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Provisional Peer-Reviewed Toxicity Values for

p-Isopropyltoluene
(CASRN 99-87-6)

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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*-ISOPROPYLTOLUENE (CASRN 99-87-6)

BACKGROUND

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

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

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

DISCLAIMERS

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

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

QUESTIONS REGARDING PPRTVS

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

INTRODUCTION

p-Isopropyltoluene, also known as *p*-cymene**,** is a naturally occurring aromatic organic compound. It is classified as a hydrocarbon related to a monoterpene. Its structure consists of a benzene ring *para*-substituted with a methyl group and an isopropyl group (U.S. EPA, 2005a). The empirical formula for *p*-isopropyltoluene is $C_{10}H_{14}$ (see Figure 1). *p*-Isopropyltoluene occurs naturally in more than 200 foods such as butter, carrots, nutmeg, orange juice, oregano, raspberries, and lemon oil, and almost every spice (U.S. EPA, 2005a) and is a constituent of a number of essential oils, most commonly the oils of cumin and thyme. The consumption of *p*-isopropyltoluene is derived predominantly from its presence in traditional foods. It has been estimated that approximately 30,000 kg of *p*-isopropyltoluene is consumed annually as a natural component food (U.S. EPA, 2005a). *p*-Isopropyltoluene is also a component of solvents used as thinners for lacquers and varnishes (HSDB, 2000) and is used in the flavor and fragrance industry (U.S. EPA, 2005a). There are two less common geometric isomers of *p*-isopropyltoluene: *o*-isopropyltoluene, in which the alkyl groups are *ortho*-substituted, and *m*-isopropyltoluene, in which the alkyl groups are *meta*-substituted. *p*-Isopropyltoluene is the only natural isomer. A table of physicochemical properties is provided below (see Table 1).

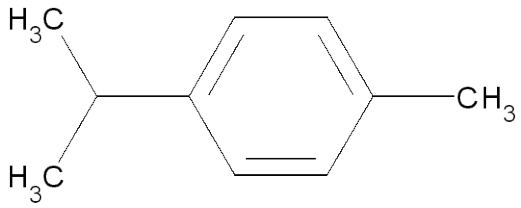

Figure 1. *p*-Isopropyltoluene Structure

Table 1. Physicochemical Properties Table for *p*-Isopropyltoluene (CASRN 99-87-6)[a]

Property (unit)	Value
Boiling point (ºC)	177
Melting point (ºC)	-68
Density (g/cm^3)	0.85
Vapor pressure (Pa at 25ºC)	200
pH (unitless)	Not available
Solubility in water (mg/L)	0.002
Relative vapor density (air = 1)	4.62
Molecular weight (g/mol)	134.2
Flash point (°C)	Not available
Octanol/water partition coefficient (unitless)	4.1

[a]Source: IPCS (1997); NLM (2011)

The IRIS database (U.S. EPA, 2011a) does not list a chronic oral reference dose (RfD), a chronic inhalation reference concentration (RfC), or a cancer assessment for *p*-isopropyltoluene. The HEAST (U.S. EPA, 2011b) does not list subchronic or chronic RfDs or RfCs for *p*-isopropyltoluene. The Drinking Water Standards and Health Advisories list (U.S. EPA, 2009) does not list any values for *p*-isopropyltoluene, and the Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1994) does not report any assessments for *p*-isopropyltoluene. The CalEPA (2008, 2009) has not derived toxicity values for exposure to *p*-isopropyltoluene.

No occupational exposure limits for *p*-isopropyltoluene have been derived by the American Conference of Governmental Industrial Hygienists (ACGIH, 2011), the National Institute of Occupational Safety and Health (NIOSH, 2010), or the Occupational Safety and Health Administration (OSHA, 2010). Russia and Sweden have assigned short-term occupational exposure limits of 10 mg/m^3 (skin) and 190 mg/m^3 (inhalation), respectively, for *p*-isopropyltoluene. Denmark and Sweden have assigned *p*-isopropyltoluene a time-weighted average threshold limit value (TWA-TLV) of 25 ppm (135 mg/m^3 for Denmark and 140 mg/m^3 for Sweden) for a normal 8-hour workday (RTECS, 2008).

The toxicity of *p*-isopropyltoluene has not been reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR, 2011). The World Health Organization (WHO, 2006) evaluated the safety of *p*-isopropyltoluene for use as a flavoring agent and stated that *p*-isopropyloluene did not present a safety concern at the current estimated intake (approximately 1100 µg of *p*-isopropyltoluene/person in Europe and 470 µg *p*-isopropyltoluene/person in the United States). This evaluation is based on the available toxicity and metabolism data of *p*-isopropyltoluene, which were reviewed by the WHO (2006). *p*-Isopropyltoluene is also recognized as "Generally Recognized as Safe" (GRAS) for its intended use in food by the United States Food and Drug Administration (Hall, 1960, as cited in U.S. EPA, 2005a).

The HEAST (U.S. EPA, 2011b) does not report any cancer values for *p*-isopropyltoluene. The International Agency for Research on Cancer (IARC, 2011) has not reviewed the carcinogenic potential of *p*-isopropyltoluene, and the compound is not included in the *11th Report on Carcinogens* (NTP, 2005). CalEPA (2008) has not prepared a quantitative estimate of the carcinogenic potential for *p*-isopropyltoluene.

Literature searches were conducted on sources published from 1900 through June 4, 2011, for studies relevant to the derivation of provisional toxicity values for *p*-isopropyltoluene, CAS No. 99-87-6. Searches were conducted using EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (U.S. 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 an overview of the relevant database for *p*-isopropyltoluene and includes all potentially relevant repeated short-term-, subchronic-, and chronic-duration studies. NOAELs, LOAELs, and BMDLs/BMCLs are provided in HED/HEC units for comparison except that oral noncancer values are not converted to HEDs and are identified in parentheses as (Adjusted) rather than HED/HECs. Principal studies are identified. Following the table, important aspects of all the studies are provided in the same order as the table. Reference is made to details provided in Table 2. The phrase, "statistical significance" used throughout the document, indicates a *p*-value of <0.05.

Table 2. Summary of Potentially Relevant Data for *p*-Isopropyltoluene (CASRN 99-87-6)

Notes[a]	Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b,c]	Reference (Comments)
Human								
				1. Oral (mg/kg-day)[b]				
	Subchronic			ND				
	Chronic			ND				
	Developmental			ND				
	Reproductive			ND				
	Carcinogenicity			ND				
				2. Inhalation (mg/m^3)[b]				
	Subchronic			ND				
	Chronic			ND				
	Developmental			ND				
	Reproductive			ND				
	Carcinogenicity			ND				
Animal								
				1. Oral (mg/kg-day)[b]				
	Subchronic			ND				
	Chronic			ND				
	Developmental			ND				
	Reproductive			ND				
	Carcinogenicity			ND				

Table 2. Summary of Potentially Relevant Data for *p*-Isopropyltoluene (CASRN 99-87-6)

Notes[a]	Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b,c]	Reference (Comments)
2. Inhalation (mg/m^3)[b]								
PR	Subchronic	7–12/0, Long-Evans Rat, 6 h/d, 5 d/wk, 4 wk, 8-wk recovery period	0, 49, or 245	No signs of overt toxicity were observed. Some statistically-significant changes in the synaptosomal fraction of homogenized brain: decreased yield of synaptosomal protein, and increased concentrations of synaptosomal noradrenaline (NA) and dopamine (DA) were reported.	245	Not run	NA	Lam et al. (1996)
	Chronic	ND						
	Developmental	ND						
	Reproductive	ND						
	Carcinogenic	ND						

[a]Notes: IRIS = Utilized by IRIS, date of last update; PS = Principal study, PR = Peer Reviewed, NPR = Not peer reviewed.
[b]Dosimetry: Exposure and NOAEL values are converted to human equivalent concentration (HEC in mg/m^3) units using the following equation:
HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × blood gas partition coefficient.
[c]NA = not applicable, ND = No data, NDr = Not determined, NR = Not reported, NR/Dr = Not reported by the study author, but determined from data.

HUMAN STUDIES

No studies investigating the effects of oral or inhalation exposure to *p*-isopropyltoluene in humans have been identified.

ANIMAL STUDIES

Oral Exposures

No studies investigating the health effects of short-term-, subchronic-, or chronic-duration, developmental, or reproductive oral exposure to *p*-isopropyltoluene in animals have been identified. Data on *p*-isopropyltoluene-induced toxicity in animals exposed orally are limited to a single acute toxicity study (Jenner et al., 1964, see ***"Other Data"*** section below).

Inhalation Exposures

The effects of inhalation exposure of animals to *p*-isopropyltoluene have been evaluated in one subchronic-duration study (Lam et al., 1996). Two acute inhalation studies are available for *p*-isopropyltoluene (MacDonald, 1962a,b, as cited in U.S. EPA, 2005a; see ***"Other Data"*** section below).

Subchronic-duration Studies

Lam et al., 1996

In a peer-reviewed study, Lam et al. (1996) studied the effects of inhalation exposure of rats to *p*-isopropyltoluene for 4 weeks. It was not stated whether the study was performed under Good Laboratory Practice standards, but the study appears scientifically sound. Groups of 7 to 12 Long-Evans male rats were exposed to 0, 50, or 250 ppm (v/v) (equivalent to HEC_{EXRESP} of 0, 49 or 245 mg/m^3) of *p*-isopropyltoluene (purity greater than 99%) for 6 hours/day, 5 days/week, for 4 weeks with an 8-week recovery period. The animals were housed (two per cage) in stainless-steel wire cages and were kept on a 12:12-hour light–dark cycle. Exposure to *p*-isopropyltoluene vapor took place during the dark cycle. During the study, body weight was determined weekly. This study was designed to specifically examine the neurotoxic potential of inhaled *p*-isopropyltoluene, with a focus on examining the following neurochemical parameters: global, regional, and subcellular rat brain concentrations of the CNS neurotransmitters noradrenaline (NA), dopamine (DA), and 5-hydroxytryptamine (5-HT) and their metabolism. Although the study authors stated that a variety of general toxicity parameters were also monitored, no information was given on general toxicity endpoints measured. After the 8-week recovery period, rats were sacrificed by decapitation, and the cerebellum was removed, weighed, and homogenized. The remainder of the brain was also weighed and homogenized. Synaptosomes were isolated from the rat forebrain and prepared using gradient centrifugation. The two homogenates and the synaptosomes were processed for neurotransmitter analyses (i.e., determination of NA, DA, and 5-HT), and an aliquot of each homogenate and synaptosomes was reserved for determination of enzyme activities (lactate dehydrogenase [LDH], acetylcholinesterase [AChE], and butylcholinesterase [BuChE]) and protein analysis. The study authors performed statistical analysis of the neurochemical data by analysis of variance (PROC ANOVA/GLM) followed by Dunnett's two-tailed *t*-test.

The study authors stated that no treatment-related deaths or abnormal clinical signs were observed, although no information about clinical observations was reported. The study authors reported that there were no effects on body weight or terminal weight of the brain, cerebellum, or whole brain in any treatment groups (data were not given in the study). The study authors also reported that there was no effect on regional enzyme activities, regional protein synthesis, or regional neurotransmitter concentrations. The relative yield and total amount of synaptosomal protein were significantly reduced at 49 and 245 mg/m^3, and according to the study authors, they were reduced in a concentration-related manner (see Table B.1). The relative activities of LDH, AChE, and BuChE (defined as U/mg synaptosomal protein where U = 1 uM min^{-1}) were significantly increased at 49 and 245 mg/m^3 (see Table B.2). Total activity of LDH, AChE, and BuChE (defined as U in the synaptosomal fraction per whole brain minus cerebellum) was unaffected (data were not reported in the study). In relation to total LDH activities, a cytoplasmatic marker enzyme, the relative synaptosomal choline esterase activities (AChE and BuChE), and synaptosomal concentrations of NA, DA, and 5-HT were unaffected by *p*-isopropyltoluene exposure (see Table B.3). Relative to synaptosomal protein, the NA and DA concentrations were significantly increased at 49 and 245 mg/m^3, whereas 5-HT was unaffected (see Table B.4). Conversely, the total amount of NA and DA in the synaptosomal fraction was unaffected by treatment, whereas, the total amount of 5-HT was statistically significantly decreased at 245 mg/m^3 (see Table B.5). According to the study authors, these findings suggest that noradrenergic and dopaminergic neurons may be vulnerable to *p*-isopropyltoluene exposure, giving rise to the hypothesis that the density and total number of synapses is reduced by *p*-isopropyltoluene, which is functionally compensated for by increased NA and DA neurotransmitter release from noradrenergic and dopaminergic neurons. This compensation could also be linked to a reduced potential for serotonergic activity. The study authors also addressed whether or not these changes "implicate toxicity" as follows: "No generally accepted parameter or test system is as yet established to document or predict central nervous system neurotoxicity from neurochemical, electrophysiological, pathological, or behavioral approaches. The present effects of *p*-isopropyltoluene following four weeks of exposure and an exposure free period of 8 weeks are long-lasting effects present at a time where *p*-isopropyltoluene is supposed to be eliminated from the body. It is not possible to conclude that these long-lasting effects are truly irreversible" (Lam et al., 1996, p. 229). The study authors stated that the pattern of changes induced by *p*-isopropyltoluene may be a reflection of "first stage organic affective syndrome," in which the pathophysiology is unclear, the time period is days to weeks without sequelae, and the clinical manifestations are depression, irritability, and loss of interest in daily activities.

In summary, inhalation exposure of rats for 4 weeks to *p*-isopropyltoluene resulted in long-lasting changes in synaptosomal neurochemistry (yield of synaptosomal protein was decreased, while synaptosomal NA and DA concentrations were increased) (Lam et al., 1996). These changes were reported to be unaccompanied by clinical signs of toxicity. The study authors considered that, with the present state of knowledge, it was impossible to conclude whether or not these changes in synaptosomal neurochemistry were indicative of any neurotoxicity. The study authors did not identify a NOAEL or LOAEL from the study. However, EPA (2005a) identified a NOAEL of 245 mg/m^3 from this study based on the lack of overt toxicity. EPA and the study authors, therefore, do not consider the changes to the neurochemical parameters to be an adverse treatment-related effect.

Chronic-duration Studies
No chronic-duration inhalation studies were identified for *p*-isopropyltoluene.

Developmental Studies
No developmental inhalation studies were identified for *p*-isopropyltoluene.

Reproductive Studies
No reproductive inhalation studies were identified for *p*-isopropyltoluene.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

A few studies on genotoxicity, short-term toxicity, metabolism, and toxicokinetics of *p*-isopropyltoluene are available. These are summarized in Tables 3 and 4.

Table 3. Summary of *p*-Isopropyltoluene Genotoxicity

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in prokaryotic organisms						
Reverse mutation	*Salmonella typhimurium* TA98, TA100	0.05–100 mL/plate	NT	–	None	Rockwell and Raw (1979)
	Salmonella typhimurium TA98, TA100	0.5 ml	NT	–	The urinary solutions isolated from rats given 0.5 mL of *p*-isopropyltoluene were tested in this part of the study	Rockwell and Raw (1979)
	Escherichia coli Sd-4-73	NR	NT	–	None	Szybalski (1958, as cited in U.S EPA, 2005a)
SOS repair induction	ND					
Genotoxicity studies in nonmammalian eukaryotic organisms						
Mutation	ND					
Recombination induction	ND					
Chromosomal abberation	ND					
Chromosomal malsegregation	ND					
Mitotic arrest	ND					

Table 3. Summary of *p*-Isopropyltoluene Genotoxicity

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in mammalian cells—in vitro						
Mutation	ND					
Chromosomal aberrations	ND					
Sister chromatid exchange (SCE)	ND					
DNA damage	ND					
DNA adducts	ND					
Genotoxicity studies in mammals—in vivo						
Chromosomal aberrations	ND					
Sister chromatid exchange (SCE)	ND					
DNA damage	ND					
DNA adducts	ND					
Mouse biochemical or visible specific locus test	ND					
Dominant lethal	ND					
Genotoxicity studies in subcellular systems						
DNA binding	ND					

[a]Lowest effective dose for positive results, highest dose tested for negative results.
[b]+ = positive, ± = equivocal or weakly positive, – = negative, T = cytotoxicity, ND = no data, NR = Not reported, NT = Not tested.

Table 4. Other Studies

Tests	Materials and Methods	Results	Conclusions	References
Short-term Studies	Groups of five young adult male and five female Osborne-Mendel rats were administered a single dose of *p*-isopropyltoluene by gavage. The doses tested were not provided in the study. Animals were observed for 12 days after dosing.	Depression (which was exhibited soon after dosing), coma, bloody lacrimation, diarrhea, and irritability and scrawny appearance were observed in the treated animals. Oral LD_{50} = 4750 mg/kg-day.	*p*-Isopropyltoluene has low acute oral toxicity.	Jenner et al. (1964)
Short-term Studies	Acute toxicity studies on *p*-isopropyltoluene following inhalation exposure. Unpublished studies were summarized in a secondary source (U.S. EPA, 2005a). Rats, guinea pigs, and mice were tested with a single dose of *p*-isopropyltoluene at an atmospheric concentration of 9.7 mg/L (5 hours).	Mortality was observed in mice, but not in rats and guinea pigs. Necropsy in mice revealed hyperemic lungs, mottled liver, and pale kidneys.	*p*-Isopropyltoluene has low acute inhalation toxicity.	MacDonald (1962a,b, as cited in U.S EPA, 2005a)
Short-term Studies	Acute toxicity studies on *p*-isopropyltoluene in rabbits following dermal exposure. Unpublished study that was summarized in a secondary source (U.S. EPA, 2005a).	Unpublished study where insufficient data were reported in the secondary source. Dermal median lethal dose >5000 mg/kg.	*p*-Isopropyltoluene has low acute dermal toxicity.	Moreno (1973, as cited in U.S. EPA, 2005a)
Toxicokinetic	A single male Japanese white rabbit was administered *p*-isopropyltoluene as a single oral dose (gavage) at 670 mg/kg. Urine was collected daily for 3 days after chemical administration and stored at 0–5°C until time of analysis.	Within 72 hours after administration, 20% of the administered dose was eliminated in the urine as neutral or acidic metabolites. The main metabolites identified in the urine were *p*-cymen-9-ol and *p*-cymen-8-ol (50% and 28%, respectively, of the neutral metabolites). In total, seven metabolites were identified.	Hydroxylation at the three possible aliphatic sites of *p*-isopropyltoluene contributes to the metabolite formation in this species. However the methyl group oxidation makes a minor contribution compared with that shown by hydroxylation of the isopropyl group.	Ishida et al. (1981)

Table 4. Other Studies

Tests	Materials and Methods	Results	Conclusions	References
Toxicokinetic	Male Wistar rats or Dunkin Hartley guinea pigs were administered *p*-isopropyltoluene orally or by inhalation at a dose of 100 mg/kg. Urine was collected for analysis.	Within 48 hours after administration, approximately 60–80% of the administered dose was excreted in the form of extractable metabolites in the urine. Similar urinary metabolites were identified in both species but in different quantities.	Oxidation of both the methyl and isopropyl groups of *p*-isopropyltoluene contributed to the metabolite formation in both species. No ring-hydroxylation of *p*-isopropyltoluene was detected in rats, but trace amounts of the ring hydroxylation metabolites were detected in the urine in guinea-pigs. Ring hydroxylation in guinea pigs only occurred *ortho* to the methyl group.	Walde et al. (1983)
Metabolism	Four rabbits (2F/2M) were given *p*-isopropyltoluene orally at a dose of 1000 mg/kg. The study was designed to identify the stereochemistry of *p*-isopropyltoluene metabolites. Urine was collected 3 days after dosing.	Different hydroxylated and carboxylated metabolites were recovered in the urine. Four were optically active, and three were optically inactive. The cytochrome p450 enzymes responsible for the oxidation of *p*-isopropyltoluene seem to have different regioselective properties.	The enzymatic oxidation of *p*-isopropyltoluene occurred stereoselectively.	Matsumoto et al. (1992)
Metabolism	A variety of species (rat, brushtail possum, greater glider and ringtail possum) were administered *p*-isopropyltoluene orally at doses equivalent to 50 and 200 mg/kg. Urine and feces were collected for two 24-hour periods.	64% of the administered dose was excreted in urine within 48 hours for all of the species. Differences were observed between the species in the urinary metabolic disposition of *p*-isopropyltoluene. The rat and brushtail possum excreted metabolites containing all degrees of oxidation (one to four oxygen atoms added) but predominantly a monooxygenated metabolite. The greater glider and ringtail possum excreted metabolites containing three or four oxygen atoms. A conjugation reaction with glycine, glucuronic acid, or glutathione was observed in the rat and the brushtail possum.	All these species exhibit a complex metabolic pattern with extensive oxidation of the methyl and isopropyl groups of *p*-isopropyltoluene.	Boyle et al. (1999)

Table 4. Other Studies

Tests	Materials and Methods	Results	Conclusions	References
Metabolism	*p*-isopropyltoluene (purity = 99%) incubated in vitro with human recombinant p450 enzymes followed by GC-MS analysis. Single human volunteer swallowed 35 tablets containing 1% tea tree oil containing *p*-isopropyltoluene among other monoterpenes (dose not further discussed).	Thymol (2-isopropyl-5-methylphenol), *p*-isopropylbenzyl alcohol, *p*,α,α-trimethylbenzyl alcohol, and *p*-isopropylbenzaldehyde were identified in the extract. Thymol was recovered from both blood and urine while other monoterpenes were detected in urine.	One predicted metabolite from in vitro study (thymol) was found in human blood and urine following oral dosing with tea tree oil containing *p*-isopropyltoluene.	Meesters et al. (2009)

Genotoxicity

The genotoxic effects of *p*-isopropyltoluene were assessed in vitro in bacterial reverse mutation assays. *p*-Isopropyltoluene gave negative results in the Ames mutagenicity test using *Salmonella typhimurium* strains TA98 and TA100 in the presence of metabolic activation systems (Rockwell and Raw, 1979). Also, *p*-isopropyltoluene produced no increase in the frequency of mutations when tested in Sd-4-73 *Escherichia coli* (Szybalski, 1958, as cited in U.S. EPA, 2005a).

In a study designed to investigate the mutagenicity of the urinary metabolites of a number of food additives, two Sprague-Dawley rats were given a single dose of 0.5 mL of *p*-isopropyltoluene (approximately 1706 mg/kg bw) by gavage, and their urine was collected for 24 hours. To assess the genotoxic potential of urinary metabolites, the urine was assayed directly or extracted with ether after dilution in a phosphate buffer and treatment with P-glucuronidase to hydrolyse glucuronide conjugates. Accordingly, three types of urine samples were tested in the Ames assay with *S. typhimurium* strains TA98 and TA100 with metabolic activation: 24-hour urine samples (500 µL), ether extracts of the urine, and aqueous fractions of the extracts. No evidence of mutagenicity was observed for isopropyltoluene in this study (Rockwell and Raw, 1979).

Short-term Studies

Several studies have evaluated the acute toxicity of *p*-isopropyltoluene in animals following oral, inhalation, or dermal exposure (Jenner et al., 1964; MacDonald, 1962a,b, as cited in U.S. EPA, 2005a; Moreno, 1973, as cited in U.S. EPA, 2005a)**.**

Jenner et al. (1964) evaluated the acute oral toxicity of *p*-isopropyltoluene in rats in a study designed to investigate the acute toxicity of food flavorings in animals. Groups of five young adult male and five female Osborne-Mendel rats were given single doses of *p*-isopropyltoluene (purity was not provided in the study) by gavage. The doses tested were not provided in the study. The animals were fasted for approximately 18 hours prior to treatment, and, after dosing, the animals were observed for mortality and clinical signs of toxicity. The observation was continued for 12 days until the animals appeared normal and showed weight gain. The main clinical signs observed in the rats included depression (which was exhibited soon after dosing), coma, bloody lacrimation, diarrhea, and irritability and scrawny appearance. The acute oral LD_{50} of *p*-isopropyltoluene in rats was identified as 4750 mg/kg-day, with confidence limits of 3720–6060 mg/kg-day, calculated by the method of Litchfield and Wilcoxon (1949).

Studies available on acute inhalation and dermal exposure to *p*-isopropyltoluene are unpublished studies (MacDonald, 1962a,b) that were summarized in a secondary source (U.S. EPA, 2005a). The acute inhalation toxicity (5 hours) of *p*-isopropyltoluene at an atmospheric concentration of 9.7 mg/L was studied in a number of laboratory animal species, including rats, guinea pigs (MacDonald, 1962a, as cited in U.S. EPA, 2005a), and mice (MacDonald, 1962b, as cited in U.S. EPA, 2005a). In rats and guinea pigs, no deaths were observed at this concentration and period of exposure, but *p*-isopropyltoluene was reported to be irritating to the animals (no further details were reported as to the type of irritation). Also, transient clonic convulsions were reported within 15 minutes in rats and 90 minutes in guinea pigs. These effects were fully reversible by the following morning. In mice, similar effects as those observed in rats and guinea pigs were reported; however, mortality was observed (two

mice died during the exposure period, and a third mouse died during the night after the exposure). Gross necropsy in mice revealed hyperemic lungs, mottled liver, and pale kidneys. The inhalation LC_{50} values for *p*-isopropyltoluene were not identified in the secondary source.

Moreno (1973, as cited in U.S. EPA, 2005a) reported a dermal median lethal dose for *p*-isopropyltoluene of >5,000 mg/kg-bw in rabbits (additional details regarding this study are not available).

Toxicokinetics

Studies in animals (rats, rabbits, guinea pigs, and marsupials [possum and greater glider]) have shown that *p*-isopropyltoluene is well absorbed from the gastrointestinal tract, widely distributed in the body, metabolized, and excreted mainly in the urine (Ishida et al., 1981; Walde et al., 1983; Matsumoto et al., 1992; Boyle et al., 1999). Walde et al. (1983) administered a single dose of 100 mg/kg to rats and guinea pigs by either oral (gavage) or inhalation exposure; the equivalent dose in mg/m^3 administered by inhalation was not provided in the study), 60–80% of the administered dose was excreted as metabolites in the urine within 48–72 hours of dosing. Eighteen urinary metabolites were identified. Most of the remaining dose was either excreted via the feces or as unextractable metabolites in the urine (Walde et al., 1983). Ishida et al. (1981) administered *p*-isopropyltoluene (670 mg/kg) via gavage to one male rabbit and identified seven metabolites. Matsumoto et al. (1992) also identified seven metabolites after oral administration of *p*-isopropyltoluene (10 g) in rabbits. In a study in marsupials (possum and greater glider) and rats, *p*-isopropyltoluene (0.37 and 1.49 mmol/kg; equivalent to 50 and 200 mg/kg) was administered orally to the animals (Boyle et al., 1999), with nine metabolites identified in rats, eight in brushtail possum, four in ringtail possum, and three in greater glider (all in the urine). Recovery of the metabolites in the urine ranged from 52–74% of the administered dose. No metabolites were identified in the feces.

In an in vitro metabolism study, Meesters et al. (2009) incubated *p*-isopropyltoluene with human recombinant p450 enzymes and identified the following products: thymol (2-isopropyl-5-methylphenol), *p*-isopropylbenzyl alcohol, *p*,α,α-trimethylbenzyl alcohol, and *p*-isopropylbenzaldehyde. In the same study (Meesters et al., 2009), only thymol was recovered from the blood and urine of a single human subject orally dosed with *p*-isopropyltoluene. The results of the in vivo metabolism studies demonstrated that *p*-isopropyltoluene undergoes extensive oxidation of the methyl substituent and isopropyl side-chain to yield polar oxygenated metabolites (see Figure 2). The main metabolites include monohydric alcohols, diols, mono- and dicarboxylic acids, and hydroxyacids. No ring-hydroxylation was identified. These metabolites are either excreted unchanged in the urine or undergo conjugation with glucuronic acid and/or glycine, followed by excretion in the urine.

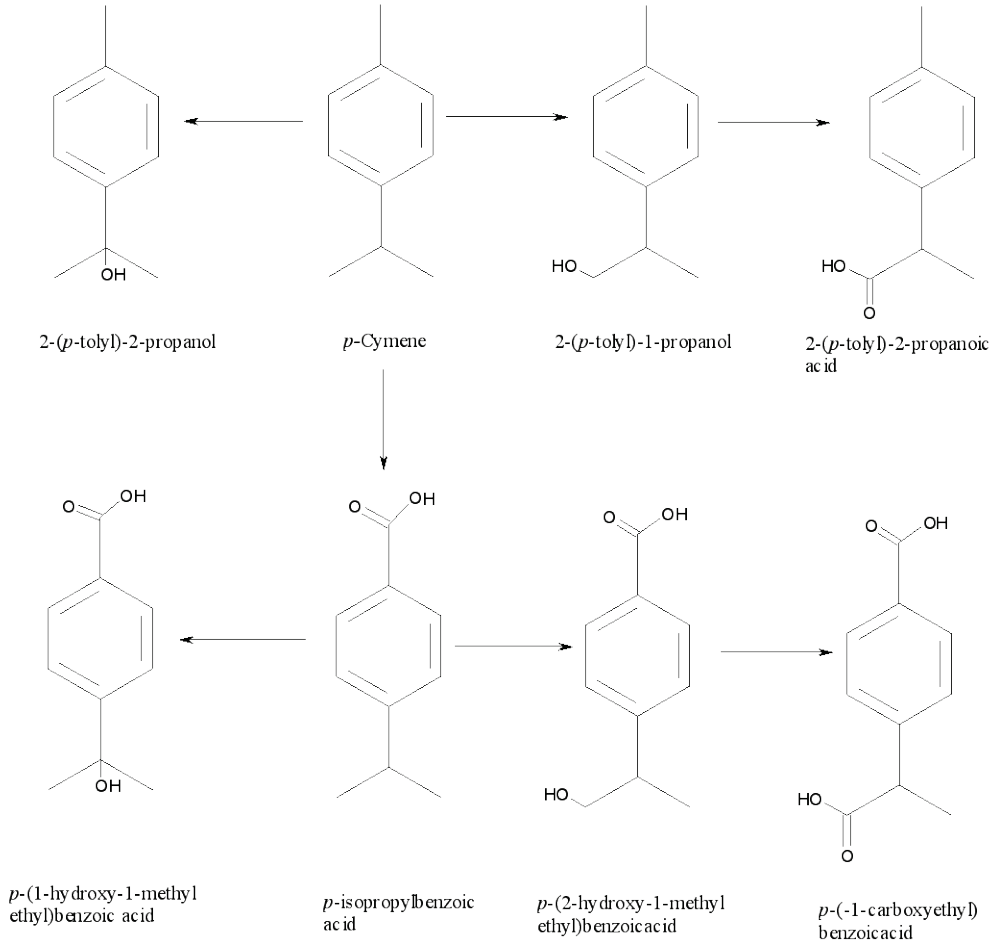

Figure 2. *p*-Isopropyltoluene Metabolism

DERIVATION OF PROVISIONAL VALUES

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

Table 5. Summary of Noncancer Reference Values for *p*-Isopropyltoluene (CASRN 99-87-6)

Toxicity Type (units)	Species/Sex	Critical Effect	*p*-Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic *p*-RfD (mg/kg-day)	None	None	None	None	None	None	None
Chronic *p*-RfD (mg/kg-day)	None	None	None	None	None	None	None
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

Table 6. Summary of Cancer Reference Values for *p*-Isopropyltoluene (CASRN 99-87-6)

Toxicity Value	Reference Value	Tumor Type or Precursor Effect	Species/Sex	Principal Study
p-OSF	None	None	None	None
p-IUR	None	None	None	None

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

A subchronic p-RfD was not derived for *p*-isopropyltoluene due to inadequate data.

Derivation of Chronic Provisional RfD (Chronic p-RfD)

A chronic p-RfD was not derived for *p*-isopropyltoluene due to inadequate data.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic Provisional RfC (Subchronic p-RfC)

There is limited information on the inhalation toxicity of *p*-isopropyltoluene in humans and animals. Only one short-term inhalation study was identified (Lam et al., 1996). In this study, rats were exposed to *p*-isopropyltoluene for 4 weeks. Therefore, this is the only study that can be considered as the principal study for derivation of the subchronic p-RfC.

Although this study is presented in a peer-reviewed journal and is defined by the EPA (2005a) as an acceptable and well-documented publication that meets basic scientific principles, it is considered inadequate with respect to the examination of potential toxicity endpoints. This study focused on only a few neurochemical parameters: global, regional, and subcellular rat brain concentrations of the CNS neurotransmitters NA, DA, and 5-HT and their metabolism. These parameters provide supportive evidence for neurotoxicity, but, without additional information, these parameters cannot be used to detect or assess neurotoxicity. This study lacks the examination of other toxicity endpoints, which are needed to fully assess the toxicity of *p*-isopropyltoluene. The study authors stated that there was no difference in body weight between the groups of animals during the study, but no data were provided on this endpoint. In addition, the study authors reported that there were no clinical signs of overt toxicity, but no additional information was provided on the endpoints examined to support this statement. In summary, this study is considered of limited usefulness for two reasons: (1) it is not known if toxic levels of *p*-isopropyltoluene were achieved based on the limited number of endpoints for which data were presented and (2) there is no scientific basis established for interpreting the biological significance of the neurochemical effects induced by *p*-isopropyltoluene. The only changes observed in rats exposed to inhaled *p*-isopropyltoluene for 4 weeks were a decrease in the synaptosomal protein yield and an increase in synaptosomal NA and DA concentrations at both exposure levels. The study author stated that these effects were not accompanied with clinical signs of overt toxicity, and they were unable to predict if these effects are indicative of toxic effects on CNS functioning. There are a great many uncertainties involved in interpreting the results from this study, and, therefore, the derivation of a subchronic p-RfC for *p*-isopropyltoluene is not recommended due to the inability to identify the target organ and critical effect from this study.

Derivation of Chronic Provisional RfC (Chronic p-RfC)

Chronic-duration toxicity studies for inhaled *p*-isopropyltoluene are not available. Derivation of a chronic p-RfC based on Lam et al. (1996) is not recommended due to the study limitations described above.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTION

The EPA has not assigned a carcinogenicity classification to *p*-isopropyltoluene under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005b). In accordance with these

guidelines, data are inadequate for an assessment of the human carcinogenic potential of *p*-isopropyltoluene (see Table 5). This WOE determination is based on the fact that no adequate data, such as reliable human epidemiological studies or well-conducted long-term animal studies, are available to perform a carcinogenicity assessment for *p*-isopropyltoluene.

There is some evidence that suggests that *p*-isopropyltoluene is unlikely to be a human carcinogen. *p*-Isopropyltoluene is a naturally occurring component of food that has been used as a food additive for many years. This use has been reviewed by the FDA, and *p*-isopropyltoluene was granted GRAS status (Hall, 1960, as cited in U.S. EPA, 2005a). Moreover, in a review of the safety of *p*-isopropyltoluene for use as a flavoring agent performed by the WHO (2006), it was concluded that *p*-isopropyltoluene did not present a safety concern at the current estimated intake (approximately 1100 µg of *p*-isopropyltoluene/person in Europe and 470 µg *p*-isopropyltoluene/person in the United States). In addition, *p*-isopropyltoluene does not appear to be metabolized to any highly reactive chemical species. *p*-Isopropyltoluene appears to be analogous to cumene in terms of its metabolism, and cumene was classified as a carcinogen category D ("*Not Classifiable as to Human Carcinogenicity"*), indicating inadequate or no human or animal data, according to the 1986 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986).

Table 7 identifies the cancer WOE descriptor for *p*-isopropyltoluene.

Table 7. Cancer WOE Descriptor for *p*-Isopropyltoluene

Possible WOE Descriptor	Designation	Route of Entry (Oral, Inhalation, or Both)	Comments
"Carcinogenic to Humans"	N/A	N/A	
"Likely to Be Carcinogenic to Humans"	N/A	N/A	
"Suggestive Evidence of Carcinogenic Potential"	N/A	N/A	
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**N/A**	**No adequate information available to assess the carcinogenic potential by the inhalation or oral routes of exposure.**
"Not Likely to Be Carcinogenic to Humans"	N/A	N/A	

MODE-OF-ACTION (MOA) DISCUSSION

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

There are no studies available that examine the carcinogenic activity of *p*-isopropyltoluene. However, the metabolic pathways of this compound have not been shown to involve any suspect reactive species. Also, based on in vitro bacterial assays, there is some evidence that suggests that p-isopropyltoluene is not genotoxic, and, therefore, it is unlikely that the genotoxic mode-of-action would be applicable for *p*-isopropyltoluene.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

No p-OSF can be derived due to a lack of carcinogenicity data.

Derivation of Provisional Inhalation Unit Risk (p-IUR)

No p-IUR can be derived due to a lack of carcinogenicity data.

APPENDIX A. PROVISIONAL SCREENING VALUES

Appendix A is not applicable.

APPENDIX B. DATA TABLES

Table B.1. Yield of Protein in the Synaptosomal Fraction of the Whole Brain Minus Cerebellum in Rats[a,b]

	0 mg/m^3	49 mg/m^3	245 mg/m^3
Relative yield[c]	16.4 ± 3.1 (7)	9.20 ± 2.11* (11)	8.62 ± 1.71* (12)
Total amount[c]	29.1 ± 5.8 (7)	16.4 ± 3.6* (11)	15.1 ± 3.0* (12)

[a]Lam et al. (1996).
[b]Results are mean ± 1 standard deviation, with number of rats in parentheses.
[c]Synaptosomal protein (mg)/whole brain-cerebellum (g).
*p < 0.05 between values from control and exposed rats .

Table B.2. Relative Enzyme Activities in the Synaptosomal Fraction of Whole Brain-Cerebellum in Rats[a,b]

	0 mg/m^3	49 mg/m^3	245 mg/m^3
LDH[c]	2.70 ± 0.40 (7)	4.87 ± 0.87* (11)	5.33 ± 0.61* (12)
AChE[c]	159 ± 30 (7)	291 ± 66* (11)	288 ± 52* (12)
BuChE[c]	209 ± 36 (7)	386 ± 93* (11)	358 ± 74* (12)

[a]Lam et al. (1996).
[b]Results are mean ± 1 standard deviation, with number of rats in parentheses.
[c]mU/mg synaptosomal protein.

*p < 0.05 between values from control and exposed rats.

Table B.3. Relative Concentration of Noradrenaline, Dopamine, and 5-Hydroxytryptamine and of Esterase Activities in the Synaptosomal Fraction of Whole Brain-Cerebellum in Rats[a,b]

	0 mg/m^3	49 mg/m^3	245 mg/m^3
AChE/LDH[c]	58.9 ± 6.0 (7)	59.6 ± 6.1 (11)	54.5 ± 10.3 (12)
BuChE/LDH[c]	77.5 ± 8.3 (7)	78.9 ± 9.1 (11)	67.8 ± 13.8 (12)
NA/LDH[d]	6.86 ± 0.75 (7)	7.07 ± 0.85 (11)	5.89 ± 1.09 (12)
DA/LDH [d]	7.31 ± 1.18 (7)	7.79 ± 0.82 (11)	6.93 ± 1.09 (12)
5-HT/LDH[d]	3.39 ± 0.91 (7)	2.55 ± 0.69 (11)	2.46 ± 1.05 (12)

[a]Lam et al. (1996).
[b]Results are mean ± 1 standard deviation, with number of rats in parentheses.
[c]Esterase Activity (mU)/LDH Activity (U).
[d]pmol/U LDH.

Table B.4. Relative Concentration of Noradrenaline, Dopamine, and 5-Hydroxytryptamine in the Synaptosomal Fraction of Whole Brain-Cerebellum in Rats[a,b]

	0 mg/m^3	49 mg/m^3	245 mg/m^3
NA[c]	18.4 ± 3.0 (7)	34.4 ± 7.2* (11)	31.3 ± 6.2* (12)
DA[c]	19.8 ± 4.6 (7)	38.0 ± 8.8* (11)	36.8 ± 6.5* (12)
5-HT[c]	8.98 ± 2.32 (7)	12.4 ± 4.2 (11)	13.1 ± 5.9 (12)

[a]Lam et al. (1996).
[b]Results are mean ± 1 standard deviation, with number of rats in parentheses.
[c]pmol/mg synaptosomal protein.

*$p < 0.05$ between values from control and exposed rats.

Table B.5. Total Amount of Noradrenaline, Dopamine, and 5-Hydroxytryptamine in the Synaptosomal Fraction of Whole Brain-Cerebellum in Rats[a,b]

	0 mg/m^3	49 mg/m^3	245 mg/m^3
NA[c]	522 ± 36 (7)	544 ± 82 (11)	461 ± 75 (12)
DA[c]	553 ± 27 (7)	600 ± 86 (11)	541 ± 62 (12)
5-HT[c]	255 ± 53 (7)	194 ± 44 (11)	189 ± 63* (12)

[a]Lam et al. (1996).
[b]Results are mean ± 1 standard deviation, with number of rats in parentheses.
[c]pmol/whole brain-cerebellum.

*$p < 0.05$ between values from control and exposed rats.

APPENDIX C. BMD OUTPUTS

Appendix C is not applicable.

APPENDIX D. REFERENCES

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