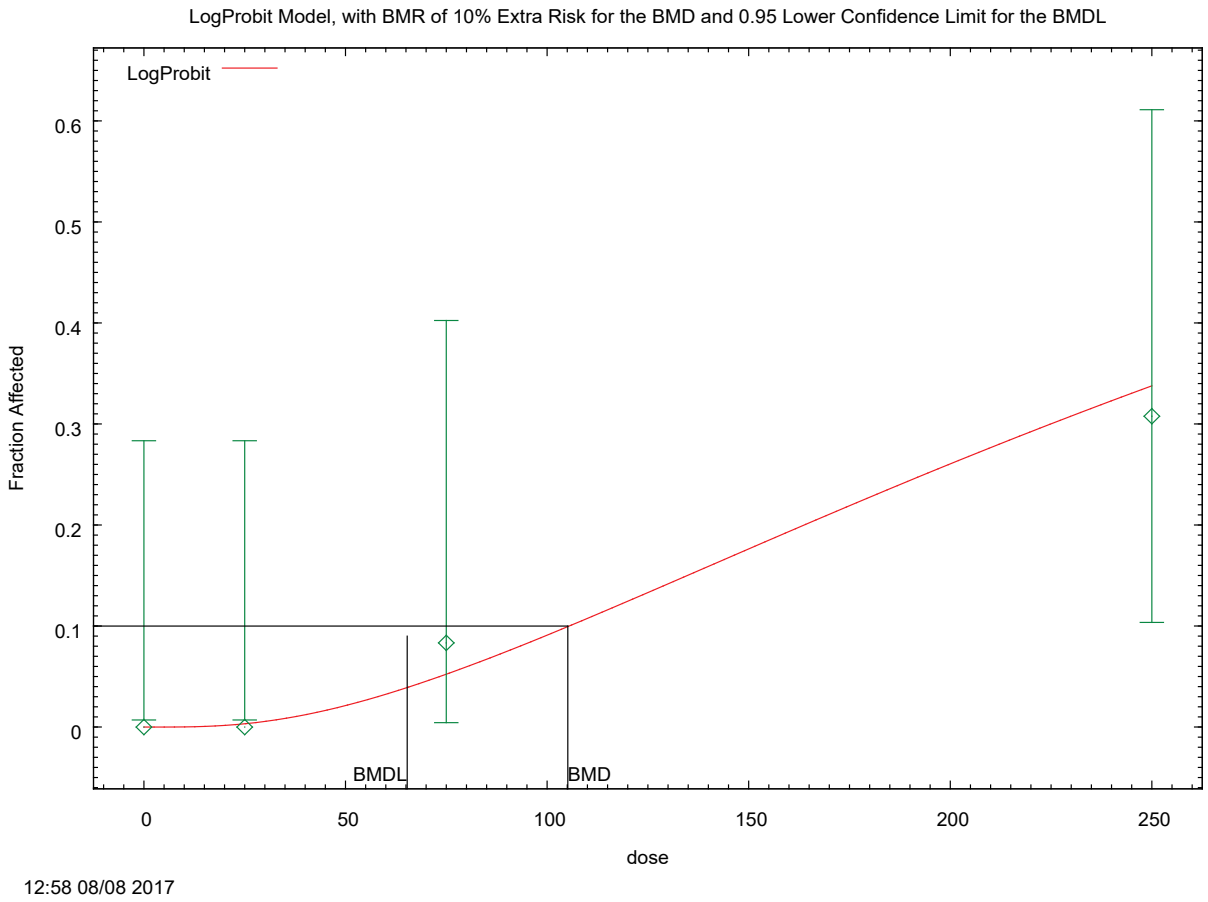

Figure C-6. LogProbit Model for Decreased Fertility Index in Male Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation (Shirota et al., 2008)

Text Output for Figure C-6:

```
  Probit Model. (Version: 3.3;  Date: 2/28/2013)
        Input Data File: C:/Users/JREID/Desktop/BMDS2601/lnp_Male
fertility_Lnp-BMR10-Restrict.(d)
        Gnuplot Plotting File:  C:/Users/JREID/Desktop/BMDS2601/lnp_Male
fertility_Lnp-BMR10-Restrict.plt
                                                Tue Aug 08 12:58:32 2017
 ================================================================================

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

   The form of the probability function is:

   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function


   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 (and Specified) Parameter Values
                    background =            0
                     intercept =     -5.78433
                         slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

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

              intercept

 intercept            1



                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background                0              NA
      intercept         -5.93689
0.300506            -6.52587            -5.34791
          slope                1              NA

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        -11.4662         4
   Fitted model        -11.6345         1      0.336559      3           0.953
  Reduced model        -16.3584         1       9.78448      3         0.02049

           AIC:         25.2689


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

```
    0.0000     0.0000         0.000     0.000      13.000        0.000
   25.0000     0.0033         0.043     0.000      13.000       -0.207
   75.0000     0.0527         0.632     1.000      12.000        0.475
  250.0000     0.3389         4.406     4.000      13.000       -0.238

 Chi^2 = 0.33      d.f. = 3        P-value = 0.9552


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        105.145

            BMDL =        65.3087
```

Decreased Absolute Epididymis Weight in Male Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation

The procedure outlined above was applied to the data for decreased absolute epididymal weights in male rats in Shirota et al. (2008) (see Table 7). Table C-7 summarizes the BMD modeling results. The constant variance model provided adequate fit to the variance data. All models except the Exponential 5 and Hill models provided adequate fit to the data. BMDLs for models providing adequate fit were considered to be sufficiently close (differed by <threefold), so the model with the lowest AIC was selected (Linear).

Table C-7. Modeling Results for Decreased Absolute Epididymis Weight in Male Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation[a]

Model	Variance *p*-Value[b]	*p*-Value for Fit[b]	Scaled Residual for Dose Group[c]	AIC	BMD_{1SD}	$BMDL_{1SD}$
Exponential (model 2)[d, e]	0.8461	0.9604	0.1715	−208.3524	122.396	89.77
Exponential (model 3)[d, e]	0.8461	0.9522	−0.02663	−206.4297	135.354	90.121
Exponential (model 4)[d, e]	0.8461	0.9604	0.1715	−208.3524	122.396	60.493
Exponential (model 5)[d, e]	0.8461	NA	1.11×10^{-6}	−204.4333	131.034	61.182
Hill[d, e]	0.8461	NA	-1.80×10^{-7}	−204.43333	131.39	60.546
Linear[d, e, f]	**0.8461**	**0.977**	**0.111**	**−208.38682**	**126.584**	**94.617**
Polynomial (2-degree)[d, e]	0.8461	0.9145	−0.037	−206.42179	137.436	94.772
Polynomial (3-degree)[d, e]	0.8461	0.9145	−0.037	−206.42179	137.436	94.772
Power[d, e]	0.8461	0.9415	−0.0332	−206.42795	136.291	94.8

[a]Shirota et al. (2008).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[d]Coefficients restricted to be negative.
[e]Power restricted to ≥1.
[f]Selected model.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD; BMR = benchmark response; LD = lactation day; NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested); SD = standard deviation.

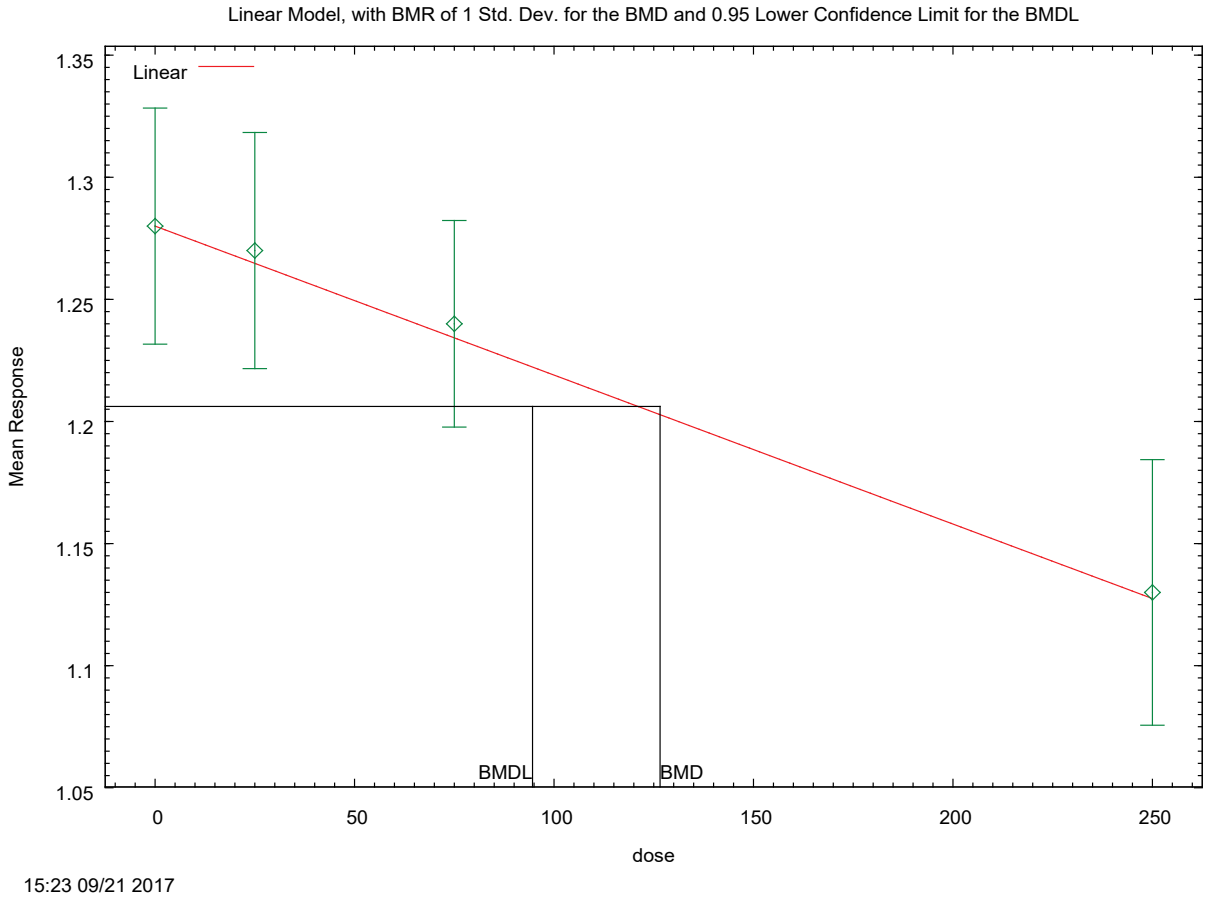

Figure C-7. Linear Model for Decreased Absolute Epididymis Weight for Male Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation (Shirota et al., 2008)

Text Output for Figure C-7:

```
Polynomial Model. (Version: 2.20;  Date: 10/22/2014)
         Input Data File: C:/Users/JREID/Desktop/BMDS2601/lin_epdid
abs_Lin-ConstantVariance-BMR1Std.(d)
         Gnuplot Plotting File:  C:/Users/JREID/Desktop/BMDS2601/lin_epdid
abs_Lin-ConstantVariance-BMR1Std.plt
                                                Thu Sep 21 15:23:28 2017
 ================================================================

 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
   rho is set to 0
```

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

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



                  Default Initial Parameter Values
                          alpha =      0.00645
                            rho =            0   Specified
                         beta_0 =      1.28336
                         beta_1 = -0.000609836


           Asymptotic Correlation Matrix of Parameter Estimates

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

                   alpha       beta_0       beta_1

     alpha             1     6.8e-009     2.1e-010

    beta_0     6.8e-009            1        -0.67

    beta_1     2.1e-010        -0.67            1


                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
          alpha       0.00595917       0.00116869          0.00366858
0.00824976
         beta_0          1.28336        0.0143755             1.25519
1.31154
         beta_1     -0.000609836
0.000109652         -0.00082475        -0.000394922


     Table of Data and Estimated Values of Interest

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

    0    13       1.28         1.28         0.08       0.0772         -0.157
   25    13       1.27         1.27         0.08       0.0772         0.0881
   75    13       1.24         1.24         0.07       0.0772          0.111
  250    13       1.13         1.13         0.09       0.0772        -0.0421


 Model Descriptions for likelihoods calculated
```

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

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

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

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


                     Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1          107.216664            5    -204.433329
              A2          107.623729            8    -199.247457
              A3          107.216664            5    -204.433329
          fitted          107.193408            3    -208.386817
               R           95.057526            2    -186.115053


                   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              25.1324          6       0.0003227
   Test 2             0.814129          3          0.8461
   Test 3             0.814129          3          0.8461
   Test 4             0.046512          2           0.977

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

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


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

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


              Benchmark Dose Computation

Specified effect =             1

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

```
Confidence level =          0.95

             BMD =       126.584


            BMDL =       94.6168
```

Decreased Relative Epididymis Weight in Male Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation

The procedure outlined above was applied to the data for decreased absolute epididymal weights in male rats in Shirota et al. (2008) (see Table 7). Table C-8 summarizes the BMD modeling results. Neither constant variance or nonconstant variance models provided adequate fit to the variance data. Therefore, the decreased relative epididymal data in male rats could not be modeled.

Table C-8 Modeling Results for Decreased Relative Epididymis Weight in Male Rats Exposed to *p*-Toluic Acid via Gavage during Premating, Mating, Gestation, and Lactation[a]

Model	Variance *p*-Value[b]	*p*-Value for Fit[b]	Scaled Residual for Dose Group[c]	AIC	BMD_{1SD}	$BMDL_{1SD}$
Exponential (model 2)[d, e]	0.003362	0.4022	−0.002952	−345.2806	202.695	132.478
Exponential (model 3)[d, e]	0.003362	0.4022	−0.002953	−345.2806	202.695	132.478
Exponential (model 4)[d, e]	0.003362	0.3279	1.064	−344.145	149.468	53.5089
Exponential (model 5)[d, e]	0.003362	0.3279	1.064	−344.145	149.468	53.5089
Hill[d, e]	0.003362	0.367	1.16	−344.28841	149.705	42.7573
Linear[d, e]	0.003362	0.3868	−0.00128	−345.20218	205.854	138.049
Polynomial (2-degree)[d, e]	0.003362	0.3868	−0.00128	−345.20218	205.854	138.049
Polynomial (3-degree)[d, e]	0.003362	0.3868	−0.00128	−345.20218	205.854	138.049
Power[d, e]	0.003362	0.3868	−0.00128	−345.20218	205.854	138.049

[a]Shirota et al. (2008).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[d]Coefficients restricted to be negative.
[e]Power restricted to ≥1.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD; BMR = benchmark response; LD = lactation day; NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested); SD = standard deviation.

APPENDIX D. REFERENCES

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