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Provisional Peer-Reviewed Toxicity Values for

o-Chlorotoluene
(CASRN 95-49-8)

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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 *o*-CHLOROTOLUENE (CASRN 95-49-8)

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

o-Chlorotoluene is used as a basic chemical for the production of intermediates in the synthesis of other organic chemicals, dyes, pharmaceuticals, and synthetic rubber chemicals, and as a solvent for chemical processing and for the formulation of agricultural pesticides. It is a colorless liquid with an aromatic odor. *o*-Chlorotoluene is produced commercially by chlorinating toluene at 50°C in the presence of ferric chloride; the chlorotoluene isomers are then separated by fractional distillation (HSDB, 2005). The molecular formula for *o*-chlorotoluene is C_7H_7Cl (see Figure 1). A table of chemico-physical properties is provided below (see Table 1). In this document, "statistically significant" denotes a *p*-value of <0.05.

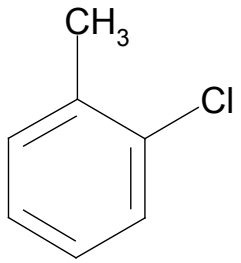

Figure 1. *o*-Chlorotoluene Structure

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

Property (unit)	Value
Boiling point (ºC)	158.97
Melting point (ºC)	−35.59
Density (g/cm^3)	1.0826
Vapor pressure (at 25ºC)	3.43 mm Hg
pH (unitless)	Not available
Solubility in water (mg/L at 25ºC)	374
Relative vapor density (air = 1)	4.38
Molecular weight (g/mol)	126.6
Flash point (°C)	47
Octanol/water partition coefficient (unitless)	3.42 (Log Kow)

[a]Values from HSDB (searched online 03/16/2010; last reviewed 09/19/1996; last revised 06/23/2005).

The EPA IRIS database (U.S. EPA, 1990) reports a noncancer chronic oral RfD for *o*-chlorotoluene of 0.02 mg/kg-day based on decreased body-weight gains in a subchronic oral toxicity study in rats (Gibson et al., 1974a) but does not report an RfC. The Drinking Water Standards and Health Advisories List (U.S. EPA, 2006) reports an RfD of 0.02 mg/kg-day, a Drinking Water Equivalent Levels (DWELs) of 0.7 mg/L, and a lifetime Health Advisory (HA) of 0.1 mg/L for *o*-chlorotoluene. CalEPA (2009a,b) has not derived toxicity values for exposure to *o*-chlorotoluene but lists a drinking water action level of 140 µg/L. A subchronic oral RfD of 0.02 mg/kg-day was reported in the HEAST (U.S. EPA, 1997), derived from a 103-day oral gavage study in rats with a LOAEL of 80 mg/kg-day (based on decreased body-weight gains) and an uncertainty factor (UF) of 100 (same study used by IRIS). The most recent EPA Regional Screening Level (RSL) Master Table for December 2009 continued to list this value as the oral RfD based on IRIS. The American Conference of Governmental Industrial Hygienists (ACGIH, 2001) reported a threshold limit value (TLV) of 50 ppm, 259-mg/m^3 time-weighted average (TWA), and the National Institute of Occupational Safety and Health (NIOSH, 2005) set a Recommended Exposure Limit (REL) at 50 ppm, 250 mg/m^3. The Occupational Safety and Health Administration (OSHA, 2009) set a permissible exposure limit (PEL) of 50 ppm for *o*-chlorotoluene. The toxicity of *o*-chlorotoluene has not been reviewed by the ATSDR (2009) to determine oral or inhalation Minimal Risk Levels (MRLs). The World Health Organization (WHO) did not include *o*-chlorotoluene in the *WHO Chemical Safety - Activity Report* (WHO, 2009).

The IRIS database (U.S. EPA, 1990) stated that *o*-chlorotoluene had not undergone a complete evaluation and determination under the IRIS program for evidence of human carcinogenic potential. The Drinking Water Standards and Health Advisories List (U.S. EPA, 2006) reported an EPA cancer weight-of-evidence (WOE) classification of Group D (*Not Classifiable as to Human Carcinogenicity*) for *o*-chlorotoluene based on the lack of carcinogenicity studies in humans or animals. *o*-Chlorotoluene has not been evaluated under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005). The International Agency for Research on Cancer (IARC, 2009) has not reviewed the carcinogenic potential of *o*-chlorotoluene. *o*-Chlorotoluene is not included in the National Toxicology Program's *11th Report on Carcinogens* (NTP, 2005). CalEPA (2009b) has not prepared a quantitative estimate of carcinogenic potential for *o*-chlorotoluene.

Literature searches were conducted from 1900 through August 2010 for studies relevant to the derivation of provisional toxicity values for *o*-chlorotoluene, CAS No. 95-49-8. We used the EPA Health and Environmental Research Online (HERO) evergreen database of scientific literature that searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration; DOE: Information Bridge; DOE: Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics; JSTOR: 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 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. Entries for the principal study are in bold and labeled "PS."

Table 2. Summary of Potentially Relevant Data for *o*-Chlorotoluene (CASRN 95-49-8)

Notes[a]	Category	Number of Male/Female Species and Strain, Study Type, and Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (Comments)
Human								
				1. Oral (mg/kg-day)[b]				
	Subchronic	None						
	Chronic	None						
	Developmental	None						
	Reproductive	None						
	Carcinogenic	None						
				2. Inhalation (mg/m^3)[b]				
	Subchronic	None						
	Chronic	None						
	Developmental	None						
	Reproductive	None						
	Carcinogenic	None						
Animal								
				1. Oral (mg/kg-day)[b]				
PS IRIS (1990), NPR	**Subchronic**	**20/20 Harlan rat, subchronic toxicity, daily oral gavage for 103 (males) or 104 (females) days**	**0, 20, 80, or 320**	**Decreased body-weight gains and decrease in absolute body weight in males**	**20**	**NA**	**80**	**Gibson et al. (1974a)**
IRIS (1990), NPR	**Subchronic**	4/4 beagle dog, subchronic toxicity, daily capsule for 96 (females) or 97 (males) days	0, 5, 20, or 80	None observed	80	NA	NA	Gibson et al. (1974b)
	Metabolism	5/5 Harlan rat, subchronic toxicity, daily oral gavage for 14 days, or 103−104 days 4/4 beagle dog, subchronic toxicity, daily capsule for 96−97 days	0, 20, 80, or 320 (rat) 0, 5, 20, or 80 (dog)	Separate report of enzyme activity analysis from Gibson et al. (1974a) No effects of treatment on *O*-demethylation of *p*-nitroanisole	320 (rat) 80 (dog)	NA	NA	Hoffman and Bernhard (1974)
	Chronic	None						
	Developmental	None						
	Reproductive	None						
	Carcinogenic	None						

Table 2. Summary of Potentially Relevant Data for *o*-Chlorotoluene (CASRN 95-49-8)

Notes[a]	Category	Number of Male/Female Species and Strain, Study Type, and Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (Comments)
2. Inhalation (mg/m^3)[b]								
	Subchronic	None						
	Chronic	None						
IRIS (1990)	**Developmental**	25 female Sprague-Dawley rat, 14 days (GDs 6−19)	0, 250, 750, or 2250	Dams: slight ataxia; decreased body-weight gains and food consumption; increased water consumption	250	NA	750	Edwards et al., (1982)
				Fetuses: decreased mean litter weight and mean fetal weight, and increased incidence of malformation (brachydactyly) at 2250 mg/m^3	750		2250	
IRIS (1990)	**Developmental**	16 female New Zealand White rabbit, 23 days (GDs 6−28)	0, 375, 1000, or 2500	Does: partial ptosis; rapid respiration; decreased body-weight gains and food consumption	375	NA	1000	Edwards et al., (1983)
				Fetuses: slightly but not statistically significantly decreased mean fetal weight	1000		2500	
	Reproductive	None						
	Carcinogenic	None						

[a]Notes: a: IRIS = Utilized by IRIS, date of last update; PS = Principal study, b: 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.

HUMAN STUDIES

Oral and Inhalation Exposure

No studies investigating the effects of subchronic or chronic oral exposure to *o*-chlorotoluene in humans have been identified. No quantitative data were located regarding the toxicity of *o*-chlorotoluene to humans following chronic or subchronic inhalation exposure. The ACGIH reported a TLV of 50 ppm (259 mg/m^3 TWA) and stated that this value was recommended based on good occupational hygiene practice, rather than on supporting data. Further, unpublished communications regarding worker experience from exposure to *o*-chlorotoluene indicated a lack of irritant or pulmonary effects and recommended an exposure value (maximum allowable concentration) of 75 to 200 ppm, which is equivalent to 390 to 1040 mg/m^3 (ACGIH, 2001). An online search of Haz-map (2010) reported that *o*-chlorotoluene is a respiratory irritant and that exposure to high concentrations may produce "systemic toxic effects." Additionally, *o*-chlorotoluene may cause skin irritation.

ANIMAL STUDIES

Oral Exposure

The effects of oral exposure of animals to *o*-chlorotoluene have been evaluated in unpublished subchronic (Gibson et al., 1974a,b) toxicity studies that were used as principal studies by the IRIS Summary for *o*-Chlorotoluene (U.S. EPA, 1990). No chronic oral toxicity studies or oral developmental or reproductive toxicity studies were located. A report summarizing the acute oral toxicity of *o*-chlorotoluene (Kodak, 1994) is presented in ***Other Data*** below.

***Subchronic Studies*—The study by Gibson et al. (1974a) is selected as the principal study for deriving the subchronic p-RfD.** Male and female (20/sex/dose) weanling Harlan rats were administered *o*-chlorotoluene (purity not provided) in 5% aqueous acacia at doses of 0, 20, 80, or 320 mg/kg-day (dose volume 2 mL/kg) by daily oral gavage for 103 (males) or 104 (females) days. Dosing emulsions were prepared daily. The rats were observed for signs of toxicity daily; body weights and food consumption were recorded weekly. On Day 14, five rats/sex/dose were killed by carbon dioxide asphyxiation, and portions of the livers were processed for determination of microsomal enzyme activities. At termination, the livers of an additional five rats/sex/dose were processed for similar determinations. The results of the enzyme activity determinations were presented in a separate report (Hoffman and Bernhard, 1974). This report indicated there were no treatment-related effects by *o*-chlorotoluene on hepatic *O*-demethylation activity. Hematology parameters (hematocrit, hemoglobin, erythrocyte count, leukocyte count) were measured on all rats; prothrombin time was determined for half of the animals; and clinical chemistry parameters (blood urea nitrogen [BUN], glutamic pyruvic transaminase, and glucose) were measured on the remaining half of the rats. At termination, the rats were necropsied, organ weights (liver, kidney, heart, spleen, thyroid, adrenal, prostate, testes, and/or uterus and ovaries) were recorded, and histopathological examinations (weighed organs, colon, duodenum, ileum, jejunum, lungs, lymph nodes, mammary gland, pancreas, parathyroid, salivary gland, skin, stomach, skeletal muscle, thymus, and urinary bladder) were performed. In the males, body-weight gains were statistically significantly decreased by 15 and 22%, absolute body weight was decreased by 11 and 16% (see Appendix B, Table B.1), and feed efficiency was decreased by 9 and 16% at 80 and 320 mg/kg-day, respectively. In addition, a statistically significant increase in adrenal glands, heart and testes weights, and white blood cell count, and a decrease in prothrombin time were observed in males in the 320-mg/kg-day dose

group. At the 80-mg/kg-day dose level, BUN was statistically significantly increased in males. No other changes were observed in histopathological examinations or hematological parameters. A NOAEL of 20 mg/kg-day is identified, and the LOAEL is 80 mg/kg-day.

In a companion study by Gibson et al. (1974b), male and female (four/sex/dose) beagle dogs (age not provided) were administered *o*-chlorotoluene (purity not provided) in 5% aqueous acacia at doses of 0, 5, 20, or 80 mg/kg-day (dose volume 0.5 mL/kg) daily by capsule for 97 (males) or 96 (females) days. Dosing emulsions were prepared daily. The dogs were observed for signs of toxicity daily; body weights were recorded weekly. Physical and ophthalmological examinations, and hematology (leukocyte counts, erythrocyte counts, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, prothrombin time, sedimentation rate, blood clotting time, platelet count, leukocyte differential count, nucleated erythrocytes, and erythrocyte morphology), clinical chemistry (calcium, inorganic phosphorus, glucose, BUN, uric acid, cholesterol, total protein, albumin, total bilirubin, alkaline phosphatase, lactic acid dehydrogenase, and serum glutamic oxaloacetic transaminase), and urinalysis (specific gravity, sugar, pH, protein occult blood, and abnormal color and appearance) parameters were measured on all dogs prior to the initiation of treatment, and at 1, 2, and 4 weeks, and monthly thereafter. At termination, the dogs were necropsied, organ weights (liver, kidney, heart, spleen, thyroid, adrenal, testes, and/or ovaries) were recorded, and histopathological examinations (weighed organs, colon, duodenum, ileum, jejunum, lungs, lymph nodes, mammary gland, pancreas, parathyroid, prostate, salivary gland, skin, stomach, skeletal muscle, thymus, urinary bladder, and uterus) were performed. A liver sample from each dog was used to determine microsomal enzyme activities; the results of these determinations were presented in a separate report. No treatment-related effects by *o*-chlorotoluene on hepatic O-demethylation activity in dogs treated for 96−97 days were observed (Hoffman and Bernhard, 1974). Overall, no treatment-related findings were reported at any dose level (see Appendix B, Table B.2.). The NOAEL was 80 mg/kg-day at the highest dose tested; no LOAEL was identified.

The results of a metabolism study by Hoffman and Bernhard (1974) concerning the effect of *o*-chlorotoluene on hepatic *O*-demethylation of *p*-nitroanisole were cited in both of the subchronic studies above. This additional study indicated there were no treatment-related effects by *o*-chlorotoluene on hepatic *O*-demethylation activity in rats treated for 14 days or 103−104 days, or in dogs treated for 96−97 days.

Chronic Studies—No studies could be located regarding the effects of chronic oral exposure of animals to *o*-chlorotoluene.

Developmental and Reproduction Studies—No studies could be located regarding the effects of oral exposure of animals to *o*-chlorotoluene on fetal development or reproduction.

Inhalation Exposure

The effects of inhalation exposure of animals to *o*-chlorotoluene have been evaluated in two developmental toxicity studies (Edwards et al., 1982; 1983). Furthermore, a short-term inhalation study (Arthur and Owen, 1974) and a report summarizing acute dermal, ocular, and inhalation toxicity (Kodak, 1994) were located and are presented in ***Other Data*** below.

Subchronic Studies—No studies could be located regarding the effects of subchronic inhalation exposure of animals to *o*-chlorotoluene.

Chronic Studies—No studies could be located regarding the effects of chronic inhalation exposure of animals to *o*-chlorotoluene.

Developmental and Reproduction Studies—No studies could be located regarding the effects of inhalation exposure of *o*-chlorotoluene on reproductive toxicity.

Edwards et al. (1982) exposed groups of 25 time-mated Sprague-Dawley female rats (body weights 166−208 g) via whole-body inhalation exposure to *o*-chlorotoluene (purity 96.5% w/v) at nominal concentrations of 0, 1, 3, or 9 mg/L (equivalent to 0, 250, 750, or 2250 mg/m^3 after duration and concentration adjustments; see Appendix A, Table A.1) for 6 hours per day during Gestation Days (GDs) 6−19. Vapor generation was achieved by atomizing *o*-chlorotoluene, heating the atomized liquid to approximately 100°C, and delivering the vapor to the exposure chamber by dilution with heated air. The desired exposure concentrations were maintained in 1-m^3 stainless steel, glass-fronted chambers using a target total airflow of 250 L/min, yielding a calculated 95% equilibration time of 12 minutes. *o*-Chlorotoluene concentrations were measured at 30-minute intervals using a portable infrared gas analyzer. The variation of chamber concentrations during exposures was small and within acceptable limits. In the dams, clinical signs observed included slight ataxia at 3 mg/L (750 mg/m^3), and slight-to-moderate ataxia and occasional lacrimation and/or salivation at 9 mg/L (2250 mg/m^3). Food consumption was decreased during treatment (GDs 6−19) at 3 and 9 mg/L ($p \leq 0.001$ at 9 mg/L). Cumulative body-weight gains (relative to GD 6) were decreased during treatment at 3 and 9 mg/L. There was an increase in water consumption at 3 and 9 mg/L. In the fetuses, mean litter weight and mean fetal weight were both decreased ($p \leq 0.01$) at 9 mg/L. Additionally, at this dose, an increased incidence of brachydactyly, a malformation, was observed (6 fetuses; 4 litters). A NOAEL of 1 mg/L (250 mg/m^3) for maternal toxicity is identified for this report, and the LOAEL is 3 mg/L (750 mg/m^3). A NOAEL of 3 mg/L (750 mg/m^3) for developmental toxicity is identified, and the LOAEL is 9 mg/L (2250 mg/m^3).

Edwards et al. (1983) exposed groups of 16 mated New Zealand White rabbits (group mean body weights 3240−3290 g) via whole-body inhalation exposure to *o*-chlorotoluene (purity 96.5% w/v) at nominal concentrations of 0, 1.5, 4, or 10 mg/L (equivalent to 0, 375, 1000, or 2500 mg/m^3 after duration and concentration adjustment; see Appendix A, Table A.2) for 6 hours per day during GDs 6−28. Vapor generation and exposure parameters were the same as described above. In the does, clinical signs observed included partial ptosis and rapid respiration at 4 mg/L (1000 mg/m^3), and lacrimation and salivation, partial or complete ptosis, and rapid respiration following exposure at 10 mg/L (2500 mg/m^3). There was a dose-related decrease in mean food consumption at 4 and 10 mg/L during GDs 6−13. Cumulative body-weight gains (relative to GD 6) were decreased during GDs 6−14 at 4 mg/L and during GDs 6−19 at 10 mg/L. In the fetuses, mean fetal weight was slightly but not statistically significantly ($p > 0.05$) decreased at 10 mg/L. A NOAEL of 1.5 mg/L (375 mg/m^3) for maternal toxicity is identified for this report, and the LOAEL is 4 mg/L (1000 mg/m^3). A NOAEL of 4 mg/L (1000 mg/m^3) for developmental toxicity is identified, and the LOAEL is 10 mg/L (2500 mg/m^3). Both developmental studies (Edwards et al., 1982; 1983) are not published and

have not been peer-reviewed but were mentioned in the IRIS Summary for *o*-Chlorotoluene as additional studies (U.S. EPA, 1990).

Other Data (Short-Term Tests, Other Examinations)

Acute Studies—Kodak (1994) performed an abbreviated acute toxicity test on three rats (strain not provided) and concluded that the oral LD_{50} was >1600 mg/kg. When undiluted *o*-chlorotoluene (purity not provided) was held in occluded contact with the skin of guinea pigs for 24 hours, it was moderately irritating. There was some evidence of systemic toxicity due to dermal absorption, but the LD_{50} was >10 cc/kg (1100 mg/kg). One drop of undiluted *o*-chlorotoluene in the eye of a rabbit produced moderate irritation; however, the eye recovered and was normal after 14 days. Rats exposed by inhalation to a calculated concentration of 14,000 ppm (72,000 mg/m^3) for 6 hours showed respiratory tract irritation and sympathetic nerve stimulation. When the calculated concentration was increased to 175,000 ppm (906,000 mg/m^3), one of the three rats died. The surviving two rats displayed prostration.

Short-term Studies—In a short-term inhalation study by Arthur and Owen (1974), groups of 10 Harlan rats/sex/dose group were exposed to aerosolized *o*-chlorotoluene (purity not provided) by head-only inhalation exposure at concentrations of either 33,000 or 62,000 mg/m^3 for 1 hour per day, 5 days a week, for 3 weeks (15 exposures). A control group was similarly exposed to an aerosol of tap water. The test material was sprayed from a nebulizer into a 61-L exposure chamber. The nebulizer was designed to produce aerosol particles from 3−10 microns in diameter at a controlled air flow of 388 L/hour. The volume of aerosolized solvent was recorded daily to facilitate the calculation of mean chamber concentrations. Several of the 33,000-mg/m^3 rats displayed slight ataxia immediately following each exposure. One female in this group became emaciated and died on Day 5; this death was attributed to acute necrotizing pneumonia in lungs. At 62,000 mg/m^3, animals developed severe ataxia following each exposure, and approximately half of the animals became prostrate for 15−30 minutes. One female in this group lost 50 g of body weight during the last nine exposures. Additionally at this dose, two males died on Day 12, and two females died on Day 10; these deaths were attributed to "respiratory embarrassment." The experimental design was modified by decreasing the exposure time of the 62,000-mg/m^3 group to 30 minutes for the last three exposures. Another 62,000-mg/m^3 female suffocated in the holding chamber on Day 1. None of the deaths at either dose were attributed to treatment with *o*-chlorotoluene. All other findings were considered incidental to treatment by the study authors.

Metabolism Studies—In a metabolism study by Wold (1974), ^{14}C-*o*-chlorotoluene (position of radiolabel not specified) in 1% aqueous Span 80/Tween 80 (1:1) was administered by oral gavage to three male Harlan rats at a dose level of 320 mg/kg (1.25 µCi/kg) in a dose volume of 0.5 mL/100 g body weight. The rats were housed individually in glass metabolism cages for the first 24 hours after dosing; they were then transferred to stainless steel metabolism cages for the remainder of the study. Air was drawn through the glass metabolism cages and into two traps; the traps consisted of two, 500-mL gas washing bottles, each filled with methanol at room temperature. The efficiency of the trap system was confirmed by introducing a known quantity of ^{14}C-*o*-chlorotoluene in ethanol into a cage and drawing air through the cage and traps for 3-hour periods. The recovery of ^{14}C-*o*-chlorotoluene was 98.2%. At 24 and 48 hours postdosing, urine and feces were collected, and the cages were rinsed with distilled water. Radioactivity in aliquots of urine and cage wash was quantitated by liquid scintillation counting;

feces were air-dried for 48 hours, weighed, powdered, and aliquots were combusted. Urine samples were acidified to pH 1, vortexed with ethyl acetate, and centrifuged. The aqueous layer was reextracted with ethyl acetate; the organic extracts were combined and evaporated to dryness. The residue was resuspended in methanol, derivatized with diazomethane, and analyzed by gas chromatography (GC) or GC/mass spectrometry (MS) for metabolite identification. Urine samples were also subjected to enzyme hydrolysis; conjugates were identified by thin-layer chromatography (TLC). Urinary metabolites were quantified by TLC. Total recovery of radioactivity was 94.3−97.9% of the administered dose (AD). Unmetabolized *o*-chlorotoluene was present in the expired air and accounted for 11.3% AD. The majority of radioactivity was found in the urine (81.7% AD) with a minor amount in the feces (3.5% AD). *o*-Chlorotoluene was rapidly and extensively metabolized and excreted by the rat. Unmetabolized *o*-chlorotoluene was not found in the urine. The major urinary metabolite was *o*-chlorobenzyl alcohol glucuronide (37.5−45.8% AD), followed by chloro-methyl-phenylmercapturic acid (21−22% AD) and *o*-chlorohippuric acid (17−20% AD). The following urinary metabolites were also identified but were present at ≤2.4% AD: *o*-chlorobenzyl alcohol; *o*-chlorobenzoic acid; *o*-chlorobenzoic acid glucuronide; and unidentified polar metabolites.

In a study by Quistad et al. (1983), [U-ring-^{14}C]-*o*-chlorotoluene (2-chloro[U-ring-^{14}C]toluene) in corn oil was administered by oral gavage to four Sprague-Dawley rats/sex at a dose level of 1 mg/kg. One additional female was treated at 91 mg/kg; another female was treated at 102 mg/kg. All animals were fasted 16 hours prior to dosing. Animals were housed in all-glass metabolism chambers; expired air was trapped in 5% KOH (for CO_2) and Amberlite XAD-2 resin (volatile organics). An additional three male rats were dosed with 1 mg/kg as above, and blood samples were obtained from the orbital sinus at regular intervals for determination of pharmacokinetics. The general method for analysis of urinary metabolites involved mild acidification followed by liquid chromatography (LC). The identities of individual metabolites were confirmed by MS. Total recovery ranged from 97.8−103% AD, with the majority of radioactivity found in the urine (85−92% AD), feces (5−8%), and expired air (1−4%). At least 84% of the volatile ^{14}C was identified as unmetabolized *o*-chlorotoluene. The major metabolites found in both urine and feces were *o*-chlorohippurate, *o*-chlorobenzyl alcohol glucuronide, and *o*-chlorobenzyl alcohol mercapturic acid. Additionally, a small amount of unmetabolized *o*-chlorotoluene was found in the feces (<2% AD). *o*-Chlorotoluene was quickly absorbed, with a peak concentration in plasma observed at approximately 2 hours postdosing. Virtually all of the administered dose was eliminated within 4 days, with <1% AD remaining in the carcass. No significant sex-related metabolic differences were detected.

Genotoxicity Studies—In an Ames *Salmonella* mutagenicity test (Hooker Chem. and Plastics Corp., 1982), the mutagenic activity of *o*-chlorotoluene (96.6% *o*-chlorotoluene, 3.4% *p*-chlorotoluene, 0.1% toluene) was tested in the presence and absence of liver microsomal enzyme preparations (S9 homogenate) on *S. typhimurium* indicator organisms. The strains used were TA1535, TA1537, TA1538, TA98, and TA100. A preliminary cytotoxicity test using the TA100 strain was performed, followed by the mutagenicity assays. Positive and negative controls were included. It was concluded that *o*-chlorotoluene was not considered mutagenic under these test conditions.

In a mouse lymphoma forward mutation assay (Occidental Chemical Corp., 1985), the mutagenic activity of *o*-chlorotoluene was tested in the presence and absence of liver microsomal

enzyme preparations (S9 homogenate) on L5178Y TK +/- mouse lymphoma cells. A preliminary cytotoxicity test was performed, followed by the mutagenicity assays. Positive and negative controls were included. It was concluded that *o*-chlorotoluene was not considered mutagenic under these test conditions.

Table 3 summarizes studies on acute toxicity, short-term inhalation, metabolism, and genotoxicity of *o*-chlorotoluene.

DERIVATION OF PROVISIONAL VALUES

Table 4 below presents a summary of noncancer reference values. No cancer values could be derived (see Table 5). For the oral noncancer studies by gavage, the only conversion was to provide an average daily dose.

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic p-RfD

The study by Gibson et al. (1974a) is selected as the principal study for derivation of the subchronic p-RfD because it presents data to support the critical effects of decreased body-weight gain (statistically significant) and decrease in absolute body weight (biologically significant) in male rats as the most sensitive effect observed in response to subchronic oral exposure to *o*-chlorotoluene (see Appendix B, Table B.1). This study is a nonpeer-reviewed, unpublished report, but otherwise meets the standards of study design and performance with numbers of animals. This study was conducted prior to implementation of GLP (Good Laboratory Practice) standards. However, the study was used by IRIS for deriving a chronic RfD for *o*-chlorotoluene (U.S. EPA, 1990). The test compound was administered as an emulsion by oral gavage to avoid loss due to volatility (purity not provided). Not all toxicological endpoints (e.g., neurological evaluations, urinalysis) were examined, but most endpoints were evaluated. Details of study design are provided in the ***Review of Potentially Relevant Data*** section. BMD modeling analysis is not possible with these data because standard deviations were not provided, and individual data were not available for calculations. The POD derived from this study is the NOAEL of 20 mg/kg-day based on decreased body-weight gain and absolute body weight in male rats (Gibson et al., 1974a).

Table 3. Other Studies				
Tests	**Materials and Methods**	**Results**	**Conclusions**	**References**
Acute Toxicity	Administered orally to three rats at up to 1600 mg/kg; applied undiluted to the skin of guinea pigs at up to 10 cc/kg; placed undiluted in the eye of rabbit; exposed rats to concentrations of 14,000 ppm for 6 hours by inhalation, then increased concentration to 175,000 ppm	All rats survived oral exposure; moderately irritating to skin of guinea pigs with some systemic toxicity; moderately irritating to eye in rabbit; inhalation at 14,000 ppm (72,000 mg/m^3) caused respiratory tract irritation and sympathetic nerve stimulation, inhalation of 175,000 ppm (906,000 mg/m^3) was fatal to one rat, prostration in the surviving two rats	Oral LD_{50} >1600 mg/kg Dermal LD_{50} >10 cc/kg (1100 mg/kg) Moderately irritating to skin and eye Exposure to high vapor concentration may cause respiratory irritation	Kodak (1994)
Short-term Inhalation Rat	10 Harlan rats/sex exposed to 0, 33,000, or 62,000 mg/m^3 aerosol 1 hour per day, 5 days per week, for 3 weeks	Slight ataxia at 33,000 mg/m^3, with one death; severe ataxia at 62,000 mg/m^3 with five deaths	Death at 33,000 mg/m^3 attributed to acute necrotizing pneumonia; deaths at 62,000 mg/m^3 attributed to suffocation in holding chamber or "respiratory embarrassment"	Arthur and Owen (1974)
Metabolism Rat	Administered to three male Harlan rats at a dose level of 320 mg/kg in aqueous Span 80/Tween 80 by oral gavage. Recovery determined in expired air, urine, and feces. Identified urinary metabolites.	Unmetabolized compound detected in expired air. Major urinary metabolites were *o*-chlorobenzyl alcohol glucuronide, *o*-chlorohippuric acid, and chloro-methyl-phenylmercapturic acid	Compound is rapidly and extensively metabolized and excreted.	Wold (1974)

Table 3. Other Studies

Tests	Materials and Methods	Results	Conclusions	References
Metabolism Rat	Administered to four Sprague-Dawley rats/sex at 1 mg/kg in corn oil by oral gavage; also to 3 males at 1 mg/kg for pharmacokinetics, 1 female at 97 mg/kg and 1 female at 102 mg/kg	Unmetabolized compound detected in expired air. Major urinary and fecal metabolites were *o*-chlorohippurate, *o*-chlorobenzyl alcohol glucuronide, and *o*-chlorobenzyl alcohol mercapturic acid. Unmetabolized *o*-chlorotoluene was found in the feces. Compound was quickly absorbed, with a peak concentration in plasma observed at approximately 2 hours postdosing. Virtually all of the administered dose was eliminated within 4 days. No significant sex-related metabolic differences were detected.	Compound is rapidly and extensively metabolized and excreted.	Quistad et al. (1983)
Genotoxicity	Tested for reverse mutation in *Salmonella typhimurium* (Ames assay) with and without metabolic activation.	Negative in strains TA1535, TA1537, TA1538, TA98, and TA100 with or without S9 activation.	Compound is not mutagenic under the conditions of this assay	Hooker Chem. and Plastics Corp. (1982)
Genotoxicity	Tested for reverse mutation in L5178Y TK +/- cells (mouse lymphoma forward mutation) with and without metabolic activation.	Negative with or without S9 activation.	Compound is not mutagenic under the conditions of this assay	Occidental Chemical Corp. (1985)

Table 4. Summary of Noncancer Reference Values for *o*-Chlorotoluene (CASRN 95-49-8)

Toxicity Type (Units)	Species/ Sex	Critical Effect	Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic p-RfD (mg/kg-day)	Rat/M	Decreased body-weight gains and decrease in absolute body weight	2×10^{-2}	NOAEL	20	1000	Gibson et al. (1974a)
Chronic p-RfD (IRIS) (mg/kg-day)	Rat/M	Decreased body-weight gains	2×10^{-2}	NOAEL	20	1000	Gibson et al. (1974a)
Screening Subchronic p-RfC (mg/m^3)	Rat/F	Slight ataxia, decreased body-weight gains and food consumption, and increased water consumption	8×10^{-1}	NOAEL	250	300	Edwards et al. (1982)
Chronic p-RfC	None	None	None	None	None	None	None

Table 5. Summary of Cancer Values for *o*-Chlorotoluene (CASRN 95-49-8)

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

Adjusted for Daily Exposure

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

$$\begin{aligned} NOAEL_{ADJ} &= NOAEL \times [\text{conversion to daily dose}] \\ &= 20 \text{ mg/kg-day} \times (\text{days of week dosed} \div 7) \\ &= 20 \times (7 \div 7) \\ &= 20 \text{ mg/kg-day} \end{aligned}$$

The subchronic p-RfD for *o*-chlorotoluene, based on the NOAEL of 20 mg/kg-day (POD) in male Harlan rats (Gibson et al., 1974a), is derived as follows:

$$\begin{aligned} \textbf{Subchronic p-RfD} &= NOAEL_{ADJ} \div UF \\ &= 20 \text{ mg/kg-day} \div 1000 \\ &= \textbf{0.02 mg/kg-day or } \mathbf{2 \times 10^{-2}} \textbf{ mg/kg-day} \end{aligned}$$

Tables 6 and 7, respectively, summarize the UFs and the confidence descriptor for the subchronic p-RfD for *o*-chlorotoluene.

Table 6. Uncertainty Factors for Subchronic p-RfD for *o*-Chlorotoluene[a]

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 *o*-chlorotoluene.
UF_D	10	A UF_D of 10 is applied because there are no available developmental and reproductive studies via oral exposure.
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_L	1	A UF_L of 1 is applied because the POD was developed using a NOAEL.
UF_S	1	A UF_S of 1 is applied because a subchronic study (Gibson et al., 1974a) was utilized as the principal study.
$UF_C \leq 3000$	1000	

[a]Gibson et al. (1974a).

Table 7. Confidence Descriptor for Subchronic p-RfD for *o*-Chlorotoluene		
Confidence Categories	**Designation[a]**	**Discussion**
Confidence in Study	**M**	The study was given medium confidence because of the number of animals and doses used, and because several parameters were examined.
Confidence in Database	**L**	The database was given a low confidence because there is only one additional unpublished subchronic study available, and no developmental or reproductive studies are available.
Confidence in Subchronic p-RfD[b]	**L**	The overall confidence in the subchronic p-RfD is low because there are no chronic or pertinent oral reproductive or developmental studies available.

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

DERIVATION OF CHRONIC p-RfD

A chronic RfD of 0.02 mg/kg-day is available on the IRIS database (U.S. EPA, 1990), based on decreased body-weight gains in male Harlan rats exposed to 0, 20, 80, or 320 mg/kg-day *o*-chlorotoluene in 5% aqueous acacia by oral gavage for 103−104 days (Gibson et al., 1974a). The POD was based on the NOAEL of 20 mg/kg-day in male rats. It was stated that a screening-level literature review conducted in August 2003 did not identify any significant new studies.

According to EPA (1990), "An uncertainty factor of 1000 was used: 10 to account for interspecies extrapolation, 10 for differences in individual human sensitivity, and 10 for use of a subchronic study." Notably, IRIS, at that time, did not apply a UF for database (UFD). The confidence statement in the IRIS Summary for *o*-Chlorotoluene (U.S. EPA, 1990) is as follows:

> *The confidence in the study is medium because of the number of animals and doses used and because several parameters were studied. The confidence in the database is low since no specific pattern of toxicity was observed at the higher doses. Considering no chronic or pertinent oral reproductive or developmental data are available, the overall confidence in the RfD is rated low.*

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

The available data are not sufficient for derivation of a subchronic or chronic p-RfC for *o*-chlorotoluene. However, a screening subchronic p-RfC can be derived based on a developmental study and is provided in Appendix A.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Table 8 identifies the cancer WOE descriptor for *o*-chlorotoluene.

Table 8. Cancer WOE Descriptor for *o*-Chlorotoluene

Possible WOE Descriptor	Designation	Route of Entry (Oral, Inhalation, or Both)	Comments
"Carcinogenic to Humans"	N/A	N/A	No human cancer studies are available.
"Likely to Be Carcinogenic to Humans"	N/A	N/A	No animal cancer data are available.
"Suggestive Evidence of Carcinogenic Potential"	N/A	N/A	There are no data available to suggest that there is a carcinogenic potential.
"Inadequate Information to Assess Carcinogenic Potential"	**X**	**Both**	**There is not adequate information available to assess carcinogenic potential.**
"Not Likely to Be Carcinogenic to Humans"	N/A	N/A	No strong evidence of noncarcinogenicity in humans is available.

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 include mutagenic, mitogenic, antiapoptotic (inhibition of programmed cell death), cytotoxic with reparative cell proliferation, and immune suppression.

No chronic toxicity or carcinogenicity data are available on *o*-chlorotoluene. *o*-Chlorotoluene tested negative in both a Ames *Salmonella* mutagenicity test (Hooker Chem. and Plastics Corp, 1982) and a mouse lymphoma forward mutation assay (Occidental Chemical Corp, 1985). It was not considered mutagenic in these tests.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of p-OSF

No human or animal studies examining the carcinogenicity of *o*-chlorotoluene following oral exposure have been located. Therefore, derivation of a p-OSF is precluded.

Derivation of p-IUR

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

APPENDIX A. PROVISIONAL SCREENING VALUES

For the reasons noted in the main document, it is inappropriate to derive a subchronic p-RfC for *o*-chlorotoluene. However, information is available 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 a supplemental appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the main document to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in a supplement to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of a supplement 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 Heath Risk Technical Support Center.

DERIVATION OF SCREENING SUBCHRONIC INHALATION REFERENCE CONCENTRATION

Subchronic toxicity studies for inhalation *o*-chlorotoluene exposures are not available. However, there are two developmental studies (Edwards et al., 1982; 1983) that can be considered for deriving a screening subchronic p-RfC. Between the two developmental studies in rats and rabbits, respectively, the maternal effects observed in the rat study (Edwards et al., 1982) were the most sensitive effects in response to *o*-chlorotoluene via inhalation. Therefore, the rat study by Edwards et al. (1982) is chosen as the principal study. The critical effects were slight ataxia (dose-dependent effect), decreased body-weight gains and food comsumption, and increased water consumption at the LOAEL of 750 mg/m^3. The NOAEL was 250 mg/m^3.

The screening subchronic p-RfC is based on the NOAEL of 250 mg/m^3 (adjusted for HEC) in female dams exposed to *o*-chlorotoluene for 14 days in a rat developmental study (Edwards et al., 1982). Because *o*-chlorotoluene is fairly insoluble (slightly soluble in water), may be rapidly reversibly reactive in the surface-liquid/tissue of the respiratory tract, and can cause both respiratory and systemic toxicity, it is considered to be a Category 2 gas. Furthermore, exposure to *o*-chlorotoluene via inhalation caused extrarespiratory effects (e.g., ataxia, etc.); therefore, HECs were calculated using the Category 3 equation (the Category 3 equation is used for Category 2 gases causing extrarespiratory effects; U.S. EPA, 1994). The concentration adjustment data for the maternal effects in the Edwards et al. (1982) study based on the critical effects of ataxia, decreased body-weight gain and food consumption, and increased water consumption are presented in Table A.1. Similarly, the concentration adjustment data for the maternal effects in the Edwards et al. (1983) study are presented in Table A.2.

Table A.1. Concentration-Adjustment Data for *o*-Chlorotoluene (With Concentrations Expressed in Terms of HEC for Systemic Effects) in Female Rats Exposed by Inhalation for 14 Days[a]

Conc (mg/L)	$Conc_{ADJ}$ (mg/m^3)[b]	$Conc_{HEC}$ (mg/m^3)[c]
0	0	0
1	250	250
3	750	750
9	2250	2250

[a]Edwards et al. (1982)
[b]$Conc_{[ADJ]}$ = Conc × 6 ÷ 24 h × 7 ÷ 7 d
[c]$Conc_{[HEC]}$ = $Conc_{[ADJ]}$ × Cat. 3 Regional Gas Deposition Ratio (RGDR)

1) Exposure concentration adjustment for continuous exposure

$\mathbf{Conc_{ADJ}}$ = **Conc × (hours exposed ÷ 24 hours) × (days exposed ÷ 7 days)**
= 1 mg/L × (6 hours ÷ 24 hours) × (7 days ÷ 7 days)
= 0.25 mg/L
= 0.25 mg/dm^3 × 1000 dm^3/m^3
= **250 mg/m^3**

2) HEC conversion

$\mathbf{Conc_{HEC}}$ = **$Conc_{ADJ}$ × Category 3 RGDR[1]**
= $Conc_{ADJ} \times (H_{b/g})_A \div (H_{b/g})_H$
= 250 × 1
= **250 mg/m^3**

Table A.2. Concentration-Adjustment Data for *o*-Chlorotoluene (With Concentrations Expressed in Terms of HEC for Systemic Effects) in Female Rabbits Exposed by Inhalation for 23 Days[a]

Conc (mg/L)	$Conc_{ADJ}$ (mg/m^3)[b]	$Conc_{HEC}$ (mg/m^3)[c]
0	0	0
1.5	375	375
4	1000	1000
10	2500	2500

[a]Edwards et al. (1983)
[b]$Conc_{[ADJ]}$ = Conc × 6 ÷ 24 h × 7 ÷ 7 d
[c]$Conc_{[HEC]}$ = $Conc_{[ADJ]}$ × Cat. 3 RGDR

[1]RGDR for Category 3 gas of 1.0 is used for the ratio of $(H_{b/g})_A/(H_{b/g})_H$ if $(H_{b/g})_A > (H_{b/g})_H$ or if these partition coefficient values are unknown.

The screening subchronic p-RfC for *o*-chlorotoluene based on the rat $NOAEL_{HEC}$, is derived as follows:

$$\begin{aligned} \textbf{Screening Subchronic p-RfC} &= NOAEL_{HEC} \div UF \\ &= 250\ mg/m^3 \div 300 \\ &= \textbf{0.8 mg/m}^{\mathbf{3}}\textbf{ or 8} \times \mathbf{10}^{\mathbf{-1}}\textbf{ mg/m}^{\mathbf{3}} \end{aligned}$$

Table A.3 summarizes the UFs for the screening subchronic p-RfC for *o*-chlorotoluene. Due to the short duration of developmental studies (14−23 days) and lack of longer-term studies to detect more sensitive respiratory or systemic effects, no screening chronic p-RfC is derived.

Table A.3. Uncertainty Factors for Screening Subchronic p-RfC for *o*-Chlorotoluene

UF	Value	Justification
UF_A	3	A UF_A of 3 is applied for animal to human extrapolation to account for the toxicodynamic portion of a UF_A because the toxicokinetic portion ($10^{0.5}$) has been addressed in dosimetric conversions.
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 to humans.
UF_D	10	A UF_D of 10 is selected because there are no two-generation reproduction studies and neurotoxicity studies, as there are indications of potential neurotoxicity (e.g., ataxia) that may be relevant for the database uncertainty factor.
UF_L	1	A UF_L of 1 is applied because the POD was developed using a NOAEL.
UF_S	1	A UF_S of 1 is applied because a short-term study was used as the principal study.
UF_C	300	

APPENDIX B. DATA TABLES

Table B.1. Body-weight Gains and Feed Efficiency in Harlan Rats Exposed to *o*-Chlorotoluene via Oral Gavage for 103−104 Days[a,b]

Parameter	Exposure Group (mg/kg-day)			
	0	20	80	320
Males (103 days)				
Body-weight Gains (g)	356.5	346.9	301.3[c] (↓15)	276.7[c] (↓22)
Feed Efficiency (%)	13.64	13.36	12.44	11.48
Average Absolute Body Weight (g)[d]	486.5	476.9	431.3 (↓11)	406.7 (↓16)
Females (104 days)				
Body-weight Gains (g)	172.9	181.1	174.9	151.1
Feed Efficiency (%)	7.90	8.39	8.66	7.57

[a]Gibson et al. (1974a). Data were obtained from Table 1 on page 11 of the study report.
[b]Means only, () = percent change compared to control.
[c]Significantly different from control, Dunnett's test.
[d]Original body weight for male rats was read off directly from Figure 1 on page 10 of the study report as 130 g (Week 0). The absolute weight was calculated by adding the body-weight gain to the original body weight at Week 0, e.g., 130 + 356.5 = 486.5 g.

Table B.2. Body-weight Gains in Dogs Exposed to *o*-Chlorotoluene via Capsule for 96−97 Days[a,b]

Body-weight Gains (g)	Exposure Group (mg/kg-day)			
	0	5	20	80
Males (97 days)	−175 ± 854	425 ± 888	400 ± 294	375 ± 171
Females (96 days)	500 ± 752	175 ± 655	725 ± 330	550 ± 645

[a]Gibson et al. (1974b). Data were obtained from Table 1 on page 11 of the study report.
[b]Means ± SD.

APPENDIX C. BMD MODELING OUTPUTS FOR o-CHLOROTOLUENE

There are no BMD modeling outputs for *o*-chlorotoluene.

APPENDIX D. REFERENCES

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