FINAL
11-14-2012

Provisional Peer-Reviewed Toxicity Values for

p-Toluidine
(CASRN 106-49-0)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS

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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR *p*-TOLUIDINE (CASRN 106-49-0)

BACKGROUND

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

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

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

DISCLAIMERS

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

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

QUESTIONS REGARDING PPRTVs

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

INTRODUCTION

p-Toluidine occurs as white or colorless leaflets or lustrous plates with an aromatic odor and burning taste (HSDB, 2009). Its major uses include the manufacture of dyes (basic red 9 and acid green 25); organic synthesis; reagent for lignin, nitrite, and phloroglucinol; and the preparation of ion exchange resins. Occupational exposure to *p*-toluidine may occur through inhalation and dermal contact with this compound at workplaces where *p*-toluidine is produced or used. The general population may be exposed to *p*-toluidine via inhalation of ambient air and tobacco smoke, ingestion of contaminated food and drinking water, and/or dermal contact with this compound. The empirical formula for *p*-toluidine is C_7H_9N, and the molecular structure of *p*-toluidine is presented in Figure 1. Some physicochemical properties of *p*-toluidine are provided in Table 1.

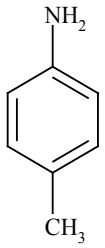

Figure 1. *p*-Toluidine Structure

Table 1. Physicochemical Properties for *p*-Toluidine[a]

Property (unit)	Value
Boiling point (ºC)	200.4
Melting point (ºC)	44−45
Density (g/cm^3 at 20ºC)	0.9619
Vapor pressure (mm Hg at 25ºC)	0.286
pH (unitless)	Not available
Solubility in water (g/L at 20ºC)	6.64
Relative vapor density (air = 1)	3.9
Molecular weight (g/mol)	107.16
Octanol/water partition coefficient (log Kow, unitless)	1.39

[a]Values were obtained from HSDB (2009).

No reference dose (RfD), reference concentration (RfC), or cancer assessment for *p*-toluidine is included in the IRIS database (U.S. EPA, 2010a) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2009). The HEAST (U.S. EPA, 2010b) reports an OSF of 0.19 per mg/kg-day and an oral unit risk of 5.4×10^{-6} per µg/L. These values were based on liver tumors following dosing for 18 months in the mouse. A PPRTV document also exists for *p*-toluidine (U.S. EPA, 2002) examining the potential derivation of a chronic p-RfD. The 2002 PPRTV states that a p-RfD could not be derived for *p*-toluidine due to the lack of human data and inadequate animal data. Since that time a new subchronic study has become available (Jodynis-Liebert, 2005). For this reason, the database for this chemical has been reviewed.

The CARA list (U.S. EPA, 1994) includes a Health and Environmental Effects Profile (HEEP) for *p*-toluidine (U.S. EPA, 1985). The toxicity of *p*-toluidine has not been reviewed by ATSDR (2008). The toxicity of *p*-toluidine has not been reviewed by the World Health Organization (WHO, 2010). CalEPA (2008, 2010) has not derived toxicity values for exposure to *p*-toluidine. The American Conference of Governmental Industrial Hygienists (ACGIH, 2010) reports a threshold limit value (TLV) of 2 ppm, 8.8-mg/m^3 time-weighted average (skin). The Occupational Safety and Health Administration (OSHA, 2010) reports a vacated permissible exposure limit (PEL) of 2 ppm, 8.8-mg/m^3 time-weighted average (skin). Both the TLV and PEL are based on a calculated permeability coefficient for *o*-toluidine (U.S. EPA, 1992). The National Institute of Occupational Safety and Health (NIOSH, 2010) identifies *p*-toluidine as a potential carcinogen and recommends that occupational exposures to carcinogens be limited to the lowest feasible concentration.

The HEAST (U.S. EPA, 2010b) reports an OSF of 0.19 per mg/kg-day for *p*-toluidine based on liver tumors in CD-1 mice exposed to *p*-toluidine in the diet at 1000 or 2000 ppm for 6 months followed by 12 months on a 500- or 1000-ppm diet, respectively (Weisburger et al., 1978). The International Agency for Research on Cancer (IARC, 2010) has not reviewed the carcinogenic potential of *p*-toluidine. *p*-Toluidine is not included in the National Toxicology Program's *12th Report on Carcinogens* (NTP, 2011). CalEPA (2008) has not derived a quantitative estimate of carcinogenic potential for *p*-toluidine.

Literature searches were conducted on sources published from 1900 through July 2011 for studies relevant to the derivation of provisional toxicity values for *p*-toluidine (CAS No. 106-49-0). Searches were conducted using EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI, and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); World Health Organization; and

Worldwide Science. The following databases outside of HERO were searched for health-related values: ACGIH, ATSDR, CalEPA, EPA IRIS, EPA HEAST, EPA HEEP, EPA OW, EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides an overview of the relevant database for *p*-toluidine and includes all potentially relevant repeated short-term-, subchronic-, and chronic-duration studies. NOAELs, LOAELs, and BMDL/BMCLs are provided in HED/HEC units for comparison except that oral noncancer values are not converted to HEDs and are identified in parentheses as (Adjusted) rather than HED/HECs. Principal studies are identified. Entries for the principal studies are bolded.

Table 2. Summary of Potentially Relevant Data for *p*-Toluidine (CASRN 106-49-0)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry	Critical Effects	NOAEL	BMDL/ BMCL	LOAEL[a]	Reference (Comments)	Notes[b]
Human								
1. Oral (mg/kg-day)								
No studies were located.								
2. Inhalation (mg/m^3)								
No studies were located.								
Animal								
1. Oral (mg/kg-day)								
Subchronic	**8/0, Wistar rat, dietary, 7 days/week, 1 or 3 months**	**0, 40, 80, or 160 for 1 or 3 months**	**Increased methemoglobin content in blood**	**N/A**	**No adequate BMD model fits to data**	**40**	**Jodynis-Liebert and Bennasir (2005); LOAEL identified from a statistical significant increase in methemoglobin levels for both exposure durations (i.e., 1 or 3 months) and both diet types (4 or 14% fat)**	**PS PR**
	10/0, rat, dietary, 7 days/week, 28 days	0, 14, 67, or 126	Increased relative liver weight	14	Not performed	67	IBT (1973) Information from ACGIH (2001); the full primary reference for this study is not available	NPR
Chronic	**0/8, Wistar rat, dietary (24% or 8% protein), 7 days/week, 6 or 12 months**	**0, 40, 80, or 160**	**Increased methemoglobin content in blood, findings, clinical signs, kidney and liver effects, and decreased body weight**	**N/A**	**Not Performed**	**40**	**Malik-Bryś and Seńczuk (1995a,b,c)**	**PS PR**

Table 2. Summary of Potentially Relevant Data for *p*-Toluidine (CASRN 106-49-0)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry	Critical Effects	NOAEL	BMDL/ BMCL	LOAEL[a]	Reference (Comments)	Notes[b]
Developmental	None							
Reproductive	None							
Carcinogenicity	25/0, Cr1:CDBL rat, dietary, 7 days/week, 18 months exposure followed by 6 months control diet prior to sacrifice	0, 20, or 40	No increase in tumors was observed	N/A	Not performed	N/A	Weisburger et al. (1978a)	PR
Carcinogenicity	**25/25, CD-1 mouse, dietary, 7 days/week, 18 months followed by 3 months control diet prior to sacrifice**	**0, 15, or 30**	**Incidences of liver tumors in male mice were increased in both treated groups (47−50%) compared to concurrent controls (17%)**	**N/A**	**Male: 3 Female: 8.3**	**N/A**	**Weisburger et al. (1978b)**	**PS PR**
2. Inhalation (mg/m^3)								
No studies were located.								

[a]Not reported by the study author but determined from data.
[b]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-day) for oral noncancer effects and a human equivalent dose (HED in mg/kg-day) for oral carcinogenic effects. All long-term exposure values (4 weeks and longer) are converted from a discontinuous to a continuous (weekly) exposure. HED_n = (avg. mg test article ÷ avg. kg body weight ÷ number daily dosed)$^{1/4}$.

HUMAN STUDIES

Oral Exposures

No oral studies were found on the subchronic, chronic, developmental, or reproductive toxicity or on the carcinogenicity of *p*-toluidine in humans.

Inhalation Exposures

No inhalation studies were found on the subchronic, chronic, developmental, or reproductive toxicity or on the carcinogenicity of *p*-toluidine in humans.

ANIMAL STUDIES

Oral Exposure

The effects of oral exposure of animals to *p*-toluidine were evaluated in two subchronic-duration studies: Jodynis-Liebert and Bennasir (2005) and IBT (1973) and one chronic-duration study: Malik-Bryś and Seńczuk (1995).

Subchronic-duration Studies

Jodynis-Liebert and Bennasir (2005) is selected as the principal study for deriving the screening subchronic p-RfD. In this peer-reviewed study, *p*-toluidine (99.7% purity) was administered in the diet to eight male Wistar rats/dose group/diet type at nominal doses of 0, 40, 80, and 160 mg/kg-day[1] for 1 or 3 months. Two diet types were used: *p*-toluidine was mixed with standard diet (4% fat) or standard diet supplemented with 10% sunflower oil (14% fat). The animals were obtained from the University of Medical Sciences in Poznań, Poland, and housed under acceptable conditions. This study also evaluated the toxicity of *o*-toluidine and *m*-toluidine; however, the results from those tests are not germane to this report. The content of toluidines in the diet and homogeneity were determined every 2 weeks. The stability of the compound in the diet under test conditions was not reported. Body weight, food consumption, and water consumption were measured every third day. Rats were placed in metabolic cages every week (1-month treatment) or 2 weeks (3-month treatment), and urine was collected over 24 hours for quantification of the toluidines by gas chromatography. Rats were euthanized via cardiac puncture under narcotan anesthesia, and blood was collected. Plasma was separated, and livers were perfused with cold 1.15% KCl. Liver samples were stored at −70°C until analyzed. Liver homogenates were prepared for the lipid peroxidation assay. A marker of lipid peroxidation, malondialdehyde concentration, was measured in the liver by the thiobarbituric acid reactive substances (TBARS) assay. From the blood, methemoglobin (MetHb), serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), sorbitol dehydrogenase (SDH), and blood urea nitrogen (BUN) concentrations were measured, as was hepatic glutathione. Gross or histological pathology was not performed. Statistical analyses were performed using analysis of variance and Student's *t*-test, or the Kruskal-Wallis and Newman-Keuls tests if the variances were not homogeneous. Treated groups were compared to controls, and the two types of diet were compared to each other. Differences with *p*-values of 0.01 or less were reported as statistically significant.

The study authors stated that there were no remarkable changes in the general appearance of the rats (Jodynis-Liebert and Bennasir, 2005). Treatment-related effects were observed in this study and are described below. The mean body-weight gain for the 3-month study was decreased by 29−31%, 21−27%, and 62−80% at 40, 80, and 160 mg/kg-day, respectively.

[1]Doses were provided in Jodynis-Liebert and Bennasir (2005).

Body-weight losses were infrequently observed at 160 mg/kg-day. The study authors stated that similar effects were noted in the 1-month study animals. Methemoglobin content was increased ($p \leq 0.01$) by 113−843% in all treated groups (see Table B.1). Typically, the increases were similar at 40 and 80 mg/kg-day, and increases were greater in magnitude at 160 mg/kg-day. Increases in MetHb content were also statistically significantly greater ($p < 0.01$) in the standard diet groups compared to the high-fat diet groups at the two highest dose groups. Reduced glutathione (GSH) concentrations in the liver were increased by 90−233% in all treated groups. In the high-fat diet groups, the magnitude of the increase was greatest at 40 mg/kg-day and least at 160 mg/kg-day (seemingly unrelated to dose). In the standard diet groups, the magnitude of increase was similar at 40 and 80 mg/kg-day, but higher at 160 mg/kg-day. The GSH content in liver between the different diets (based on fat content) differed significantly ($p < 0.01$) at 40 and 160 mg/kg-day. Lipid peroxidation (nmol TBARS/g tissue) was increased (not statistically significant) in the 160 mg/kg-day, high-fat, 3-month group by 24% and was increased ($p < 0.01$) by 65−352% in the other treated groups. A dose-related effect was only obvious in the standard diet, 1-month group. In the other groups, lipid peroxidation levels were similar at 40 mg/kg-day to 80 mg/kg-day but were less at 160 mg/kg-day. Serum ALT levels were generally increased, but the effects were unrelated to dose and not sufficient to be indicative of a biologically adverse effect. Levels of serum AST, SDH, and BUN were similar to controls.

It was not stated if stability of the *p*-toluidine in the diet was confirmed or whether this study was conducted according to Good Laboratory Practice (GLP) standards (40 CFR Part 160; Jodynis-Liebert and Bennasir, 2005). However, this study supports the development of a p-RfD because of the well documented and scientifically acceptable nature of the publication. The LOAEL for Jodynis-Liebert and Bennasir (2005) is identified to be 40 mg/kg-day for significantly increased methemoglobin content in blood; no NOAEL is identified.

An unpublished study by IBT (1973) administered *p*-toluidine (purity not reported) in the diet to 10 male rats (strain not reported) per dose group at nominal doses of 0, 14, 67, or 126 mg/kg-day for 4 weeks. Decreased body-weight gain was noted at 126 mg/kg-day, and significantly increased relative liver weights were observed at 67 and 126 mg/kg-day. The full primary reference for this study is not available. In limited microfiche copies of this reference, few data were reported, no explanation of study design was given, and the data tables are barely legible, making this study unusable for derivation of a subchronic p-RfD. Additional data from this study were provided in the review by ACGIH (2001).

Chronic-duration Studies

Malik-Bryś and Seńczuk (1995a,b,c) is selected as the principal study for deriving the screening chronic p-RfD. In this peer-reviewed study, young female Wistar rats were divided into 14 experimental groups. Each toluidine isomer (*ortho, meta, or para)* was administered separately in the diet at 0, 40, 80, 160 mg/kg-day to 8 rats/group for periods of 6 months or at 160 mg/kg-day for 12 months. Dietary administration (unknown purity of compound) was via a 24% protein diet (standard diet) or 8% protein diet. This study was designed to examine the impact of dietary protein levels on blood and urine concentrations of the test chemicals, and the effects of the test chemicals and dietary protein on blood and liver activities of certain enzymes, body weights, clinical signs, and histological findings. It is unknown if the study was performed under GLP standards. Urine was collected in metabolic cages for 24 hours after compound administration. Blood was collected from the rats' hearts 1 hour after *o*- and *m*-toluidine were administered, and 2 hours after *p*-toluidine was

administered, which corresponds to the maximal concentration of the compounds in the blood. Toluidine was isolated from the blood and urine samples by chloroform extraction, and toluidine concentrations were determined by gas chromatography. The methemoglobin content in the same blood samples was assayed by spectrophotometry. Measurements of the following blood serum enzymes' activity were also taken using commonly known methods: aniline hydroxylase, amidopyrine demethylase, and β-glucuronidase. Morphological evaluation of the blood was also performed. Complete hemograms of the blood collected from animals exposed to toluidine and from the control animals were also performed. The levels of hemoglobin, erythrocytes, leukocytes, hematocrit, thrombocytes, and reticulocytes were measured. The results obtained were statistically analyzed using the Student, Cochran-Cox, or Duncan tests.

After 6 months of dietary exposure to *p*-toluidine, the methemoglobin content was reported by the study authors to be statistically significantly increased in animals at all doses tested compared to the control animals (Malik-Bryś and Seńczuk, 1995a,b,c). An increase in *p*-toluidine concentration in blood and urine was noted as the administered dose increased. Treatment at 40, 80, and 160 mg/kg-day in the 8% protein diets resulted in 2.2%, 6.7%, and 10.5% methemoglobin, respectively. Treatment at 40, 80, and 160 mg/kg-day in the 24% protein diets resulted in approximately 4.7%, 7.0%, and 10.4% methemoglobinemia, respectively. Methemoglobin values in controls were 0.8%. Significant decreases in the quantity of thrombocytes, erythrocytes, and leukocytes were observed, as well as an increase in the number of reticulocytes (actual data not reported).

Treatment with *p*-toluidine (Malik-Bryś and Seńczuk, 1995a,b,c) in the 8% protein diet (dose level not reported) resulted in the following effects compared to treatments in the 24% protein diet: less toluidine in the blood, less toluidine in the urine, and differential effects in MetHb values compared to those presented above. The following findings were listed for the 8% protein dietary formulations but were not listed for the 24% protein dietary formulations: limb paresis, convulsion, alopecia, blood in the urine, frequent falls, increased β-glucuronidase in liver (not dose- or time-dependent), and increased analine hydroxylase (not dose-dependent, but time-dependent; unknown toxicological significance). Treatment at 160 mg/kg-day in the 8% protein diet for 12 months resulted in the following kidney findings: inflammation of the parenchyma, hyaline droplet degeneration, homogeneous protein masses, congestive cysts, and dystrophic calcification. Treatment (dose not reported) in the 8% protein diet treatment group also resulted in adrenal neutrophilic adenomas, which the study authors stated were associated with the decreased protein content in the feed and probably had no relationship with the effects of *p*-toluidine. Liver effects were noted in animals from both diets (doses not specified) but were most evident in animals receiving the 8% protein diet. These effects included enlarged portal area, necrosis, focal steatosis, infiltration of lymphocyte-like mononuclear cells, and multiplication of nuclei. Decreased body weights were noted with treatment in both diets. In the 24% protein diet, decreased thrombocytes, erythrocytes, leukocytes, and reticulocytes were observed, but the actual doses at which the effects were noted were not reported.

Although the study by Malik-Bryś and Seńczuk (1995a,b,c) does not present quantitative data, only a bar graph, for any effects due to *p*-toluidine, the study authors do report statistical significant changes. Specifically, a dose-related increase in methemoglobin blood levels due to *p*-toluidine was noted to be statistically significant at all doses tested following 6 months of *p*-toluidine exposure in the diet. Because data were not presented and means with standard deviations were not reported, benchmark dose modeling of treatment-related effects is not

possible. However, a LOAEL of 40 mg/kg-day can be identified from this study based on statistically significant increases in methemoglobin levels after 6 months dietary treatment of *p*-toluidine. Because 40 mg/kg-day is the lowest dose tested, a NOAEL cannot be identified.

Developmental and Reproductive Studies

No studies could be located regarding the effects of *p*-toluidine on development and reproduction in animals.

Carcinogenicity Studies

In a peer-reviewed study, Weisburger et al. (1978a) administered *p*-toluidine (≥97% purity) in the diet to 25 male Sprague-Dawley rats/dose group at nominal doses of 1000 or 2000 mg/kg dietary concentration for 18 months. Animals were maintained on control diets for an additional 6 months prior to study termination. The calculated human equivalent doses are 20 and 40 mg/kg-day.[2] Many other compounds were similarly tested in this study, but the results from these tests are not discussed because these chemicals are not the subject of this report. A necropsy was performed on all animals that survived at least 6 months on test and/or were euthanized at the end of the experimental period. Histological examination was done on all grossly abnormal organs, tumor masses, lung, liver, spleen, kidney, adrenal, heart, bladder, stomach, intestines, reproductive organs, and pituitary glands. Statistical analysis of tumor data was performed using the Fisher's Exact Test. Two control groups were used: a matched control group (by sex and compound) that was conducted concurrently with the treated animals and a pooled control group, which included the control data for all tested compounds grouped by sex. Tumors in treated groups with *p*-values of 0.05 or less for both matched and pooled controls were deemed statistically significant. The study authors stated that the primary goal of the study was to assess the possible carcinogenic effect of these compounds; nonneoplastic degenerative or inflammatory lesions were recorded when they occurred but were only mentioned when considered treatment related. Other parameters (such as body-weight gain and clinical chemistry) were not reported. No nonneoplastic findings were reported for *p*-toluidine, and no treatment-related neoplastic findings were observed in the male rat.

The mouse study by Weisburger et al. (1978b) is selected as the principal study for deriving the provisional oral slope factor (p-OSF). In a peer-reviewed study, Weisburger et al. (1978b) administered *p*-toluidine (≥97% purity) in the diet to 25 CD-1 mice/sex/dose group at nominal doses of 1000 or 2000 mg/kg dietary concentration for 6 months. The mice were treated an additional 12 months with lowered doses of 500- or 1000-mg/kg dietary concentration. Animals were maintained on control diets for an additional 3 months prior to study termination. The nominal time-weighted-average total dietary concentrations are 571 mg/kg ([(1000 mg/kg × 6 months) + (500 mg/kg × 12 months)] ÷ 21 months total) and 1143 mg/kg ([(2000 mg/kg × 6 months) + (1000 mg/kg × 12 months)] ÷ 21 months total). The nominal time-weighted-average human equivalent doses are 15 and

[2]Human Equivalent Dose = Feed Concentration × Food Consumption per Day × (1 ÷ Body Weight) × (Months Dosed ÷ Total Months) × $[BW_{animal} \div BW_{human}]^{0.25}$, where body weights used were from EPA's (1994b) chronic values for male Sprague-Dawley Rats (0.523 kg) and where feed intakes used were from EPA's (1988) chronic values for male Sprague-Dawley Rats (0.036 kg) and where BW_{human} (70 kg) was obtained from EPA's *Exposure Factors Handbook* (1997); Months Dosed was 18, and Total Months was 24.

30 mg/kg-day.[3] Histological examination of pituitary glands was not performed, but other details of methodology were as described above for rats (Weisburger et al., 1978a).

No nonneoplastic findings were reported for *p*-toluidine (Weisburger et al., 1978b). In male mice, the incidences of liver tumors were increased in the treated groups (47−50%) compared to the concurrent control (17%) and the pooled controls for the entire study (7%; see Table B.2). The difference was significant in the low dose compared to the pooled controls ($p < 0.025$) and in the high dose compared to both the simultaneous and the pooled controls ($p < 0.05$). In female mice, the incidences of liver tumors were increased in the treated groups (10−18%) compared to the simultaneous control (0%) or the pooled controls for the entire study (1%). The difference was significant at the high dose compared to only the pooled controls ($p < 0.025$). No information was provided regarding age of tumor onset.

It is unclear if this study (Weisburger et al., 1978a,b) was conducted according to GLP standards (40 CFR Part 160; November 26, 1983). Only limited details of the animal husbandry were provided: mice were housed up to 5 animals per plastic cage, and rats were housed up to 3 animals per cage, and the temperature was maintained at 23 ± 2°C. The stability of the *p*-toluidine in the diet was tested; however, it was not stated if homogeneity and concentration analyses were performed for the dietary formulations. It was not clear exactly which parameters (e.g., hematology, clinical chemistry, histology) were evaluated, and the study authors did not report results of these evaluations if they did not consider them related to treatment. The focus of this study was the incidence of neoplastic lesions. The type and incidence of each liver tumor were not reported nor was mean time-to-tumor onset. The actual time-weighted-average intakes were also not reported.

Inhalation Exposure

No inhalation studies were found on the subchronic, chronic, developmental, or reproductive toxicity or carcinogenicity of *p*-toluidine in animals.

[3]Human Equivalent Dose = Time-Weighted Food Concentration × Food Consumption per Day × (1 ÷ Body Weight) × $[BW_{animal} \div BW_{human}]^{0.25}$, where body weights used were from EPA's (1994) chronic values by averaging the body weights for the total female and male mouse strains (0.030225 kg) and where feed intakes used were from EPA's (1988) chronic values by averaging the feed intakes for the total female and male mouse strains (0.0055 kg) and where BW_{human} (70 kg) was obtained from EPA's *Exposure Factors Handbook* (1997).

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Genotoxicity	Male Crl:CD®BR rats were treated by gavage with 500-mg/kg radiolabeled toluidine in corn oil. Rats were treated with either *o*- or *p*-toluidine and sacrificed (4−5 rats/time point) at various times up to 48 hours postdose. Liver samples were prepared for quantitation of DNA, RNA, and total protein binding. Additionally, blood samples were obtained at various time points up to 72 hours postdose from another group of rats to determine plasma kinetics. Various tissues were sampled at termination to determine tissue distribution of radioactivity.	DNA, RNA, and total protein binding occurred and were more prominent with *p*-toluidine than *o*-toluidine. The plasma elimination half-life was approximately 12−15 hours. Highest tissue concentrations of *p*-toluidine residues were found in liver, kidney, skin, and fat.	DNA-binding occurs indicating that *p*-toluidine may be an initiator.	Brock et al. (1990)
Genotoxicity	An in vitro chemical hydroxylation system (Udenfriend) was used to evaluate the genotoxicity of breakdown products of *p*-toluidine in *Saccharomyces cerevisiae.*	The resulting breakdown products of *p*-toluidine incubated in Udenfriend hydroxylation medium induced reciprocal recombination in diploid strain D-3 but not in the parent compound.	The study author suggests that *N*-hydroxylation of *p*-toluidine in vivo may result in bioactivation to a carcinogenic product.	Mayer (1977)
Genotoxicity	In vitro mutagenicity tests were performed in *Salmonella typhimurium* strains TA1535 and TA1538. The DNA-modifying capacity was determined with normal and DNA polymerase-deficient *Escherichia coli*.	Induction of mutations and DNA-modification by *p*-toluidine were not noted.	*p*-Toluidine genotoxicity was negative in these tested systems.	Rosenkranz and Poirier (1979)
Genotoxicity	This report summarizes the genotoxicity of *p*-toluidine. Tests were performed in *S. typhimurium*, *E. coli*, *S. cerevisiae,* primary rat hepatocytes, Chinese hamster lung fibroblasts, and other test systems.	The summarized results regarding *p*-toluidine genotoxicity were generally negative.	*p*-Toluidine was generally negative in these tested systems.	ACGIH (2001)
Acute Toxicity	This report summarizes the acute effects of *p*-toluidine in humans and animals.	LD_{50} values for *p*-toluidine in the rat, mouse, and rabbit were reported. It was an ocular and upper respiratory irritant in a rat inhalation study, and a dermal sensitizer in a guinea pig study. *p*-Toluidine intoxication results in methemoglobinemia and hematuria in humans.	The acute toxicity is slight compared to other toxic compounds.	ACGIH (2001)

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Metabolism	A single oral dose of 500-mg/kg *p*-toluidine was administered to male S-D rats ($n = 4$), and urine was collected for 24 hours. Metabolites were isolated and identified.	Parent compound represented only 2.5% of the dose, and a single metabolite was identified.	Metabolism proceeds mainly through ring hydroxylation with subsequent conjugation.	Cheever et al. (1980)
Mode of action	*p*-Toluidine was administered in sunflower oil (76 mg/kg-day) by intraperitoneal injection for 3 consecutive days to male Wistar rats. Microsome enzyme activities were measured from liver, kidney, and lung samples.	The major effects included increased epoxide hydrolase (↑172%) and glutathione S-transferase (↑53%) activities.	The compound affects the activity of metabolic enzymes.	Gnojkowski et al. (1984)

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Genotoxicity Studies

The following studies on the genotoxicity and mutagenicity of *p*-toluidine are listed and summarized in Table 3. Brock et al. (1990) administered 500-mg/kg *p*-[ring-U-^{14}C] toluidine in corn oil by gavage to male Crl:CD®BR rats. Rats were sacrificed at 4, 8, 12, 24, or 48 hours after dosing (4−5 rats at each time point), and the livers were excised and homogenized. Samples were prepared for the quantitation of DNA, RNA, and total protein binding. Additionally, jugular-vein cannulas were inserted into male rats, and oral doses of the radiolabeled compounds in corn oil/methanol (8:2, v/v) were administered on the day following surgery. Blood samples were drawn from each of four rats via the cannula at 30 minutes and 2, 6, 12, 24, 36, 48, and 72 hours. Rats were euthanized, and selected organs and tissues were excised. Radioactive residues were quantified in the samples. Peak blood levels of radioactivity were observed at 12 hours, and the plasma elimination half-life was approximately 12−15 hours. The highest concentrations of radioactive residues were found in the liver, kidneys, subcutaneous abdominal fat, and abdominal skin (15.5−26.4 µg Eq./g). *p*-Toluidine was found to bind to DNA, RNA, and total protein.

Mayer (1977) used an in vitro chemical hydroxylation system (i.e., Udenfriend) to evaluate the genotoxicity of breakdown products of *p*-toluidine. A diploid strain of *S. cerevisiae* designated D-3 was used. Cells were suspended in the reaction mixture with *p*-toluidine at 1 mg/mL in an oxygen or nitrogen atmosphere. It was found that the resulting breakdown products in the oxygen atmosphere induced reciprocal mitotic recombination, while the parent compound in the nitrogen atmosphere did not. The study authors suggest that *N*-hydroxylation of *p*-toluidine in vivo may result in bioactivation to a carcinogenic product.

Rosenkranz and Poirier (1979) evaluated the mutagenicity of 99 chemicals in standard *S. typhimurium* assays with and without S9 using strains TA1535 and TA1538. The DNA-modifying capacity was determined with normal and DNA polymerase-deficient *E. coli* strains. *p*-Toluidine did not induce mutations or cause DNA modification.

The ACGIH (2001) report detailed the acute toxicity of *p*-toluidine, which is briefly summarized as follows. Evidence was negative for a role of para-toluidine in the induction of mutation in *Salmonella typhimurium* strains G46, TA1535, TA1537, TA1538, TA98, or TA100 or in *Escherichia coli* strains WP2, WP2 uvrA, C3076, and D3052 when tested in the absence or presence of rat a liver activation (S9) system. In *Saccharomyces cerevisiae* strains D3 and D4, *p*-toluidine did not induce mitotic crossing-over or mitotic recombination. Employing a modified *E. coli* DNA repair test (pol A^-/A^+), 5-µg/ml *p*-toluidine was not mutagenic in the absence or presence of an exogenous metabolic activation system (Rozenkranz and Poiner, 1979). In the presence of induced rat liver microsomes, *p*-toluidine attenuated unscheduled DNA synthesis in primary rat hepatocytes (Thompson et al., 1983) and was also shown at a concentration of 10 mm for 2 hours to not increase single-strand DNA breaks in Chinese hamster lung fibroblasts (Zimmer et al., 1980). In male Swiss CD-1 mice, a dose of 35 mg/kg body weight delivered via intraperitoneal injection increased single-strand hepatic and renal DNA breaks (Cesarone et al., 1982). Testicular DNA synthesis was inhibited in male Swiss CD-1 mice following oral intubation of *p*-toluidine at a dose of 200-mg/kg body weight (Seiler, 1977).

Acute Toxicity Studies

The ACGIH (2001) report detailed the acute toxicity of *p*-toluidine, which is briefly summarized as follows. Clinical signs of *p*-toluidine exposure in humans included methemoglobinemia and hematuria. *p*-Toluidine has been shown to be absorbed via the respiratory tract and skin (Scott et al., 1983), and prolonged exposure to as little as 10 ppm of a toluidine mixture was reported to cause symptoms of illness (Goldblatt, 1955). The oral LD_{50} of *p*-toluidine was 656 mg/kg in the rat and 794 mg/kg in the mouse (IBT, 1973). The LD_{50} for topical application was 890 mg/kg in the rabbit (IBT, 1973). A 1-hour exposure to 640 mg/kg of *p*-toluidine in air failed to cause mortality in rats but was an ocular and upper respiratory irritant. It is also a dermal sensitizer in guinea pigs (IBT, 1973).

Metabolism/Toxicokinetic Studies

Cheever et al. (1980) administered a single oral dose of *p*-toluidine (500 mg/kg) to male S-D rats and collected the urine for 24 hours. Other animals were treated with *m*- or *o*-toluidine, but these results are not relevant to this report. Metabolites were isolated and identified using gas-liquid chromatography and mass spectrometry. Only 2.5% of the administered parent compound was found in the urine. Metabolism proceeded primarily through ring hydroxylation with subsequent conjugation. The major urinary metabolite was 2-amino-5-methylphenol. No other metabolites were identified, and the toxicodynamics and toxicokinetics of *p*-toluidine were not determined in this study.

Mechanistic/Mode of Action Studies

Gnojkowski et al. (1984) administered 76-mg/kg-day *p*-toluidine in sunflower oil by intraperitoneal injection for 3 consecutive days to male Wistar rats. Other groups were treated with *m*- or *o*-toluidine, but these results are not relevant to this report. On the fourth day, the rats were euthanized, and their livers, kidneys, and lungs were excised. Microsomes were prepared from the tissue samples. The activities of microsomal aryl hydrocarbon hydroxylase (AHH), aminopyrine demethylase, NADPH-cytochrome *c* reductase, epoxide hydrolase, cytosolic glutathione S-transferase, as well as the concentration of cytochrome P450 and cytochrome b_5, were determined in the samples. Differences ($p < 0.05$) between the treated groups and controls were as follows: (1) cytochrome P450 decreased by 17%; (2) AHH decreased by 37%; (3) aminopyrine demethylase decreased by 25%; (4) epoxide hydrolase increased by 172%; and (5) glutathione S-transferase increased by 53%.

DERIVATION OF PROVISIONAL VALUES

Table 4 presents a summary of noncancer reference values. Table 5 presents a summary of cancer reference values.

Table 4. Summary of Noncancer Reference Values for *p*-Toluidine (CASRN 106-49-0)

Toxicity Type (Units)	Species/ Sex	Critical Effect	Reference Value	POD Method	POD	UF_C	Principal Study
Screening Subchronic p-RfD (mg/kg-day)	Rat/M	Increased methemoglobin content in blood	4×10^{-3}	LOAEL	40	10,000	Jodynis-Liebert and Bennasir (2005)
Screening Chronic p-RfD (mg/kg-day)	Rat/F	Increased methemoglobin content in blood	4×10^{-3}	LOAEL	40	10,000	Malik-Bryś and Seńczuk (1995a,b,c)
Subchronic p-RfC (mg/m^3)	None						
Chronic p-RfC (mg/m^3)	None						

Table 5. Summary of Cancer Reference Values for *p*-Toluidine (CASRN 106-49-0)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	Mouse/M	Hepatic[a]	3×10^{-2} $(mg/kg\text{-}day)^{-1}$	Weisburger et al. (1978b)
p-IUR	None			

[a]Tumor type was not specified.

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

No subchronic p-RfD can be derived because the total composite UF for the derivation is greater than 3000. However, Appendix A of this document contains a screening value that may be useful in certain instances. Please see the attached appendix for details.

Derivation of Chronic Provisional RfD (Chronic p-RfD)

No chronic p-RfD can be derived because the total composite UF for the derivation is greater than 3000. However, Appendix A of this document contains a screening value that may be useful in certain instances. Please see the attached appendix for details.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No published studies investigating the effects of subchronic or chronic inhalation exposure to *p*-toluidine in humans or animals were identified that were acceptable for use in risk assessment.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 6 identifies the cancer weight-of-evidence (WOE) descriptor for *p*-toluidine. There were no studies available investigating the ability of *p*-toluidine to be carcinogenic in humans. Weisburger et al. (1978b) found that liver tumors (type not reported) resulted when *p*-toluidine was administered in the diet at doses of 17 and 35 mg/kg-day to male and female CD-1 mice for up to 18 months (followed by up to 3 months without treatment). Incidence of liver tumors was statistically significantly increased in male mice when compared to both the concurrent and pooled controls, and in female mice when compared to pooled controls only (see Table B.2). Because the incidence of liver tumors in female mice was not statistically significant compared to concurrent controls, the biological relevance of these tumors in female mice in this study may be questionable. An increased incidence of liver tumors was not observed in male Sprague-Dawley rats (the only sex tested) treated at 20 or 40 mg/kg-day for 18 months, followed by up to 6 months without treatment (Weisburger et al., 1978a). No information was provided regarding age of tumor onset. As the tumor types were not identified, it is unknown if there was an increased incidence in malignant neoplasms. No other report could be located that provided in vivo long-term carcinogenicity data for *p*-toluidine. *p*-Toluidine is an oncogen in a single animal species (mouse) without any further results that demonstrate oncogenic potential due to long-term exposure in vivo. As quoted in the EPA (2005) *Guidelines for Carcinogen Risk Assessment*, one of the examples for a chemical to be considered *"Likely to be carcinogenic to humans"* is*:* "*…an agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans."* Thus, the WOE from the Weisburger et al. (1978a,b) rodent studies indicates that *p*-toluidine does not meet an examples to be considered as *"Likely to be carcinogenic to humans."* However, the available data are sufficient for *p*-toluidine to be considered to have *"Suggestive evidence of carcinogenic potential."*

Table 6. Cancer WOE Descriptor for *p*-Toluidine (CASRN 106-49-0)			
Possible WOE Descriptor	**Designation**	**Route of Entry (Oral, Inhalation, or Both)**	**Comments**
"Carcinogenic to Humans"	N/A	N/A	No human studies are available.
"Likely to be Carcinogenic to Humans"	N/A	N/A	As described above, *p*-toluidine does not meet an example to be considered "*Likely to be Carcinogenic to Humans."* (U.S. EPA, 2005)
"Suggestive Evidence of Carcinogenic Potential"	**Selected**	**Oral**	**As described above, the rodent data (Weisburger et al., 1978a,b) indicate suggestive evidence of carcinogenic potential.**
"Inadequate Information to Assess Carcinogenic Potential"	N/A	N/A	There is evidence that *p*-toluidine is carcinogenic in mice.
"Not Likely to be Carcinogenic to Humans"	N/A	N/A	There is evidence that *p*-toluidine is carcinogenic in mice.

MODE-OF-ACTION DISCUSSION

The *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) define mode of action "…as a sequence of key events and processes, starting with the interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. Examples of possible modes of carcinogenic action for a given chemical include "…mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immune suppression" (p. 1−10).

There are discordant data on the potential mode of action for *p*-toluidine is unclear. *p*-Toluidine was not mutagenic in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, or TA100 or G46, in *E. coli* strains WP2, WP2 *uvrA*, C3076, or D3052, either in the presence or absence of a rat liver activation (S9) system. Brock et al. (1990) demonstrated DNA-binding following gavage treatment of Cr1:CDBL rats; however, Weisburger et al. (1978a), a screening-level study, demonstrated the absence of an increase in tumors in Cr1:CDBL rats following administration of 20- or 40-mg/kg-day *p*-toluidine in the diet for up to 18 months. Mayer (1977) suggested that *N*-hydroxylation of *p*-toluidine in vivo may result in bioactivation to a carcinogenic product as evidenced by an induction in reciprocal mitotic recombination in *S. cerevisiae*. However, the relative amount of *p*-toluidine that may undergo *N*-hydroxylation in vivo is unclear. The only other positive indicator of genotoxicity was a report indicating that a 35-mg/kg intraperitoneal injection of *p*-toluidine induced an increase in single-strand hepatic and renal DNA breaks in male Swiss CD-1 mice (ACGIH, 2001). Thus, the mode of carcinogenic action for *p*-toluidine is unclear.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

The mouse study by Weisburger et al. (1978b) is selected as the principal study for derivation of the p-OSF. The critical endpoint is hepatic tumors (type not specified) in CD-1 HaM/ICR mice. This study is generally well conducted, and the data from this study are able to support a quantitative cancer dose-response assessment. This study is a peer-reviewed technical report from the National Cancer Institute. It is unclear if this study was conducted according to GLP standards, but it has an acceptable study design and performance with numbers of animals, examination of potential toxicity endpoints, and presentation of information. This study is the only available, acceptable study with a positive tumor response following *p*-toluidine oral exposure.

The oral data are sufficient to derive a quantitative estimate of cancer risk using benchmark dose (BMD) modeling. The dose-response data for liver tumors in male and female mice (see Table B.2) can be used to derive a p-OSF for *p*-toluidine. Statistical significance tests were conducted by the study authors (Weisburger et al., 1978b) indicating that liver tumors in male mice were statistically significant compared to pooled controls at the lowest dose tested, and a statistically significant increase in tumor incidence compared to both pooled and concurrent controls was observed at the highest dose. In female mice, incidence of liver tumors was only statistically significant compared to pooled controls at the highest dose. Statistical analyses performed in the principal study were done by Fisher's Exact Test.

Dosimetric adjustments were made for oral dietary administration of *p*-toluidine in adjusting doses for oral cancer analysis (p-OSF). A sample calculation for the lowest dose tested is shown below. Because the food concentration is a time-weighted average, it is not necessary to include a duration adjustment in the human equivalent dose calculation.

Time-weighted Food Concentration = **(**[(Nominal Dose × Months Dosed) + (Lower Dose × Months Dosed)] ÷ Total Months)

= ([(1000 mg/kg × 6 months) + (500 mg/kg × 12 months)] ÷ 21 months total)

= 571 mg/kg

$DOSE_{HED}$ = Time-weighted Food Concentration × Food Consumption per Day × (1 ÷ Body Weight) × (Body Weight Animal ÷ Body Weight Human)$^{0.25}$

= 571 mg/kg × 0.0055 kg/day × (1 ÷ 0.030225 kg) × (0.030225 kg ÷ 70 kg)$^{0.25}$

= **15.0 mg/kg-day**

Table B.2 presents BMD input data for incidence of liver tumors in mice exposed to *p*-toluidine in feed for 18 months. The curve and BMD output text are provided in Appendix C. Summary results for the BMDL modeling are presented in Table 7. The incidence of liver tumors in male mice was considered the most sensitive tumor response because the modeled data produced a slightly lower BMD_{10} and $BMDL_{10}$ of 5.3 and 3.0 mg/kg-day, respectively, compared to those from female mice.

Table 7. Goodness-of-Fit Statistics, BMD_{10HED}, and $BMDL_{10HED}$ Values for a Dichotomous Model for Liver Tumors in CD-1 Mice Treated with *p*-Toluidine in the Diet for 18 Months[a]

Multistage Cancer Model	Goodness-of-fit *p*-Value[b]	AIC	BMD_{10HED} (mg/kg-day)	$BMDL_{10HED}$ (mg/kg-day)
Multistage Cancer Male	**0.426**	**69.31**	**5.3**	**3.0**
Multistage Cancer Female	0.999	31.05	16	8.3

[a]Weisburger et al. (1978b).
[b]Values >0.1 meet conventional goodness-of-fit criteria.

$$\textbf{p-OSF} = BMR \div BMDL_{10HED}$$
$$= 0.1 \div 3.0 \text{ mg/kg-day}$$
$$= \mathbf{3 \times 10^{-2} \text{ (mg/kg-day)}^{-1}}$$

Derivation of Provisional Inhalation Unit Risk (p-IUR)

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

APPENDIX A. PROVISIONAL SCREENING VALUES

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

DERIVATION OF SCREENING PROVISIONAL ORAL REFERENCE DOSES

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

Jodynis-Liebert and Bennasir (2005) is selected as the principal study for derivation of the screening subchronic p-RfD. The study by Jodynis-Liebert and Bennasir (2005) was not stated to comply with GLP standards, and only a few selected parameters were evaluated. However, pertinent data were reported to allow for the derivation of a screening subchronic p-RfD, and this study was presented in a peer-reviewed journal. The critical endpoint is increased methemoglobin content in blood, a clinical sign of *p*-toluidine exposure in humans (ACGIH, 2001). The study by Jodynis-Liebert and Bennasir (2005) is detailed in the "Review of Potentially Relevant Data" section.

Increases in methemoglobin content were statistically significant ($p < 0.01$) at all dose groups for both exposure durations (i.e., 1 or 3 months) and both diet types (i.e., 4 or 14% fat). For example, there was a 208% increase in methemoglobin blood content compared to controls at 40 mg/kg-day in rats that received the 4% fat dietary treatment. There was also a statistical significant increase in hepatic lipid peroxidation, a marker of oxidative stress. However, no other indicators of liver pathology were assessed. Thus, it is impracticable to link this marker of oxidative stress (i.e., liver peroxidation) to a toxicological outcome in the liver; therefore, hepatic lipid peroxidation data are not considered relevant POD candidates and are not modeled by Benchmark Dose Software (BMDS). Because increased methemoglobin content in blood was the only potential critical effect observed in this study, it was the only endpoint modeled. Specifically, all of the common continuous models (i.e., Linear, Polynomial, Power, and Hill) available in the EPA's BMDS, version 2.1.2 were fit to the data. In general, model fit was assessed by a χ^2 goodness-of-fit test (i.e., models with $p < 0.1$ failed to meet the goodness-of-fit criterion) and the Akaike Information Criterion (AIC) value (i.e., a measure of the deviance of the model fit that allows for comparison across models for a particular endpoint). BMD input for the methemoglobin data are presented in Table B.1. The modeling of the increased methemoglobin data failed to provide an adequate fit as assessed by the χ^2 goodness-of-fit test. **Therefore, the LOAEL of 40 mg/kg-day based on increased methemoglobin content in male rats (Jodynis-Liebert and Bennasir, 2005) was chosen as the POD to derive a screening subchronic p-RfD.**

Adjusted for daily exposure:

The following dosimetric adjustments were made for each dose in the principal study for dietary treatment.

$$\begin{aligned}\mathbf{DOSE_{ADJ}} &= DOSE_{\text{Jodynis-Liebert and Bennasir, 2005}} \times [\text{conversion to daily dose}] \\ &= 40 \text{ mg/kg-day} \times (\text{days of week dosed} \div 7 \text{ days in week}) \\ &= 40 \text{ mg/kg-day} \times 7 \div 7 \\ &= \mathbf{40 \text{ mg/kg-day}}\end{aligned}$$

After considering all treatment-related endpoints, the screening subchronic p-RfD for *p*-toluidine, based on the LOAEL of 40 mg/kg-day for increased methemoglobin levels in male rats (Jodynis-Liebert and Bennasir, 2005), is derived as follows:

$$\begin{aligned}\mathbf{Screening\ Subchronic\ p\text{-}RfD} &= LOAEL_{ADJ} \div UF_C \\ &= 40 \text{ mg/kg-day} \div 10{,}000 \\ &= \mathbf{4 \times 10^{-3} \text{ mg/kg-day}}\end{aligned}$$

Table A.1 summarizes the uncertainty factors for the screening subchronic p-RfD for *p*-toluidine.

Table A.1. Uncertainty Factors for Screening Subchronic p-RfD of *p*-Toluidine[a]

UF	Value	Justification
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans. There are no data to determine whether humans are more or less sensitive than rats to increased methemoglobin content due to *p*-toluidine.
UF_D	10	A UF_D of 10 is applied because there are no acceptable two-generation reproduction studies or developmental studies.
UF_L	10	A UF_L of 10 is applied because the POD was developed using a LOAEL.
UF_S	1	A UF_S of 1 is applied because a subchronic-duration study was utilized as the principal study.
UF_C	10,000	

[a]Jodynis-Liebert and Bennasir (2005).

Derivation of Screening Chronic Provisional RfD (Screening Chronic p-RfD)

Malik-Bryś and Seńczuk (1995a,b,c) is selected as the principal study for derivation of the screening chronic p-RfD. The study by Malik-Bryś and Seńczuk (1995a,b,c) is the only acceptable study observing the toxicological effects due to chronic exposure of *p*-toluidine. It was not stated if this study complies with GLP standards, and only a few selected parameters were evaluated. However, pertinent data were reported to allow for the derivation of a screening

chronic p-RfD, and this study was presented in a peer-reviewed journal. The critical endpoint is increased methemoglobin content in blood, a clinical sign of *p*-toluidine exposure in humans (ACGIH, 2001). Malik-Bryś and Seńczuk (1995a,b,c) is detailed in the "Review of Potentially Relevant Data" section.

Although no quantitative data were presented besides a bar graph, increases in methemoglobin content were reported by the study authors to be statistically significant at all dose groups for both diet types (8 or 24% protein) following 6 months exposure to dietary administration of *p*-toluidine. Because no quantitative data were available, it is unclear what the percent difference in methemoglobin levels was at the various dose groups. Other changes observed included a decrease in the number of thrombocytes, erythrocytes, and leukocytes, as well as an increase in the number of reticulocytes in animals exposed to the effect of toluidines; however, the toxicological significance of these effects is unknown. Because increased methemoglobin content in blood was the only critical effect observed in this study, it was the only endpoint considered for derivation of a screening chronic p-RfD. As mentioned previously, the absence of quantitative means and standard deviations prevents these data from being modeled. **Therefore, the LOAEL of 40 mg/kg-day based on increased methemoglobin content in female rats (Malik-Bryś and Seńczuk (1995a,b,c) was chosen as the POD to derive a screening chronic p-RfD.**

Adjusted for daily exposure:

The following dosimetric adjustments were made for each dose in the principal study for dietary treatment.

$$\begin{aligned} \mathbf{DOSE_{ADJ}} &= \mathrm{DOSE}_{\text{Malik-Bryś and Seńczuk (1995a,b,c)}} \times [\text{conversion to daily dose}] \\ &= 40\ \text{mg/kg-day} \times (\text{days of week dosed} \div 7\ \text{days in week}) \\ &= 40\ \text{mg/kg-day} \times 7 \div 7 \\ &= \mathbf{40\ mg/kg\text{-}day} \end{aligned}$$

After considering all treatment-related endpoints, the screening chronic p-RfD for *p*-toluidine, based on the LOAEL of 40 mg/kg-day for increased methemoglobin levels in female rats (Malik-Bryś and Seńczuk, 1995a,b,c), is derived as follows:

$$\begin{aligned} \mathbf{Screening\ Chronic\ p\text{-}RfD} &= \mathrm{LOAEL_{ADJ}} \div \mathrm{UF_C} \\ &= 40\ \text{mg/kg-day} \div 10{,}000 \\ &= \mathbf{4 \times 10^{-3}\ mg/kg\text{-}day} \end{aligned}$$

Table A.2 summarizes the uncertainty factors that would be required to derive a screening chronic p-RfD for *p*-toluidine.

Table A.2. Uncertainty Factors for the Screening Chronic p-RfD of *p*-Toluidine[a]

UF	Value	Justification
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans. There are no data to determine whether humans are more or less sensitive than rats to increased methemoglobin content due to *p*-toluidine.
UF_D	10	A UF_D of 10 is applied because there are no acceptable two-generation reproduction studies or developmental studies.
UF_L	10	A UF_L of 10 is applied because the POD was developed using a LOAEL.
UF_S	1	A UF_S of 1 is applied because a chronic-duration study was utilized as the principal study.
UF_C	10,000	

[a]Malik-Bryś and Seńczuk (1995a,b,c).

APPENDIX B. DATA TABLES

Table B.1. Mean ± SD Methemoglobin Content (%) in the Blood of Rats Receiving *p*-Toluidine in the Diet[a]

Month	Dose (mg/kg-day)			
	0	40	80	160
4% Dietary fat				
1	1.2 ± 0.2	3.7 ± 0.6[b] (+208)	4.3 ± 0.5[b] (+258)	7.6 ± 0.9[b] (+533)
3	1.4 ± 0.2	6.6 ± 2.30[b] (+371)	6.5 ± 0.9[b] (+364)	13.2 ± 2.4[b] (+843)
14% Dietary fat				
1	1.5 ± 0.2	3.6 ± 0.5[b] (+140)	3.2 ± 0.4[b] (+113)	6.1 ± 0.6[b] (+307)
3	1.5 ± 0.1	4.2 ± 1.7[b] (+180)	4.1 ± 0.5[b] (+173)	7.6 ± 2.0[b] (+407)

[a]Jodynis-Liebert and Bennasir (2005); percent difference from control, calculated from the cited data, is listed in parentheses.
[b]Difference significant from control, $p < 0.01$ determined by Newman-Keuls Test.

Table B.2. Neoplastic Liver Lesions (# Affected/Total Surviving) in Mice Receiving *p*-Toluidine in the Diet for 18 Months[a]

Sex	$Dose_{HED}$ (mg/kg-day)			
	0	15	30	Pooled Controls
Males	3/18	8/17[b]	9/18[b,c]	7/99
Females	0/20	2/21	3/17[b]	1/102

[a]Weisburger et al. (1978).
[b]Difference significant from incidence in pooled control, $p < 0.025$ determined by Fisher's Exact Test as determined by the study authors.
[c]Difference significant from incidence in concurrent control, $p < 0.05$ determined by Fisher's Exact Test as determined by the study authors.

APPENDIX C. BENCHMARK DOSE (BMD) CALCULATIONS AND BMD MODELS

BMD CALCULATIONS FOR THE RFD

Modeling Procedure for Continuous Data

The BMD modeling of continuous data was conducted with EPA's benchmark dose software (BMDS) (version 2.1.2 beta). For these data (i.e., increased methemoglobin content in blood), all continuous models available within the software were fit using a benchmark response (BMR) of one standard deviation. An adequate fit was judged based on the χ^2 goodness-of-fit *p*-value ($p > 0.1$), the magnitude of the scaled residuals in the vicinity of the BMR, and the visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination was made as to whether the variance across dose groups was homogeneous. If a homogeneous variance model was deemed appropriate based on the statistical test provided in BMDS (i.e., Test 2), the final BMD results were estimated from a homogeneous variance model. If the test for homogeneity of variance was rejected ($p < 0.1$), the model was run again while modeling the variance as a power function of the mean to account for this nonhomogeneous variance. If this nonhomogeneous variance model did not adequately fit the data (i.e., Test 3; *p*-value <0.1), the data set was considered unsuitable for BMD modeling.

Using data for increased methemoglobin content in male mice, modeling was performed without constant variance, as initial analyses with constant variance models revealed poor model fit. Data outputs from increased methemoglobin content in blood were evaluated, and the outputs from these data were deemed invalid based on inadequate fit (goodness-of-fit *p*-value <0.1) and are, therefore, not presented.

BMD CALCULATIONS FOR THE ORAL SLOPE FACTOR

Model-Fitting Procedure for Cancer Incidence Data

The model-fitting procedure for dichotomous cancer incidence data is as follows. The multistage-cancer model in the EPA BMDS is fit to the incidence data using the extra risk option. The multistage-cancer model is run for all polynomial degrees up to $n - 1$ (where n is the number of dose groups including control). An adequate model fit is judged by three criteria: goodness-of-fit *p*-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest bound of the BMD (BMDL) is selected as the point of departure when the difference between the BMDLs estimated from these models is more than 3-fold (unless it appears to be an outlier); otherwise, the BMDL from the model with the lowest (Akaike Information Criterion) AIC is chosen. In accordance with EPA (2012) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated.

Model-Fitting Results for Liver Tumors in HaM/ICR Derived CD-1 Mice (Weisburger et al., 1978)

Table B.2 shows the dose-response data on liver tumors in HaM/ICR derived CD-1 mice administered *p*-toluidine in the diet for 18 months (Weisburger et al., 1978). Modeling was performed according to the procedure outlined above using BMDS version 2.1.2 with parameter restrictions for mice based on the duration-adjusted HEDs shown in Table 2. Model predictions are shown in Table 7. For both male and female mice, the multistage-cancer model provided an adequate fit (goodness-of-fit *p*-value >0.1). The 1-degree polynomial model yielded BMD_{10HED} values of 5.3 and 16 mg/kg-day with an associated 95% lower confidence limit ($BMDL_{10HED}$) of

3 and 8.3 mg/kg-day for male and female mice, respectively. The fit of the 1-degree multistage-cancer model to the liver tumor incidence data for male and female mice is shown in Table 7.

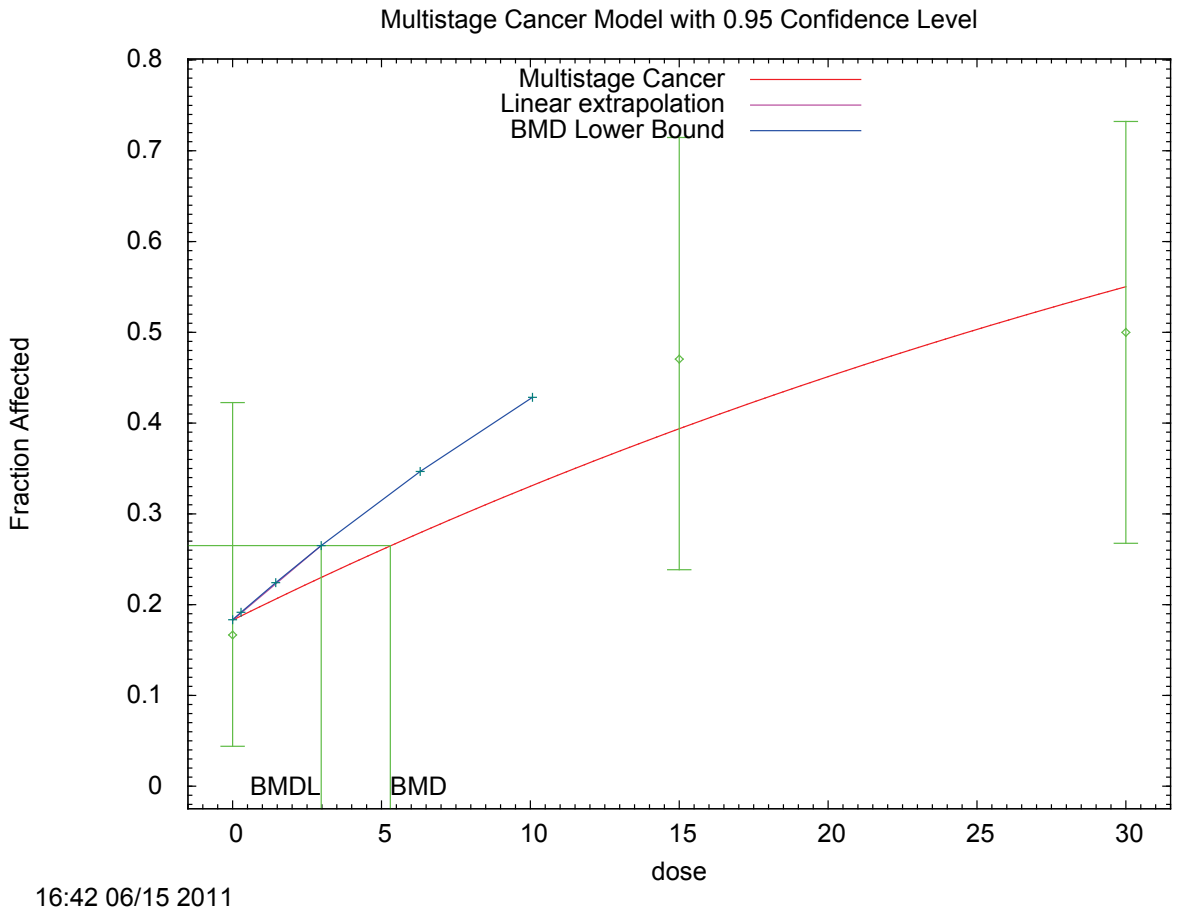

Figure C.1. Dichotomous-Multistage-Cancer BMD Model for Incidence of Liver Tumors in Male Mice (Weisburger et al., 1978)

Text Output for Dichotomous-Multistage-Cancer BMD Model for Incidence of Liver Tumors in Male Mice (Weisburger et al., 1978)

```
 ================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/Documents and Settings/JKaiser/Desktop/modeling
results/msc_ptol_ltumors_m_Msc1-BMR10.(d)
        Gnuplot Plotting File:  C:/Documents and Settings/JKaiser/Desktop/modeling
results/msc_ptol_ltumors_m_Msc1-BMR10.plt
                                          Wed Jun 15 17:08:35 2011
 ================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
```

```
   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Response
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                    Background =     0.219957
                       Beta(1) =    0.0170275


          Asymptotic Correlation Matrix of Parameter Estimates

            Background      Beta(1)

Background            1        -0.73

   Beta(1)        -0.73            1


                               Parameter Estimates

                                                        95.0% Wald Confidence
Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background         0.183476           *               *                 *
        Beta(1)         0.019892           *               *                 *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -32.3408         3
   Fitted model        -32.6546         2      0.627559      1          0.4283
  Reduced model        -35.1261         1        5.5705      2         0.06171

           AIC:         69.3092


                               Goodness  of  Fit
```

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1835	3.303	3.000	18	-0.184
15.0000	0.3941	6.700	8.000	17	0.645
30.0000	0.5504	9.908	9.000	18	-0.430

Chi^2 = 0.64 d.f. = 1 P-value = 0.4255

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 5.29662

BMDL = 2.97513

BMDU = 19.8489

Taken together, (2.97513, 19.8489) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.033612

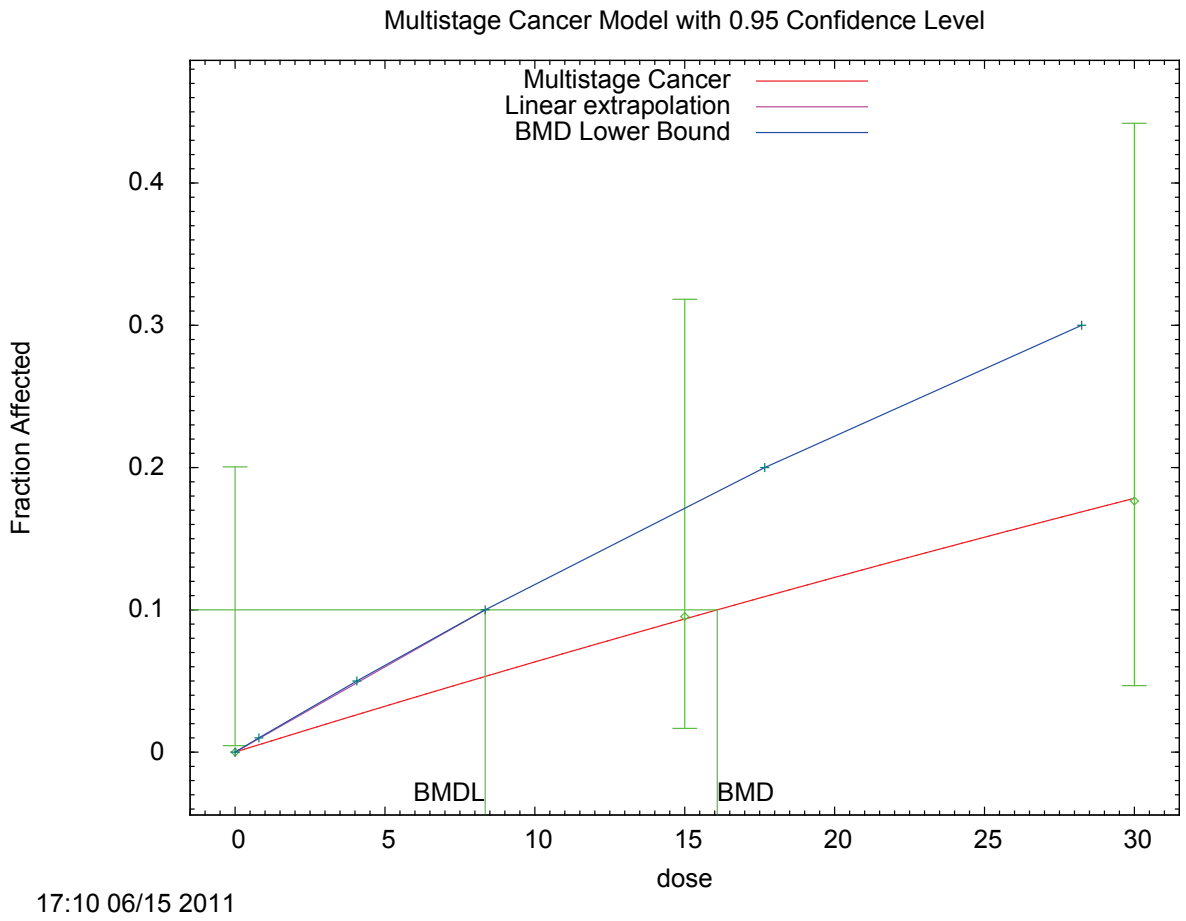

Figure C.2. Dichotomous-Multistage-Cancer BMD Model for Incidence of Liver Tumors in Female Mice (Weisburger et al., 1978)

Text Output for Dichotomous-Multistage-Cancer BMD Model for Incidence of Liver Tumors in Female Mice (Weisburger et al., 1978)

```
=================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/Documents and Settings/JKaiser/Desktop/modeling
results/msc_ptol_ltumors_f_Msc1-BMR10.(d)
        Gnuplot Plotting File:  C:/Documents and Settings/JKaiser/Desktop/modeling
results/msc_ptol_ltumors_f_Msc1-BMR10.plt
                                          Wed Jun 15 17:10:13 2011
 =================================================================

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

   The form of the probability function is:

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

   The parameter betas are restricted to be positive
```

```
  Dependent variable = Response
  Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                    Background =   0.00100132
                       Beta(1) =   0.00647187


          Asymptotic Correlation Matrix of Parameter Estimates

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

               Beta(1)

   Beta(1)            1


                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0            *               *                   *
        Beta(1)       0.00655066            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -14.5263         3
   Fitted model         -14.5269         1    0.00111128      2          0.9994
  Reduced model          -17.033         1       5.01342      2         0.08154

          AIC:          31.0538


                                Goodness  of  Fit
                                                                    Scaled
    Dose     Est._Prob.    Expected    Observed     Size        Residual
  ---------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          20       -0.000
```

```
   15.0000     0.0936         1.965     2.000          21        0.026
   30.0000     0.1784         3.033     3.000          17       -0.021

 Chi^2 = 0.00      d.f. = 2        P-value = 0.9994


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =         16.084

            BMDL =        8.34226

            BMDU =        48.3837

Taken together, (8.34226, 48.3837) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =     0.0119872
```

APPENDIX D. REFERENCES

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