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Provisional Peer-Reviewed Toxicity Values for

p-Chlorotoluene
(CASRN 106-43-4)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMD	benchmark dose
BMCL	benchmark concentration lower bound 95% confidence interval
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
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
POD	point of departure
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*-CHLOROTOLUENE (CASRN 106-43-4)

BACKGROUND

HISTORY

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) EPA's Integrated Risk Information System (IRIS)
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in EPA's Superfund Program
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR);
   - California Environmental Protection Agency (CalEPA) values; and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by a panel of six EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

DISCLAIMERS

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

p-Chlorotoluene is a disubstituted benzene ring with a chlorine and a methyl group in a para (1,4) configuration (see Figure 1). *p*-Chlorotoluene (sometimes as a mixture with *o*-chlorotoluene) is used in the production of agrochemicals, plasticizers, flame retardants for plastics, material preservatives, pigments and optical brighteners, antiaging agents, pharmaceuticals, capacitor oils, thermal oils, perfumes, and flavorings (BUA, 1989). The empirical formula for *p*-chlorotoluene is C_7H_7Cl. A table of chemicophysical properties is provided below (see Table 1). In this document, "statistically significant" denotes a *p*-value of <0.05.

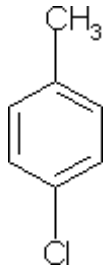

Figure 1. *p*-Chlorotoluene Structure

Table 1. Physical Properties Table (*p*-Chlorotoluene)[a]

Property (Unit)	Value
Boiling point (ºC)	161.5
Melting point (ºC)	7.6
Density (g/cm^3)	1.0677
Vapor pressure (Pa at 20ºC)	3.1 mm Hg
pH (unitless)	NA
Solubility in water (g/L at 20ºC)	0.040
Relative vapor density (air = 1)	4.37
Molecular weight (g/mol)	126.59
Flash point (°C)	49.5
Octanol/water partition coefficient (unitless; (Log K_{ow})	3.504

[a]BUA (1989); HSDB (2002)

A reference dose (RfD) of 0.02 mg/kg-day and a Drinking Water Equivalent Level (DWEL) of 0.7 mg/L are included on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2006) for *p*-chlorotoluene. The DWEL is a lifetime exposure concentration protective against adverse, noncancer health effects, assuming all of the exposure comes from drinking water. The DWEL is based on the RfD and a consumption of 2 L/day for a 70-kg individual. The Drinking Water Standards and Health Advisories (DWSHA) List also provides a Lifetime Health Advisory of 0.1 mg/L (U.S. EPA, 2006), which is derived from the DWEL using a relative source contribution value. No RfD or reference concentration (RfC) is included in the IRIS database (U.S. EPA, 2010). No toxicological reference values are reported in the HEAST, and a comment in HEAST states that data are inadequate to support a quantitative risk assessment for *p*-chlorotoluene (U.S. EPA, 1997). The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1994) includes a Health and Environmental Effects Profile (HEEP) for chlorotoluenes, but no HEEP has been issued specifically for *p*-chlorotoluene. The toxicity of *p*-chlorotoluene has not been reviewed by ATSDR (2008) or the World Health Organization (WHO, 2010). CalEPA (2008a,b) has not derived toxicity values for exposure to *p*-chlorotoluene in air or water. No occupational exposure limits for *p*-chlorotoluene have been derived by the American Conference of Governmental Industrial Hygienists (ACGIH, 2009), the National Institute of Occupational Safety and Health (NIOSH, 2003), or the Occupational Safety and Health Administration (OSHA, 2005).

No IRIS cancer assessment has been performed for *p*-chlorotoluene (U.S. EPA, 2010). *p*-Chlorotoluene has not been evaluated under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005); the DWSHA List provides a Cancer Descriptor of "D" (*Not Classifiable as to Human Carcinogenicity*) for *p*-chlorotoluene (U.S. EPA, 2006). The International Agency for Research on Cancer (IARC, 2010) has not assessed the carcinogenic potential of *p*-chlorotoluene. *p*-Chlorotoluene is not included in the National Toxicology Program's (NTP's) *11th Report on Carcinogens* (NTP, 2005). However, an NTP genotoxicity study (Ames assay) of *p*-chlorotoluene produced negative results with and without metabolic

activation (NTP, 1986; Zeiger et al., 1992). CalEPA (2008b) has not prepared a quantitative estimate of the carcinogenic potential of *p*-chlorotoluene.

Literature searches were conducted on sources published from 1900 through September, 2010 for studies relevant to the derivation of provisional toxicity values for *p*-chlorotoluene, CAS No. 106-43-4. Searches were conducted using EPA's Health and Environmental Research Online (HERO) evergreen database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, MultiDatabase Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI; and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); World Health Organization; and Worldwide Science. The following databases outside of HERO were searched for risk assessment values: ACGIH, ATSDR, CalEPA, EPA IRIS, EPA HEAST, EPA HEEP, EPA OW, EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides information for all of the potentially relevant studies identified through the literature search. Entries for the selected principal studies (PS) are highlighted in bold.

Table 2. Summary of Potentially Relevant Data for *p*-Chlorotoluene (CASRN 106-43-4)

Notes[a]	Category	Number of Male/Female, Species, Study Type, and Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b,c]	Reference (Comments)
Human								
				1. Oral (mg/kg-day)[b]				
				None				
				2. Inhalation (mg/m^3)[b]				
	Acute	None	None	None	None	None	None	None
	Subchronic	None	None	None	None	None	None	None
	Chronic	None	None	None	None	None	None	None
	Developmental	None	None	None	None	None	None	None
	Reproductive	None	None	None	None	None	None	None
	Carcinogenic	None	None	None	None	None	None	None
Animal								
				1. Oral (mg/kg-day)[b]				
	Short-term	10 animals per sex per dose group, Sprague-Dawley rat, gavage, 14 days	0, 200, 600, 1800	Decreased body-weight gain	200	NA	600	Terrill et al. (1990)
PS	**Subchronic**	**10 animals per sex per dose group, Sprague-Dawley rat, gavage, 90 days**	**0, 50, 200, 800**	**Mortality; decreased body weight; increased blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALP), bilirubin, relative liver weight, relative kidney weight, and relative adrenal weight at high-dose only**	**200**	**NA**	**None; 800 is the frank effect level (FEL)**	**Terrill et al. (1990)**

Table 2. Summary of Potentially Relevant Data for *p*-Chlorotoluene (CASRN 106-43-4)

Notes[a]	Category	Number of Male/Female, Species, Study Type, and Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b,c]	Reference (Comments)
		190, rat (sex and strain not specified), gavage, 6 months	0.01, 0.1, 1.0	Increased hemoglobin; increased erythrocyte and leukocyte counts; changes in cholinesterase, alanine, and aspartate aminotransferase (AST) levels; increased BUN levels; disrupted carbohydrate metabolism; marked reduction in liver glucose levels; elevated cholinesterase activity and an increased content of aspartic and glutamic acids in brain homogenates; impaired texture of brain substance due to dilated perivascular spaces; capillary hyperemia and slight hemorrhage; enlarged cell nuclei and swelling of the cytoplasm in brain cells	0.01	NA	0.1	Pis'ko et al. (1981) as cited in BUA (1989) No control was specified; no details on the specific methods used, including the dosing frequency or medium, sample size per treatment group, and the sex and strain of the animals
	Chronic	None	None	None	None	None	None	None
	Developmental/ Reproductive	83 sexually mature female rats and 357 fetuses, gavage, single dose to 6 months	1100 or 1833 single; 55 or 550 for 2 months; 0.01, 0.1, or 1.0 for 6 months	Embryo mortality via preimplantation loss and liver abnormalities	55 for 2 months 1.0 for 6 months	NA	550 for 2 months NA for 6 months	Pis'ko et al. (1981) as cited in BUA (1989) No control was specified; no details on the specific methods used, including the dosing frequency or medium, sample size per treatment group, and the sex and strain of the animals

Table 2. Summary of Potentially Relevant Data for *p*-Chlorotoluene (CASRN 106-43-4)

Notes[a]	Category	Number of Male/Female, Species, Study Type, and Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b,c]	Reference (Comments)
	Carcinogenic	None	None	None	None	None	None	None
2. Inhalation (mg/m^3)[b]								
None								

[a]IRIS = Utilized by IRIS, date of last update; PS = Principal study; NPR = Not peer reviewed.
[b]Dosimetry, NOAEL, BMDL/BMCL, and LOAEL values are converted to human equivalent dose (HED in mg/kg-day) or human equivalent concentration (HEC in mg/m^3) units. Noncancer oral data are only adjusted for continuous exposure.
[c]Not reported by the study author but determined from data.

HUMAN STUDIES

Oral and Inhalation Exposure

There are no oral or inhalation single-chemical studies available in humans. However, Goldblatt (1955) states that acute mixture studies conducted by their laboratory indicate that a 60-minute exposure to a concentration of 400-ppm (equivalent to 2106 mg/m^3 at 20°C) chlorotoluene (all three isomers in unspecified proportions) causes severe (unspecified) toxicity in humans. The concentration stated to cause illness if exposure continued for more than a short time (not specified what was meant by a "short time" or "illness") was 200 ppm (equivalent to 1053 mg/m^3 at 20°C).

ANIMAL STUDIES

Oral Exposure

The effects of oral exposure of animals to *p*-chlorotoluene have been evaluated in a short-term study (Terrill et al., 1990), two subchronic-duration studies (Pis'ko et al., 1981 as cited in BUA, 1989; Terrill et al., 1990), and a developmental/reproductive study (Pis'ko et al., 1981 as cited in BUA, 1989). The studies by Pis'ko et al. (1981) are not adequately documented and, therefore, cannot be used to support the development of a PPRTV. There are also two subchronic studies available that used a mixture of *o*- and *p*-chlorotoluene (Industrial Bio-test Labs Inc., 1987a,b). These studies, likewise, are not suitable for dose-response estimation without detailed mixture-interaction studies (e.g., additive, antagonist, or synergistic). Terrill et al. (1990) presented data for 14-day and 90-day exposures with similar methods in the same publication, but results are presented as separate studies under short-term and subchronic studies.

Short-term Study—Terrill et al. (1990) administered *p*-chlorotoluene (>98% pure) via gavage at doses of 0 (vehicle only), 200, 600, or 1800 mg/kg-day in corn oil for 14 days to adult Sprague-Dawley rats (10/sex/dose). The following parameters were examined at the end of the 14-day treatment period: clinical signs of toxicity, body weight and food consumption, hematology (leukocyte and erythrocyte counts, hematocrit, hemoglobin, leukocyte differential, and cell morphology), clinical chemistry (sodium, potassium, total protein, albumin calcium, total bilirubin, creatinine, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], lactate dehydrogenase [LDH], and blood urea nitrogen [BUN]), urinalysis (pH, glucose, bilirubin, occult blood and uribilirubin), gross pathology, organ weights (liver, kidneys, spleen, adrenal glands, thymus, brain, heart, lungs, testes with epididymis, and ovaries), and histopathology (from all of the animals in the 600-mg/kg-day and five randomly selected controls; adrenal glands, thyroid, esophagus, trachea, larynx, heart, spleen, liver, kidneys, stomach, duodenum, jejunum, colon, pancreas, and gross lesions).

Eight of the 10 high-dose males and females died during treatment (Terrill et al., 1990). Clinical signs in this group included prostration, salivation, and tremors after dosing. Body weight and body-weight gain were biologically significantly reduced in both sexes administered 1800 mg/kg-day. Male rats administered 600-mg/kg-day also displayed a statistically significant decrease in body-weight gain (body-weight data not reported). There was a statistically significant decrease in food consumption in the mid- and high-dose males during the first week. There were no other findings related to treatment after 14 days of treatment. The authors did not report a NOAEL. However, a NOAEL of 200 mg/kg-day and a LOAEL of 600 mg/kg-day can be derived based on decreased body weight and body-weight gain.

Subchronic Studies—The 90-day study by Terrill et al. (1990) has been selected as the principal study for deriving the subchronic and chronic p-RfD. Terrill et al. (1990) administered *p*-chlorotoluene (>98% pure) via gavage at doses of 0 (vehicle only), 50, 200, or 800 mg/kg-day in corn oil for 90 days to Sprague-Dawley rats (10/sex/dose). The same parameters measured in the 14-day study were measured in the 90-day study, except ophthalmology (preformed using indirect ophthalmoscopic techniques with 1% Mydriacyl) was also examined in the 90-day study. Forty percent (4/10) of the males and 20% (2/10) of the females in the high-dose group died prior to termination. Clinical signs of toxicity observed in the high-dose group an hour after dosing included languid behavior, prostration, sensitivity to touch, tremors, epistaxis, dyspnea, and/or polypnea. The study authors stated that these clinical signs were closely related to the time of the animals' death. In surviving animals, these signs were less severe at the weekly detailed observations, which were conducted prior to dosing. Weekly body weights were lower in treated animals compared to the controls (all male treatment groups and high-dose females). Statistically significant reductions were only reported for body-weight gain in high-dose males and terminal body weight in high-dose females. Food consumption was not significantly different across the dose groups. The authors reported no treatment-related findings in ophthalmology or hematology.

There were several significant changes in clinical chemistry parameters (BUN, creatinine, ALP, and bilirubin) in the high-dose males (see Table B-1) (Terrill et al., 1990). LDH levels increased in a dose-related manner in the low- and mid-dose males but were comparable to controls in the high-dose group and were not statistically significant. Although there were no significant increases for any endpoint noted in the females, there was a dose-related increase in AST (not statistically signficiant) and a nearly 2-fold increase in ALT in the high-dose group. There was a significant decrease in urinary pH in mid- and high-dose males and females, but the results were not monotonic. Gross lesions (depressed areas, pale areas, mottled appearance, dilated renal pelvis, and/or granular/pitted/rough texture) accompanied by histopathological findings (chronic progressive nephropathy) were noted in high-dose males. Although all groups had dark areas in the glandular stomach, there was a slight increase in the frequency in the high-dose males and females. Although there were a number of statistically significant changes in organ weights, many were correlated with reduced body weight in the high-dose groups. Statistically significant changes in organ weights that appeared to be related to treatment independent of nutritional status occurred in the high-dose groups and included relative liver weight in males, relative kidney weight in both sexes, and absolute and relative adrenal weight in males. Histopathological changes were seen at higher frequencies in both sexes in the high-dose groups and included centrilobular hypertrophy in the liver of both animals that died during treatment and animals that were sacrified at termination, chronic progressive nephropathy, and hyperplasia of the zona fasciculata in the adrenals. There was also minimal mucosal erosion in the glandular stomach in two high-dose males, three high-dose females, and in one each of the low- and mid-dose females. Liver and kidneys are likely to be the target organs via oral exposure to *p*-chlorotoluene in both sexes. The study authors stated that the NOEL (no-observed-effect-level) was 200 mg/kg-day. Based on an increased mortality, the 800-mg/kg--day dose is a frank effect level (FEL), therefore, no LOAEL can be identified. A NOAEL of 200 mg/kg-day is identified.

BUA (1989) stated that there was a poorly documented 6-month study (Pis'ko et al., 1981) in rats. The original source (Pis'ko et al., 1981) is unavailable for review at this time (no direct English translation). The study was published in a foreign language journal (Russian), and

the publication is only two pages long, suggesting that only minimal information is available. BUA (1989) summarized the results from the original study into English. In this study, a total of 190 rats received *p*-chlorotoluene (purity not reported; control not specified) via gavage at doses of 0.01, 0.1, or 1.0 mg/kg-day in an oily solution for 6 months (specific details, e.g., dose frequency, dosing medium, and sample size per treatment group were not provided). Similar effects were noted in both the 0.1- and 1.0-mg/kg-day groups, but effects were less pronounced in the 0.1-mg/kg-day group. Effects stated to have occurred included increased hemoglobin; increased erythrocyte and leukocyte counts; impaired liver function as measured by changes in cholinesterase, alanine, and AST levels; increased BUN levels; disrupted carbohydrate metabolism; and marked reduction in liver glucose levels. The following effects on the central nervous system were reported elevated cholinesterase activity and increased content of aspartic and glutamic acids in brain homogenates, impaired texture of brain substance due to dilated perivascular spaces, capillary hyperemia and slight hemorrhage, and enlarged cell nuclei and swelling of the cytoplasm in brain cells. Histopathological findings included parenchymal dystrophy and small necrotic foci in the liver. Pronounced plethora and thickening of the arterial walls occurred in the liver, as well as the lungs. Additional findings included granular dystrophy in the epithelium of convoluted renal tubules, atrophy in the lungs and ruptured alveolar walls, and marked narrowing of the zona fasciculata in the adrenal glands. The NOAEL was 0.01 mg/kg-day. A LOAEL was not reported, but a LOAEL of 0.1 mg/kg-day can be derived based on the numerous effects listed.

There are two subchronic unpublished studies (Toxic Substance Control Act submission) available that used a mixture of *o*- and *p*-chlorotoluene (Industrial Bio-test Labs Inc, 1987a,b). In the first study (Industrial Bio-test Labs Inc., 1987a), albino rats (15/sex/dose; 38 days old) were administered 0, 100, 300, or 1,000 mg/kg-day of chlorotoluene (51% *o*-chlorotoluene and 48% *p*-chlorotoluene) via gavage in corn oil for 90 days. Animals were weighed 2–3 times a week, and weekly food consumption was measured in five rats per sex. Blood and urine were obtained from 10 rats per sex in the control and high-dose groups at 40 and 90 days to test for hematology and clinical chemistry. Urine was also obtained from the 10 rats per sex in the remaining two groups at 90 days. Animals were sacrificed on Day 90 and necropsied. At sacrifice, all rats were autopsied, and their brain, gonads, heart, kidneys, liver, and spleen were weighed. Histopathology of the major organs and tissues was conducted on tissues from 10 rats per sex in the control and high-dose groups.

Four animals died during the study due to intubation error (Industrial Bio-test Labs Inc., 1987a). Beginning 3 days after study initiation, high-dose animals developed a resistance to dosing and excessive salivation. Excessive urination also occurred in this group beginning in the 7th week of treatment. High-dose males had reduced body weight that was significantly different from the controls on a number of occasions. The body-weight gain in the high-dose males was 10% lower than the controls. There was a dose-dependent decrease in body-weight gain in the females with a 10% reduction observed in the 300-mg/kg-day group and a 19% reduction in the 1000-mg/kg-day group. In addition, no change in food consumption was observed. Although there were some statistically significant changes in hematology and clinical chemistry, the study authors stated that the values were within normal ranges. Decreased blood glucose levels, however, were consistently observed in high-dose males and females at both time points. Urinalysis findings were reported to be unremarkable. No treatment-related changes were noted in gross pathology, organ weight, or histopathology. The authors did not estimate a NOAEL.

However, a NOAEL of 300 mg/kg-day and a LOAEL of 1000 mg/kg-day can be derived, based on clinical signs of toxicity and reduced body weight.

The second study (Industrial Bio-test Labs Inc., 1987b) was conducted using dogs (beagles). Dogs (4/sex/dose; 5–5.5 months old) were administered gelatin capsules containing a corn oil suspension of 30, 100, or 300 mg/kg-day of chlorotoluene (51% *o*-chlorotoluene and 48% *p*-chlorotoluene) for 90 days. Controls received vehicle only. Blood and urine was collected on Days 42 and 85 for testing. At study termination, animals were sacrificed, autopsied, and their brain, gonads, heart, kidneys, liver, spleen, adrenal glands, thyroid gland, and pituitary gland were weighed. Histopathology of the major organs and tissues were conducted.

None of the animals died, and no clinical signs of toxicity were observed (Industrial Bio-test Labs Inc., 1987b). There was a 21% reduction in body-weight gain in high-dose males, and food consumption was unaffected. High-dose males had slightly lower erythrocyte counts (-8%), hemoglobin (-10%), and hematocrit (-11%). The study authors stated that these were not related to treatment because the results were on the low end of the normal range. It was stated that there were no treatment-related changes in clinical chemistry, gross pathology, organ weight, or histopathology. The authors did not provide a NOAEL. However, a NOAEL of 100 mg/kg-day and a LOAEL of 300 mg/kg-day can be derived from the data, based on decreased body-weight gain.

Chronic Studies—No chronic studies of *p*-chlorotoluene were identified.

Developmental and Reproduction Studies—BUA (1989) provided information on a reproduction/developmental study (Pis'ko et al., 1981). The original source (Pis'ko et al., 1981) is unavailable for review at this time (no direct English translation). The study was published in a foreign language journal (Russian). However, the publication is only two pages long, which suggests that only minimal documentation was provided. Very few details are provided on the study design. Eighty-three sexually mature rats with 357 fetuses were examined (control was not specified). Animals received either a single dose of 1100 or 1833 mg/kg; 55 or 550 mg/kg-day for 2 months; or 0.01, 0.1, or 1.0 mg/kg-day for 6 months. No details on mating or the relationship of dosing to time of mating were provided. Animals were sacrificed on Gestational Day 20. The number of corpora lutea, implantations, malformed fetuses, and interuterine and postnatal deaths were evaluated. Statistically significant effects were seen only in the group receiving the 550 mg/kg-day dose for 2 months. At this dose, there was a significant increase in embryo mortality caused by preimplantation loss, 12.7% of the embryos developed liver hypertrophy while 47% had hypotrophy. No teratogenic or cytogenic effects were noted, but offspring from of the 1833-mg/kg dose displayed a slight tendency for chromosomal fragmentation (method not specified). The authors did not provide a NOAEL. Although details are lacking in the study, a NOAEL of 55 mg/kg-day and a LOAEL of 550 mg/kg-day for a 2-month exposure can be tentatively derived from the data, based on embryo mortality via preimplantation loss and liver hypertrophy in the embryos. A NOAEL of 1 mg/kg-day for a 6-month exposure based on minimal biological significance can be identified; a LOAEL is not identified.

Inhalation Exposure

There are no short-term, subchronic, or chronic inhalation studies available for *p*-chlorotoluene.

Developmental and Reproduction Studies—No studies could be located regarding the effects of inhaled *p*-chlorotoluene on reproduction and fetal development.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Undiluted *p*-chlorotoluene (purity not specified) was administered to five male Wistar rats (10–12 weeks of age; approximately 230 grams), for 5 days, at a dose of 250 mg/kg-day (Bomhard et al., 1991). A number of compounds were tested, and the control consisted of a peanut oil vehicle. Animals were sacrificed 2–3 hours after the last dose, and the kidneys were removed for histopathology. Semiquantitative analysis of hyaline droplet accumulation on a scale of 0 (no droplets) to 4 (extensive response with marked increase and widespread distribution) and renal marker protein measurements were conducted. *p*-Chlorotoluene had a mean hyaline droplet accumulation score of 2.0, which was the same as the peanut oil control. The protein level after *p*-chlorotoluene exposure (2.69 ± 0.71 µg) was also similar to the control (2.45 ± 0.39 µg). The study authors judged *p*-chlorotoluene to be inactive.

Stadler and Kennedy (1996) tested 11 compounds found in carpet samples, including *p*-chlorotoluene, for sensory irritation potential by measuring the airborne concentration that caused a 50% decrease in the respiration rate (RD_{50}). Male Swiss-Webster mice (number not specified) were used. The RD_{50} for *p*-chlorotoluene can be estimated to be approximately 750 ppm (3880 mg/m^3) from the figure presented in the study. There was a steep decrease in respiration rate with increasing concentration of *p*-chlorotoluene.

The genotoxicity of *p*-chlorotoluene has been tested in numerous in vitro and in vivo studies (see Table 3). These eight tests indicate that *p*-chlorotoluene is not mutagenic or clastogenic in the large majority of test systems. The only exception was Huang et al. (1997) who found *p*-chlorotoluene to be active in a micronuclei test (however, a positive control was not used; the negative control was dimethyl sulfoxide [DMSO]). This study contradicts the other independent micronuclei test in mice by Herbold (1992), in which *p*-chlorotoluene was found to be not clastogenic (both a negative control [corn oil] and a positive control [cyclophosphamide] were indicated).

Table 3. Other Studies

Tests	Materials and Methods	Results	Conclusions	References
Genotoxicity	*p*-Chlorotoluene was tested for mutagenic activity with five strains of *Salmonella typhimurium* in a standard and modified (conducted in a desiccator to ensure adequate dispersion of a volatile compound) Ames assay. The assay was performed in the presence and absence of a metabolic-activation system. Concentrations tested were not reported.	*p*-Chlorotoluene was not mutagenic.	*p*-Chlorotoluene was not mutagenic.	Simmon et al. (1977)
Genotoxicity	*p*-Chlorotoluene was tested for mutagenic activity in yeast (*Saccharomyces cerevisiae* D3). The assay was performed in the presence and absence of a metabolic-activation system. Concentrations were not reported.	*p*-Chlorotoluene was not mutagenic.	*p*-Chlorotoluene was not mutagenic.	Simmon et al. (1977)
Genotoxicity	*p*-Chlorotoluene was tested for mutagenic activity with five strains of *Salmonella typhimurium* in a standard and modified (conducted in a desiccator to ensure adequate dispersion of a volatile compound) Ames assay. The assay was performed in the presence and absence of a metabolic-activation system at concentrations ranging from 10 µg/plate to 5000 µg/plate or 0.05 mL to 1.00 mL per desiccator.	Toxicity was observed at doses of 500 and 1000 µg/plate. No mutagenic response was obtained using either of the procedures.	*p*-Chlorotoluene was not mutagenic with or without metabolic activation.	Simmon and Kauhanen (1978)
Genotoxicity	*p*-Chlorotoluene was tested for mutagenic activity in yeast (*Saccharomyces cerevisiae* D3). The assay was performed in the presence and absence of a metabolic-activation system at concentrations of 0.0005 to 0.05%.	Survival was decreased by 50% at concentration between 0.02 and 0.03%, but did not cause an increase in mitotic recombinants.	*p*-Chlorotoluene was not recombinogenic in *S. cerevisiae.*	Simmon and Kauhanen (1978)
Genotoxicity	The genotoxicity of *p*-chlorotoluene was determined using the umu-test without activation in *Salmonella typhimurium* TA1535/p3K1002. The umu-test can detect the induction of an error-prone repair gene when DNA is damaged by chemicals.	At concentrations of 100-µg/ml chlorotoluene, the toxicity values were 0.77 (+S9) and 0.58 (-S9), where values of less than 1.0 are negative.	*p*-Chlorotoluene was considered to be negative for genotoxicity in this test.	Ono et al. (1992)

Table 3. Other Studies

Tests	Materials and Methods	Results	Conclusions	References
Genotoxicity	Three hundred and eleven chemicals were tested for mutagenicity in *Salmonella typhimurium*. The tests were conducted using a preincubation protocol in the absence of exogenous metabolic activation, and in the presence of liver S-9 from Aroclor-induced male Sprague-Dawley rats and Syrian hamsters.	*p*-Chlorotoluene was negative.	*p*-Chlorotoluene was not mutagenic.	Zeiger et al. (1992)
Genotoxicity	A mouse micronuclei test was performed. Male and female mice were administered a single intraperitoneal dose of 1000 mg/kg of *p*-chlorotoluene and were sacrificed at 16, 24, or 48 hours.	There was no change in the ratio of polychromatic to normo-chromatic erythrocytes.	*p*-Chlorotoluene was not clastogenic.	Herbold (1992)
Genotoxicity	The genotoxicity of 26 hydrocarbons was studied via a micronuclei test in human lymphocytes.	The micronuclei frequency was 8, 12, and 17% at concentrations of 27.2, 54.4, and 108.8 ppm, respectively.	The study authors characterized *p*-chlorotoluene as an active compound.	Huang et al. (1997)

DERIVATION OF PROVISIONAL VALUES

Tables 4 and 5 below present a summary of noncancer and cancer reference values, respectively. IRIS values are indicated in the table if available.

DERIVATION OF ORAL REFERENCE DOSE

Derivation of Subchronic p-RfD

Of the two subchronic studies available to be considered for the derivation of the subchronic p-RfD (i.e., Pis'ko et al., 1981; Terrill et al., 1990), only the Terrill et al. (1990) provides sufficient details even though the results of the Pis'ko et al. (1981) study may be consistent with a lower NOAEL. The Pis'ko et al. (1981) study is poorly documented (purity of material not provided), and there was no indication that a control was used. There were no details on the specific methods used, including the dosing frequency or medium, sample size per treatment group, and the sex and strain of the animals. In addition, there is no indication that the study adhered to any standard laboratory practices such as Good Laboratory Practice (GLP). Furthermore, the neurotoxicity was only observed in the low doses (<0.1 mg/kg-day) in the Pis'ko et al. (1981) study, while the Terrill et al. (1990) study observed neurotoxicity only at the highest dose tested (800 mg/kg-day). The two mixture studies (Industrial Bio-test Labs Inc., 1987a,b) administered with 51% *o*-chlorotoluene and 48% *p*-chlorotoluene did not observe neurotoxicity after conducting histopathology in the brain. The results from the Pis'ko et al. (1981) study are inconsistent with other studies that showed similar observations with regards to neurotoxicity.

The 90-day study by Terrill et al. (1990) is selected as the principal study for derivation of a subchronic p-RfD. There is no specific critical effect and endpoint. The NOAEL was 200 mg/kg-day. The next highest dose (i.e., 800 mg/kg-day) was the FEL with an increase in mortality accompanied by statistically significant changes in histopathology, clinical chemistry, and organ weights, and increases in microscopic lesions (note the steep dose-response relationship). Details of this study are provided in the ***Review of Potentially Relevant Data*** section. Among the available acceptable studies, the Terrill et al. (1990) study represents the lowest point-of-departure (POD) for deriving a subchronic p-RfD. The POD is based on the NOAEL of 200 mg/kg-day. The data from the Terrill et al. (1990) study are not amenable to BMD analysis because the highest dose tested caused mortality; the lower doses were not significantly different from the control for all endpoints, and the data did not have a statistically significant dose-response trend.

Table 4. Summary of Reference Values for *p*-Chlorotoluene (CASRN 106-43-4)

Toxicity Type (Units)[a]	Species/Sex	Critical Effect	*p*-Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic p-RfD (mg/kg-day)	Rat/M+F	Next dose was the FEL, causing an increase in mortality.	0.2	NOAEL	200	1000	Terrill et al. (1990)
Screening chronic p-RfD (mg/kg-day)	Rat/M+F	Next dose was the FEL, causing an increase in mortality.	2×10^{-2}	NOAEL	200	10,000	Terrill et al. (1990)
Subchronic p-RfC (mg/m^3)	None	None	None	None	None	None	None
Chronic p-RfC (mg/m^3)	None	None	None	None	None	None	None

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

Table 5. Summary of Cancer Values for *p*-Chlorotoluene (CASRN 106-43-4)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	None	None	None	None
p-IUR	None	None	None	None

Adjusted Doses for Daily Exposure—No dosimetric adjustments were made for the dose in the principal study for gavage treatment because p-chlorotoluene was administered 7 days a week. Therefore, the DOSEADJ was the same as the administered dose.

The subchronic p-RfD for *p*-chlorotoluene, based on the NOAEL of 200 mg/kg-day in male and female rats (Terrill et al., 1990) is derived as follows:

$$\textbf{Subchronic p-RfD} = NOAEL_{ADJ} \div UF_C$$
$$= 200 \text{ mg/kg-day} \div 1000$$
$$= \textbf{0.2 mg/kg-day or } \mathbf{2 \times 10^{-1}} \textbf{ mg/kg-day}$$

Table 6 summarizes the uncertainty factors (UFs) applied in the derivation of the subchronic p-RfD along with the rationale for the values that were selected. The overall level of confidence in the subchronic p-RfD for *p*-chlorotoluene is judged to be low for the reasons summarized in Table 7.

Table 6. UFs for Subchronic p-RfD of *p*-Chlorotoluene

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans. There are no data to determine whether humans are more or less sensitive than rats to the general toxicity of *p*-chlorotoluene.
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_D	10	A $UF_{D\ of}$ 10 is selected because there are no acceptable two-generation reproduction studies or developmental studies of *p*-chlorotoluene.
UF_L	1	A UF_L of 1 is applied from extrapolation from a LOAEL to a NOAEL because the POD is based on a NOAEL.
UF_C ≤3000	1,000	

[a]Terrill et al. (1990).

Table 7. Confidence Descriptor for Subchronic p-RfD for *p*-Chlorotoluene		
Confidence Categories	**Designation[a]**	**Discussion**
Confidence in Study	**M**	The study was given medium confidence because it meets most of the data requirements. However, frequency and severity information for histopathological endpoints were not provided.
Confidence in Database	**L**	Confidence in the database was low because there are no supporting studies available. In addition, no acceptable reproduction/developmental studies were identified in the available literature.
Confidence in Subchronic p-RfD[b]	**L**	The overall confidence in the subchronic p-RfD is low.

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

Derivation of Chronic p-RfD

No chronic p-RfD can be derived because doing so would require the application of a UF_C of 10,000. However, a screening chronic p-RfD is provided in Appendix A.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No subchronic or chronic p-RfC values can be derived because there are no suitable studies on inhalation exposure to *p*-chlorotoluene.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Table 8 identifies the cancer WOE descriptor for *p*-chlorotoluene. Under the 2005 *Guidelines for Carcinogen Assessment* (U.S. EPA, 2005), there is "*Inadequate Information to Assess* [the] *Carcinogenic Potential*" of *p*-chlorotoluene.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

The lack of data on the carcinogenicity of *p*-chlorotoluene precludes the derivation of quantitative estimates for either oral (p-OSF) or inhalation (p-IUR) exposure.

APPENDIX A. PROVISIONAL SCREENING VALUES

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for *p*-chlorotoluene. 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 CHRONIC ORAL REFERENCE DOSE

Chronic toxicity studies for oral *p*-chlorotoluene exposures are not available. Therefore, the screening chronic p-RfD is based on the NOAEL of 200 mg/kg-day in male and female rats exposed to *p*-chlorotoluene for 90 days (Terrill et al., 1990). The screening chronic p-RfD for *p*-chlorotoluene, is derived as follows:

$$\textbf{Screening Chronic p-RfD} = NOAEL_{ADJ} \div UF_C$$
$$= 200 \text{ mg/kg-day} \div 10{,}000$$
$$= \textbf{0.02 mg/kg-day or } \mathbf{2 \times 10^{-2}} \textbf{ mg/kg-day}$$

Table A-1 summarizes the UFs for the screening chronic p-RfD for *p*-chlorotoluene.

Table A-1. UFs for Screening Chronic p-RfD for *p*-Chlorotoluene

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans. There are no data to determine whether humans are more or less sensitive than rats to general toxicity of *p*-chlorotoluene.
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_D	10	A UF_D of 10 is selected because there are no acceptable two-generation reproduction studies or developmental studies.
UF_L	1	A UF_L of 1 is applied for LOAEL to NOAEL extrapolation because the POD was based on a NOAEL.
UF_S	10	A UF_S of 10 is applied for using data from a subchronic study (Terrill et al., 1990) to assess potential effects from chronic exposure because data for evaluating responses from chronic exposure are unavailable.
UF_C	10,000	

[a]Terrill et al. (1990).

APPENDIX B. DATA TABLES

Table B-1. Selected Clinical Chemistry Parameters and Organ Weights in Sprague-Dawley Rats Exposed to Oral *p*-Chlorotoluene for 90 Days[a]

Parameter	Exposure Group (Daily Average Dose, mg/kg-day)			
	0	50 (50)	200 (200)	800 (800)
Males				
Sample size	10	10	10	6
Terminal body weight	570.7 ± 55.4[b]	583.3 ± 73.5	591.6 ± 51.1	488.8 ± 80.4
Clinical Chemistry				
BUN (mg/dl)	11 ± 1.3	11 ± 1.7	10 ± 1.6	33 ± 28.2[c]
Creatinine (mg/dl)	0.5 ± 0.05	0.6 ± 0.06	0.5 ± 0.05	1.0 ± 0.47[c]
LDH (IU/L)	769 ± 267.3	848 ± 561.9	1145 ± 514.3	658 ± 183.8
ALP (IU/L)	87 ± 29.2	93 ± 17.7	106 ± 30.4	136 ± 50.3[c]
Bilirubin (mg/dl)	0.16 ± 0.052	0.17 ± 0.048	0.16 ± 0.052	0.23 ± 0.052[c]
Organ Weight				
Absolute liver (g)	14.97 ± 2.46	14.95 ± 3.14	15.40 ± 2.29	15.11 ± 2.0
Relative liver (%)	2.616 ± 0.291	2.542 ± 0.212	2.579 ± 0.242	3.134 ± 0.453[c]
Absolute kidney (g)	3.57 ± 0.43	3.66 ± 0.56	4.04 ± 0.54	4.12 ± 0.66
Relative kidney (%)	0.628 ± 0.062	0.629 ± 0.063	0.683 ± 0.079	0.878 ± 0.299[c]
Absolute adrenal (g)	0.059 ± 0.009	0.060 ± 0.010	0.058 ± 0.007	0.076 ± 0.015[c]
Relative adrenal (%)	0.0104 ± 0.0021	0.0105 ± 0.0022	0.0098 ± 0.0017	0.0164 ± 0.0072[c]
Females				
Sample size	10	10	10	8
Terminal body weight	320.5 ± 20.7	301.5 ± 23.7	329.7 ± 42.9	282.4 ± 17.9[c]
Clinical Chemistry				
AST (IU/L)	85 ± 19.9	97 ± 20.4	103 ± 28.6	144 ± 128.6
ALT (IU/L)	34 ± 22.6	28 ± 6.0	29 ± 7.9	61 ± 79.2
Organ Weight				
Absolute liver (g)	8.83 ± 1.33	8.54 ± 1.03	9.13 ± 1.19	9.82 ± 0.96
Relative liver (%)	2.748 ± 0.316	2.847 ± 0.409	2.807 ± 0.468	3.481 ± 0.316
Absolute kidney (g)	2.22 ± 0.25	2.08 ± 0.20	2.28 ± 0.16	2.35 ± 0.28
Relative kidney (%)	0.694 ± 0.067	0.692 ± 0.071	0.699 ± 0.077	0.835 ± 0.120[c]

[a]Terrill et al. (1990).
[b]Means ± SD.
[c]Significantly different from control ($p \leq 0.05$) Dunnett's test.

APPENDIX C. BMD MODELING OUTPUTS FOR *p*-CHLOROTOLUENE

There are no BMD modeling outputs.

APPENDIX D. REFERENCES

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