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Provisional Peer-Reviewed Toxicity Values for

tert-Butylbenzene
(CASRN 98-06-6)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS

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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR *tert*-BUTYLBENZENE (CASRN 98-06-6)

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 (http://www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

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

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

QUESTIONS REGARDING PPRTVs

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

INTRODUCTION

tert-Butylbenzene—sometimes referred to as (1,1-dimethylethyl)benzene, 2-methyl-2-phenylpropane, or dimethylethylbenzene—is a colorless liquid that is used primarily as a solvent in the synthetic organic chemistry industry and as a polymer-linking agent (HSDB, 2005a). The empirical formula for *tert*-butylbenzene is $C_{10}H_{14}$ (see Figure 1). A table of physicochemical properties is provided in Table 1.

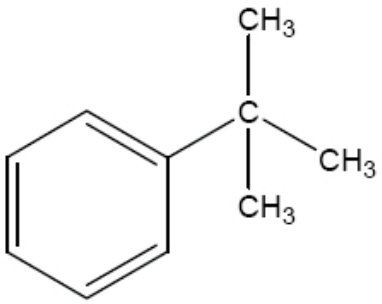


Figure 1. *tert*-Butylbenzene Structure

Table 1. Physicochemical Properties Table for *tert*-Butylbenzene (CASRN 98-06-6)

Property (unit)	Value
Boiling point (ºC)	169.1[a]
Melting point (ºC)	−57.8[a]
Density (g/cm^3)	0.8669[b]
Vapor pressure (mm Hg a at 25ºC)	1.75[a]
pH (unitless)	NA
Solubility in water (mg/L at 25ºC)	29.5[a]
Relative vapor density (air = 1)	4.62[b]
Molecular weight (g/mol)	134.22[a]
Flash point (°C)	52[b]
Octanol/water partition coefficient (unitless)	4.11[a]

[a]ChemIDplus (2010).
[b]HSDB (2005a).

No RfD, RfC, or cancer assessment for *tert*-butylbenzene is included in the IRIS database (U.S. EPA, 2010a) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2006). No RfD or RfC values are reported in the Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 2003). However, U.S. EPA (1997a) has derived a provisional chronic RfD of 1×10^{-2} mg/kg-day for *tert*-butylbenzene using cumene (isopropylbenzene) as a structural analog. The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1994) does not include any health-related documents for *tert*-butylbenzene. The potential carcinogenicity of the chemical has also not been assessed due to lack of pertinent data. The toxicity of *tert*-butylbenzene has not been reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR, 2010) or the World Health Organization (WHO, 2010). The California Environmental Protection Agency (CalEPA, 2008) has not derived toxicity values for exposure to *tert*-butylbenzene but has recommended an action level of 260 µg/L for *tert*-butylbenzene in drinking water (CalEPA, 2000). This derivation was based on a subchronic-duration rat LOAEL of 110 mg/kg-day for isopropylbenzene (similar to the structural analog approach taken by EPA [1997a], and by incorporating uncertainty factors for interspecies extrapolation, subchronic to chronic extrapolation, human variability, and database deficiencies). No occupational exposure limits for *tert*-butylbenzene have been derived by the American Conference of Governmental Industrial Hygienists (ACGIH, 2010), the National Institute of Occupational Safety and Health (NIOSH, 2010), or the U.S. Occupational Safety and Health Administration (OSHA, 2006).

The HEAST (U.S. EPA, 2003) does not report a cancer oral slope factor or inhalation unit risk value for *tert*-butylbenzene. The International Agency for Research on Cancer (IARC, 2000) has not reviewed the carcinogenic potential of *tert*-butylbenzene. *tert*-Butylbenzene is not included in the *12th Report on Carcinogens* (NTP, 2011). CalEPA (2008) has not derived a quantitative estimate of carcinogenic potential for *tert*-butylbenzene.

Literature searches were conducted on sources published from 1900 through November 2011 for studies relevant to the derivation of provisional toxicity values for *tert*-butylbenzene, CAS No. 98-06-6. 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 (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI, and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); World Health Organization; and Worldwide Science. The following databases outside of HERO were searched for health information: ACGIH, ATSDR, CalEPA, EPA IRIS, EPA HEAST, EPA HEEP, EPA OW, EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

Due to the limited toxicity data on *tert*-butylbenzene, derivation of provisional toxicity values is not possible for this chemical. As a result, a surrogate approach has been applied to derive screening toxicity values only (see Appendix A for details). Because the IRIS reassessment of isopropylbenzene (cumene; CASRN 98-82-8) will likely use newer noncancer inhalation studies in the consideration for selecting a principal study (last IRIS revision date: August 1997), toxicity data on noncancer inhalation exposures to isopropylbenzene (cumene) as the surrogate for *tert*-butylbenzene are not presented in this document. A PPRTV document on the noncancer effects of inhalation exposure to *tert*-butylbenzene could be conducted upon the completion of the isopropylbenzene (cumene) reassessment.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides information for all of the potentially relevant studies. Entries for the principal studies are bolded.

Table 2. Summary of Potentially Relevant Data for *tert*-Butylbenzene (CASRN 98-06-6)

Category	Number of Male/Female, Species, Study Type, Study Duration	Dosimetry	Critical Effects	NOAEL	BMDL/ BMCL	LOAEL[a]	Reference (Comments)
Human							
Oral (mg/kg-day)[a]							
None							
Animal							
Oral (mg/kg-day)[a]							
Acute	10/0, ChR-CD rat, gavage, single dose, observed for 14 day	3000, 3400, or 3800 mg/kg	LD_{50} value was 3503 mg/kg (95% CI: 3308−3748 mg/kg); mortality and body-weight decrease were dose-dependent and observed at all dose levels. Treatment-related effects included the following: rapid and labored respiration, salivation, prostration, lacrimation, stained nose and mouth, diarrhea, chromodacryorrhea, a stained and wet perineal area, weakness, alopecia on the abdomen, stained eyes, stained abdominal area, lethargy, and weight loss; characterized as "slightly toxic."	None	None	None	Haskell Laboratory (1978)
Acute	5/5, rat (strain not specified), method of oral administration not specified, observed for 14 day	1000, 2000, 3000, 4000, or 5000 mg/kg	LD_{50} value for male rats was 3045.4 mg/kg; LD_{50} value for females was 4079.2 mg/kg; combined male and female LD_{50} value was 3517 mg/kg; no deaths were observed at the two lower doses, but mortality increased beginning at the 3000-mg/kg dose with all males and four females dying at 5000 mg/kg; clinical signs included depression, urine stains, prostration, rough coat, tremors, salivation, hunched appearance, red stains on nose and eyes, soft feces, and ataxia; gross pathology details were not reported, but tabulated results indicated no gross changes at lower doses, but some changes were noted in various organs beginning at the 3000-mg/kg dose level.	None	None	None	Hazelton Laboratories (1982)
Acute	10, rat, sex not specified; surviving animals observed for 3 weeks after dosing	4.33 g/kg-bw[b]	Seven of 10 animals were dead; pulmonary injury likely cause of death; enlarged liver due to stress following biotransformation of *tert*-butylbenzene and other alkylbenzenes.	NA	NA	NA	Gerarde (1959, 1960)

Table 2. Summary of Potentially Relevant Data for *tert*-Butylbenzene (CASRN 98-06-6)

Category	Number of Male/Female, Species, Study Type, Study Duration	Dosimetry	Critical Effects	NOAEL	BMDL/ BMCL	LOAEL[a]	Reference (Comments)
Short-term	8/0, S-D rat, gastric intubation, 5 days/week, 2 weeks followed by 10-day observation	812[b]	No deaths, abnormal changes in body-weight gain, or evidence of ototoxicity observed; use of control group was not specified.	812	None	None	Gagnaire and Langlais (2005)
Subchronic	None						
Chronic	None						
Developmental	None						
Reproductive	None						
Carcinogenic	None						
Inhalation (mg/m^3)[b]							
Carcinogenic	None						

[a]Dosimetric conversion: mmol/kg-bw to mg/kg-bw = 8.47 mmol/kg-bw × 134.22 (molecular weight) mg/mmol = 1136.8434 (dose in mg)/kg-bw; final dose is 1136.8434 mg/kg-bw-day × 5 ÷ 7 = 812 mg/kg-bw.
[b]For *tert*-butylbenzene: 1.25 mL × 0.8669 (g/mL) ÷ 0.250 (kg-bw) = 4.33 g/kg.
NA = Not Available; S-D = Sprague-Dawley

HUMAN STUDIES

No information is available regarding oral or inhalation exposure of humans to *tert*-butylbenzene.

ANIMAL STUDIES

The effects of oral or inhalation exposure of animals to *tert*-butylbenzene have not been evaluated in any subchronic-duration, chronic-duration, developmental, reproductive, or carcinogenic studies.

Oral Exposures

The effects of oral exposure of animals to *tert*-butylbenzene have been evaluated in three acute single-dose studies (Haskell Laboratory, 1978; Gerarde, 1959, 1960, Hazelton Laboratories, 1982) and one short-term repeated-dose toxicity study (2 weeks) (Gagnaire and Langlais, 2005).

Acute and Short-term Studies

Haskell Laboratory (1978) conducted an unpublished, acute-duration, oral toxicity study of *tert*-butylbenzene in ChR-CD male rats. Single doses of 3000, 3400, or 3800 mg/kg of *tert*-butylbenzene in corn oil (purity not reported) were administered to 10 male rats per dose group by intragastric intubation. No controls were used. The methods and frequency of examination were not described in the study report, and no Good Laboratory Practice (GLP) certificate was included. Statistical analysis was not performed. Clinical signs of toxicity were only presented qualitatively. Mortality was reported as 1/10 in the low-dose group, 2/10 in the mid-dose group, and 9/10 in the high-dose group. Treatment-related effects observed in all dose groups were rapid and labored respiration, salivation, prostration, lacrimation, stained nose and mouth, diarrhea, chromodacryorrhea, a stained and wet perineal area, weakness, alopecia on the abdomen, stained eyes, stained abdominal area, lethargy, and weight loss. The authors calculated a median lethal dose (lethal dose, 50%; LD_{50}) value of 3503 mg/kg. Though statistical methods and evaluation were not presented, the study authors did provide upper and lower 95% confidence intervals of 3308 and 3748 mg/kg, respectively, for the calculated LD_{50}, and characterized *tert*-butylbenzene as "slightly toxic."

In an acute oral toxicity study conducted by Gerarde (1959, 1960), several alkylbenzenes including *tert*-butylbenzene (purity not specified) were administered as a single dose of 2.5 mL, 1:1 v/v in olive oil (hydrocarbon: olive oil) to fasted rats (n = 10; sex not specified; actual volume of *tert*-butylbenzene is 1.25 mL, or a converted dose of 4.33 g/kg; see Table 2 footnote d for dose conversion). The rats were observed for 3 weeks posttreatment for toxicological effects and sacrificed. Animals were weighed once weekly. After sacrifice, liver, spleen, and kidneys were weighed, and tissues were observed for the appearance of abnormal morphology. Out of the 10 treated rats, 7 animals died from exposure to *tert*-butylbenzene. Histopathological findings, though not specific to *tert*-butylbenzene, suggest that pulmonary injury was the likely cause of death in rats. Additionally, the study author reported a general trend of liver enlargement, which may have been due to stress following biotransformation of *tert*-butylbenzene and other alkylbenzenes. No other chemical specific toxicological effects were reported, and no data tables were presented. The study author did not provide an LD_{50} value for *tert*-butylbenzene. The dose of 4.33 g/kg is considered as a lethal dose low (LD_{lo}) for *tert*-butylbenzene.

In an unpublished acute toxicity study (submitted as part of Toxic Substances Control Act [TSCA] requirements), Hazelton Laboratories (1982) administered orally a single-dose of 1000-, 2000-, 3000-, 4000-, or 5000-mg/kg *tert*-butylbenzene (purity not reported), respectively, to 5 male and 5 female rats (strain not specified) per dose group (method of oral administration not specified). Following dosing, animals were examined for 14 days for mortality, body-weight changes, and clinical signs of toxicity. At study termination, animals were sacrificed and examined for gross pathology. Use of a control group was not specified in the report, and a statement of GLP compliance was not provided.

While the study is poorly reported, the tabulated results provided in the report indicate that no mortalities were noted in any of the animals at the two lowest administered doses (1000 and 2000 mg/kg). The study authors reported that three, four, and five male rats died in the 3000-, 4000-, and 5000-mg/kg dose groups, respectively, beginning on Observation Day 3. Mortality in females was noted in the 4000- and 5000-mg/kg dose groups with three and four animals dead in these dose groups, respectively, beginning on Observation Day 2. Clinical signs included depression, urine stains, prostration, rough coat, tremors, salivation, hunched appearance, red stains on the nose and eyes, soft feces, and ataxia. The study authors stated that all surviving rats that exhibited these clinical signs appeared normal from Days 2, 3, 4, or 5 until study termination on Day 14. Weight gain was observed in all rats that survived until study termination. Weight loss was observed in all animals that died except one (whether this was a male or female is not specified) that maintained the same weight. No notable gross pathological changes were observed in animals surviving until study termination. Pathological findings in dead animals included dark or bright red lungs; dark livers; light tan areas on the liver; reddish and yellowish fluid in the stomach and intestines; and distension of the stomach, intestines, and the urinary bladder. In addition to distension, the urinary bladder also exhibited red fluid and a foul odor. The study authors reported an LD_{50} of 3045.4 mg/kg (95% CI: 2542.8 to 3647.4 mg/kg) for male rats, an LD_{50} of 4079.2 mg/kg (95% CI: 3536.8 to 4705.1 mg/kg) for female rats, and a combined LD_{50} of 3517 mg/kg (95% CI: 3093.0 to 3999.2 mg/kg) for male and female rats.

Gagnaire and Langlais (2005) published a study investigating the effect of several aromatic solvents dissolved in olive oil administered via gastric intubation 5 days per week for 2 weeks on the ear function of groups of eight male Sprague-Dawley (S-D) rats. Observations continued for 10 days following treatment. Each dose administered was 8.47 mmol/kg-day, which is converted to 812 mg/kg-day for *tert*-butylbenzene (99% pure; see footnote c in Table 2 for dose conversion) after adjusting for administration days per week and the molecular weight. The use of a control group was not specified. Body weights, behavior, and general health were monitored daily during the treatment period and once weekly until study termination. Following the observation period, six randomly selected animals per group were sacrificed, and three left and right cochleas from these animals were processed and counted. The organs of Corti and basilar membranes were dissected and examined using light and scanning electron microscopy.

None of the animals treated with *tert*-butylbenzene died, and all animals appeared to exhibit normal weight gain. The study authors reported that *tert*-butylbenzene did not cause any ototoxicity in the treated animals. The relationship between the octanol/water partition coefficient and ototoxicity was also examined, and the study authors concluded that there was no correlation between these two parameters. A NOAEL of 812 mg/kg-day is identified for *tert*-butylbenzene in this study based on a lack of ototoxicity at this dose. The study's short-term

duration, lack of a control group, and lack of testing at higher doses at which effects may have occurred precludes its consideration for the derivation of an oral subchronic p-RfD for *tert*-butylbenzene. In addition, the study authors did not conduct a thorough toxicological evaluation of other organs to assess the possible toxicological potential of *tert*-butylbenzene at the tested dose.

Other Exposures

No studies of *tert*-butylbenzene toxicity by other exposure pathways were identified**.**

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Toxicokinetic	Male S-D rat, exposed to 100-ppm (549 mg/m^3)[a,b] *tert*-butylbenzene, 3 days, 12 hours/day.	Accumulated rapidly and reached steady-state conditions in blood, brain, liver, and kidneys; largest hydrocarbon concentrations found in the fat followed by kidneys, liver, brain, and blood; in general, higher concentrations of aromatic hydrocarbons found in blood compared to other hydrocarbons tested.	Metabolic rate of elimination for *tert*-butylbenzene comparatively high.	Zahlsen et al. (1992)
Metabolism	Animal species and strain not specified; doses not specified.	Metabolism of *tert*-butylbenzene and alkylbenzenes, in general, follow a metabolic pathway that involves oxidative changes either at beta, omega, or penultimate carbons on side-chain-forming alcohols or carboxylic acids; these alcohols and carboxylic acids subsequently conjugate with glucuronic acid or glycine and are excreted in urine.	Metabolism primarily occurs on side-chain via oxidative pathway followed by conjugation and excretion.	HSDB (2005a); Gerarde (1959, 1960)
Metabolism	Three rabbits (sex not specified) per dose group, exposed to 268 and 500 mg/kg.	*tert*-Butylbenzene was oxidized in rabbits mainly to 2,2,-dimethyl-2-phenylethanol (66−81% of the doses; averages from the two dose groups tested), which was then excreted as a glucuronide in urine. A minor metabolite, 1,1-dimethylphenylacetic acid, was detected as traces, and it could be excreted as a glycine conjugate in urine.	2,2-dimethyl-2-phenylethyl glucuronide "appears to be the major if not the only metabolite of tert butylbenzene in the rabbit.	Robinson and Williams (1955)
Tissue-specific toxicity	Animal species and strain not specified; doses not specified; acute study conducted by administering a single oral dose of 2.5-mL *tert*-butylbenzene in 1:1 v/v olive oil (1.25-mL *tert*-butylbenzene; 4.33 g/kg);[c] surviving animals were observed for 3 weeks post exposure.	Irritation in the local endothelial cells leading to changes in the capillary permeability; change in permeability may lead to increased diapedesis and petechial and gross hemorrhage and edema in surrounding tissues; effects also noted in kidneys, liver, spleen, bladder, thymus, brain, and spinal cord; accumulation of alkylbenzenes in nerve cells resulting in signs and symptoms of central nervous system depression such as sluggishness, stupor, coma, narcosis, and anesthesia. Seven out of 10 animals died following oral administration of *tert*-butylbenzene. Autopsy results indicated lung involvement with severity ranging from hyperemia to gross hemorrhage with pulmonary injury reported as cause of death.	Toxicity manifested in endothelial cells and central nervous system. Branched alkylbenzenes were reported to be more acutely toxic compared to the linear alkylbenzenes.	Gerarde (1959, 1960)
Cell signaling	Male rat (WKY/NHsd) alveolar macrophages, in vitro exposure, 25−400 µM *tert*-butylbenzene, ROS formation by DCF fluorescence and TNF-alpha release by ELISA.	No effects observed at concentration <400 µM. A 70% increase in 2,7-dichlorofluorescein observed following 400 µM. No effect noted on TNF-alpha.	Equivocal results. *tert*-Butylbenzene may have potential to cause ROS formation.	Aam et al. (2003)

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Carcinogenic potential (genotoxic and epigenetic)	Primary Syrian hamster embryo cells, in vitro exposure, transformation frequency following exposure alone and in combination with benzo(a)pyrene.	Morphological transformation of embryonic cells not observed following incubation with any of the 18 hydrocarbons. Further, no synergistic effects observed between benzo(a)pyrene and *tert*-butylbenzene.	*tert*-Butylbenzene negative in Syrian hamster embryo transformation assay.	Rivedal et al. (1992)

[a]mg/m^3 = ppm × molecular weight ÷ 24.45; molecular weight = 134.22; HEC conversion not presented because this is an acute-duration value.
[b]Not adjusted for continuous dosing.
[c]Dose conversion: g/kg = [mL dose × (g/mL) density] ÷ (kg body weight). For *tert*-butylbenzene: 1.25 mL × 0.8669 (g/ml)/0.250 (kg-bw) = 4.33 g/kg.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Toxicokinetics Studies

Zahlsen et al. (1992) investigated the toxicokinetic properties of several alkylbenzenes, alkanes, and naphthenes in rats. Four male S-D rats exposed to 100-ppm (549 mg/m^3; dose not adjusted for continuous exposure) *tert*-butylbenzene (purity > 99%) for 12 hours per day for 3 consecutive days exhibited the highest concentration of the chemical in fat followed by the kidneys, liver, brain, and blood on Day 1. The *tert*-butylbenzene concentration in fat showed a declining trend on Days 2 and 3 of chemical administration, with very little chemical remaining 12 hours after termination of exposure. In contrast, concentrations of *tert*-butylbenzene exhibited slight declines in the kidney, liver, brain, and blood on Day 2 of chemical administration, followed by a slight increase in concentrations on Day 3 of chemical administration. Concentrations in these organs were either very low or could not be detected following a 12-hour recovery period after exposure termination (see Table 3). These results may suggest that the metabolic rate of elimination is high for *tert*-butylbenzene. Gerarde (1959, 1960) corroborated absorption in the blood and stated that due to the high lipophilicity of alkylbenzenes, approximately 85% of the hydrocarbons in the blood is bound to the red blood cells.

Gerarde (1959, 1960) reported that alkylbenzenes tend to accumulate in tissues that have high lipid content. Distribution results for toluene indicated that the highest amount of the alkylbenzene was found in the adrenals followed by the cerebellum, bone marrow, brain, liver, blood, kidney, spleen, lung, thyroid, and the pituitary. Based on distribution of toluene, the author suggested that the "distribution and accumulation of other alkyl derivatives of benzene would have a similar pattern" (Gerarde, 1959, p. 34).

The metabolism of *tert*-butylbenzene and alkylbenzenes, in general, follow a metabolic pathway that involves oxidative changes either at the beta, omega, or penultimate carbons on the side-chain-forming alcohols or carboxylic acids (HSDB, 2005a; Gerarde, 1959, 1960). These alcohols and carboxylic acids subsequently conjugate with glucuronic acid or glycine and are excreted in the urine (Gerarde, 1959, 1960). Gerard also reported that "ring oxidation rarely occurs if an alkyl group is present" (Gerarde, 1959, p. 34). In a later report, Gerarde and Ahlstrom showed that ring hydroxylation increases with increasing length of the alkyl side chain of *n*-alkylbenzene, but they did not examine the biotransformation on branched alkylbenzenes (Gerarde and Ahlstrom, 1966). The mechanism of side-chain oxidation seems to facilitate detoxification and is the preferred pathway for alkylbenzenes, in general, which is exemplified when benzene is converted to methyl benzene (toluene). The addition of a methyl group to the benzene ring changes the metabolic pathway, which is reflected by the general metabolism of alkylbenzenes.

These biotransformations may take place in the liver microsomes and also other tissues including the brain, spinal cord, bone marrow, kidney, and adrenal glands. In summary, hydroxylation or carboxylation can occur at various methyl groups in linear and branched chains of alkylbenzenes followed by conjugation with glycine or glucuronic acid for excretion in urine. In addition, Gerarde and Ahlstrom (1966) stated that there could be a dual metabolic pathway of side-chain oxidation and ring hydroxylation, with the former preferred in rats.

Furthermore, Gerarde (1959, 1960) reported the excretion of several alkylbenzenes, stating that alkylbenzenes are either eliminated from the blood as unchanged hydrocarbons or as metabolites. Unchanged hydrocarbons may be exhaled through the lungs, with a small fraction excreted in the urine. Metabolites of alkylbenzenes are water soluble and are found in urine. In general, due to their low vapor pressure, alkylbenzenes are not eliminated rapidly from the blood as compared to benzene.

In an independent toxicokinetic study for *tert*-butylbenzene, Robinson and Williams (1955) specifically examined the metabolism of *tert*-butylbenzene in rabbits (3 rabbits per dose group; 268- and 500-mg/kg dose groups). They reported that the *tert*-butylbenzene was oxidized in rabbits mainly to 2,2,-dimethyl-2-phenylethanol (66−81% of the doses; averages from the two dose groups of 268 and 500 mg/kg), which was then excreted as a glucuronide in urine. A minor metabolite, 1,1-dimethylphenylacetic acid, was detected as traces, and it could be excreted as a glycine conjugate in urine. In addition, they stated that "ω-oxidation is the only possible reaction, and it is to be noted that this oxidation hardly goes beyond the primary alcohol stage" (Robison and Williams, 1955, p. 161). The study authors concluded that 2,2-dimethyl-2-phenylethyl glucuronide "appears to be the major if not the only metabolite of *tert*-butylbenzene in the rabbit" (Robison and Williams, 1955, p. 159).

Toxicity of Alkylbenzenes in Various Tissues

In addition to toxicokinetic data, Gerarde (1959, 1960) provided information regarding the effects of alkylbenzenes in various tissues following absorption. Gerarde (1959, 1960) reported that alkylbenzenes dissolved in blood cause local irritation of endothelial cells, resulting in changes in capillary permeability that may lead to increased diapedesis, petechial and gross hemorrhage, and edema in the surrounding tissues. Gerarde (1959, 1960) stated that these changes were seen frequently in lungs of animals that were treated with alkylbenzenes intragastrically, subcutaneously, or via intraperitoneal injection. Branched and unsaturated chain alkylbenzenes were reported to be more irritating than the corresponding unbranched and saturated alkylbenzene isomers. Secondary to the endothelial injury, other tissues in which effects were noted included the kidneys, liver, spleen, bladder, thymus, brain, and spinal cord.

Alkylbenzenes have a particular affinity to nerve tissues (Gerarde, 1959, 1960). The high lipid content of these tissues leads to accumulation of alkylbenzenes in nerve cells, resulting in signs and symptoms of central nervous system depression such as sluggishness, stupor, coma, narcosis, and anesthesia. The study author described the intensity and quality of these effects as dependent on the concentration or number of molecules of alkylbenzenes present in the cell at any given time. Gerarde (1959, 1960) also stated that the narcotic potency of alkylbenzenes is dependent on chain length, branching, and diversity of alkylation. Potency reportedly decreased with chain length, dropping off sharply at the four-carbon chain length and decreasing steadily from thereon as the carbon chain length decreases (i.e., central nervous system effects of toluene > ethylbenzene > propylbenzene > butylbenzene). Toluene and ethylbenzene were reported to be fast-acting narcotics, whereas *n*-propyl and *n*-butylbenzene were slow in manifesting central nervous system effects. The rate of initiation of central nervous system effects is related to the rate of absorption of these chemicals in the blood from the portal of entry and subsequent transfer to the brain. Because rate of absorption is dependent on water solubility, and water solubility decreases with increasing chain length and diversity in alkylation, the rate of absorption decreases accordingly. However, the duration of the central nervous system effects from exposure to alkylbenzenes increases with higher chain length and branching of the side

chain. As a result, isopropylbenzene and *n*-butylbenzene are long-acting central nervous system agents compared to toluene and ethylbenzene, which are short-acting nervous system agents. Gerarde (1959, 1960) stated that the long-lasting action of branched and higher chain length alkylbenzenes is most likely related to the excretion rate of these hydrocarbons from the cells in which they accumulate. Accumulation is dependent on how quickly alkylbenzenes are biotransformed in situ and in other tissues (e.g., liver, kidney) into water-soluble metabolites. Because the branched side-chain alkylbenzenes with the same number of carbon atoms are oxidized more slowly compared to the linear alkylbenzenes, the central nervous system effects of branched alkylbenzenes are longer lasting in contrast to the linear alkylbenzenes. The central nervous system effects of alkylbenzenes last as long as these hydrocarbons are present in the cells; thus, a large dose of these chemicals can produce profound narcosis and coma and may result in permanent effects in the central nervous system tissues, particularly in the brain.

Gerarde (1959, 1960) stated that branched alkylbenzenes such as isopropylbenzene, *tert*-butylbenzene, and *sec*-butylbenzene cause more irritation than the linear alkyl groups. Such irritation, as previously mentioned, might lead to hemorrhage in the brain and spinal cord, and the damage could be permanent. For hematopoietic effects, in contrast to exposure to benzene, Gerarde (1959, 1960) did not find any alkylbenzenes that cause leucopenia or injury to the blood-forming tissues.

In acute toxicity studies conducted by Gerarde (1959, 1960), groups of 10 fasting rats (sex and strain not specified) were administered a single oral dose (method of administration not specified) of 2.5 mL of *tert*-butylbenzene (purity not specified) 1:1 v/v in olive oil (1.25 mL of *tert*-butylbenzene) along with other alkylbenzenes. Following administration, three surviving rats were observed for a period of 3 weeks for signs of toxicity and abnormal activity. Animals were weighed once per week during the observation period and sacrificed at study termination. Kidneys, liver, and spleen weights were determined postmortem, and tissues were examined histopathologically for abnormal changes. A higher rate of mortality was observed in rats treated with branched alkylbenzenes (isopropylbenzene: 6/10; *sec*-butylbenzene: 8/10; *tert*-butylbenzene: 7/10) compared to linear alkylbenzenes (*n*-propylbenzene: 3/10; *n*-butylbenzene: 2/10; toluene: 3/10) with ethylbenzene (7/10) being the only exception among linear alkylbenzenes resulting in a higher mortality rate. Gerarde (1959, 1960) stated that necropsy results indicated that the lungs were one of the target organs, with the severity in lung injury ranging from hyperemia to gross hemorrhage. This lung injury was most likely the cause of death when gross hemorrhage was observed because the author stated that the principal cause of death was "chemical pneumonitis with pulmonary edema and hemorrhage." Additionally, vasodilation of the blood vessels of the gastrointestinal tract and general hyperemia were consistently noted in animals treated with alkylbenzenes. Hemorrhage in the tissues (lungs, thymus, adrenal, and bladder) was assumed to be as a result of increased capillary permeability due to irritation in the endothelial cells in contact with alkylbenzenes dissolved in blood.

Overall, Gerarde (1959, 1960) concluded that branched-chain mono-alkylbenzenes (isopropyl-, *sec*-, *tert*-butylbenzenes) are more toxic compared to the corresponding linear isomers (*n*-propylbenzene, *n*-butylbenzene) and dialkylbenzenes (di-isopropylbenzene, di-*tert*-butylbenzene). Liver enlargement was commonly observed in animals treated with various alkylbenzenes. Gerarde (1959, 1960) reported that this was probably due to exposure-induced stress on the liver that resulted from biotransformations intended to eliminate the chemicals. Animals dosed with branched-chain alkylbenzenes developed enlarged livers.

Additionally, the spleen was either normal or enlarged, but no thymus effects were noted. Gerarde (1959, 1960) stated that this was in contrast to effects observed in benzene-treated animals, where a marked involution of thymus and spleen was observed.

In conclusion, exposure to alkylbenzenes may cause various effects in various tissues. Based on the discussion presented above, it is also notable that the branched alkylbenzenes are more toxic in nature in comparison to their linear counterparts.

Genotoxicity Studies

HSDB (2005a) reports the results of an unpublished study (Shell Oil, 1980) that could not be located for this review. The excerpts of the study report conclude that *tert*-butylbenzene was negative for mutagenicity in the Ames test in five strains of *Salmonella typhimurium*, both in the presence and absence of metabolic activation; no information regarding the genotoxic effects of *sec*-butylbenzene was identified. *tert*-Butylbenzene was also negative in the mitotic gene-conversion assay, performed with and without metabolic activation. *tert*-Butylbenzene was also negative under all conditions tested in the chromosomal-aberration assay.

In Vitro Cell Signaling and Carcinogenic Potential Studies

Aam et al. (2003) investigated the effect of reactive oxygen species (ROS) production following exposure to one of several hydrocarbons, including 25−400-µM *tert*-butylbenzene, in rat alveolar macrophages. TNF-alpha release, as a proinflammatory marker and indicator of ROS, was also measured. While dose-related increases in ROS formation were observed, particularly following exposure to alicyclic hydrocarbons, results following exposure to *tert*-butylbenzene were equivocal. No concentration of *tert*-butylbenzene reportedly changed the release of TNF-alpha; however, 400-µM *tert*-butylbenzene increased 2,7-dichlorofluorescein formation, an indicator of ROS, by 70%, although the data were not included in the study report. While these results are not conclusive, they indicate that *tert*-butylbenzene may have the potential to cause ROS formation (see Table 3).

Rivedal et al. (1992) conducted a study screening for 18 hydrocarbons using the Syrian hamster embryo cell transformation assay. In doing so, they demonstrated a technique to detect potential genotoxic and epigenetic rodent carcinogens. The hydrocarbons were tested alone and in combination with benzo(a)pyrene to evaluate possible synergistic effects. None of the hydrocarbons promoted morphological cell transformation alone; however, a naphthene and two isoalkanes did enhance the effect of benzo(a)pyrene exposure (see Table 3). *tert*-Butylbenzene tested negative in all conditions of this assay.

DERIVATION OF PROVISIONAL VALUES

Table 4 presents a summary of noncancer screening oral provisional reference values (see Appendix A for details). Table 5 presents a summary of cancer values. IRIS values, if available, are included in the tables.

Table 4. Summary of Screening Oral Provisional Reference Values for *tert*-Butylbenzene (CASRN 98-06-6)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-day)[a]	Rat/Female	Increased kidney weight in female rats	1×10^{-1}	$NOAEL_{ADJ}$	110	1000	Wolf et al. (1956)
Screening chronic p-RfD (mg/kg-day)[a]	Rat/Female	Increased kidney weight in female rats	1×10^{-1}	$NOAEL_{ADJ}$	110	1000	Wolf et al. (1956)

[a]IRIS (U.S. EPA, 1997b); isopropylbenzene (cumene) used as surrogate.

Table 5. Summary of Cancer Risk Values for *tert*-Butylbenzene (CASRN 98-06-6)

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

DERIVATION OF ORAL REFERENCE DOSES

Feasibility of Deriving Subchronic and Chronic Provisional RfD (Subchronic and Chronic p-RfDs)

No chronic or subchronic toxicity data were identified for the derivation of an oral provisional RfD (p-RfD) for *tert*-butylbenzene. However, Appendix A of this document contains screening values (screening oral subchronic and chronic p-RfDs) using a surrogate (e.g., structural and metabolic) approach that may be of use under certain circumstances. Please see Appendix A for details regarding the screening values.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Table 6 identifies the cancer WOE descriptor for *tert*-butylbenzene (in bold).

Table 6. Cancer WOE Descriptor for *tert*-Butylbenzene			
Possible WOE Descriptor	**Designation**	**Route of Entry (Oral, Inhalation, or Both)**	**Comments**
"Carcinogenic to Humans"	N/A	N/A	No studies pertaining to the carcinogenicity of *tert*-butylbenzene in humans are available.
"Likely to be Carcinogenic to Humans"	N/A	N/A	No studies pertaining to the carcinogenicity of *tert*-butylbenzene in multiple species of animals are available.
"Suggestive Evidence of Carcinogenic Potential"	N/A	N/A	No data are available regarding the carcinogenic potential of *tert*-butylbenzene even in a single animal species.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**There is little or no pertinent information available to assess carcinogenic potential of *tert*-butylbenzene.**
"Not Likely to be Carcinogenic to Humans"	N/A	N/A	No data are available to suggest that *tert*-butylbenzene is not likely to be a carcinogen in humans following oral or inhalation exposure.

N/A = Not applicable

DERIVATION OF PROVISIONAL ORAL AND INHALATION CANCER VALUES

The lack of quantitative data on the carcinogenicity of *tert*-butylbenzene precludes the derivation of a quantitative estimate of risk for either oral (p-OSF) or inhalation (p-IUR) exposures.

APPENDIX A. PROVISIONAL SCREENING VALUES

DERIVATION OF SCREENING ORAL PROVISIONAL REFERENCE VALUES

For reasons noted in the main PPRTV document, it is not possible to derive provisional toxicity values for *tert*-butylbenzene. However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

Potential Principal Study

A NOAEL of 812 mg/kg-day (highest dose tested) was identified for *tert*-butylbenzene from the 2-week study by Gagnaire and Langlais (2005). However, the lack of ototoxicity in animals following exposure to *tert*-butylbenzene, the lack of a control group, and the lack of testing at higher doses that may have caused an effect precludes the use of this study for the derivation of an oral subchronic p-RfD for *tert*-butylbenzene. In addition, the study authors did not conduct a thorough toxicological evaluation of other organs to assess the possible toxicological potential of *tert*-butylbenzene at the tested dose.

ALTERNATIVE APPROACH—A SURROGATE APPROACH

Three types of potential surrogates (structural, metabolic, and toxicity-like) were identified to facilitate the final surrogate chemical selection. Details regarding searches and methods are presented in Wang et al. (2012). The surrogate approach may or may not be route-specific or applicable to multiple routes of exposure. In this document, it is limited to the oral noncancer effects only based on the available toxicity information. All information was considered together as part of the final WOE approach to select the most suitable surrogate both toxicologically and chemically.

Structural Similarity

Structural analogs or surrogates were first identified using ChemIDplus on the National Library of Medicine Web site (http://chem.sis.nlm.nih.gov/ChemIDplus/) and then the U.S. EPA DSSTox (www.epa.gov/dsstox) databases. Seventy-eight possible analogs (structural surrogates) were identified using ChemIDplus (2010) with the similarity match set to ≥50%, and 24 possible analogs were identified using DSSTox with the similarity match set to ≥70%. ChemIDplus did not identify any structural surrogate with repeated dose data within the alkylbenzene chemical class. To further filter these 24 possible analogs from DSSTox, only hits identified in the IRIS data set (IRISTR_1b) in DSSTox were first retained. Two potential structural surrogates with repeated dose data were found—isopropylbenzene (C_9H_{12}) and ethylbenzene (C_8H_{10})—as structurally similar to *tert*-butylbenzene with a similarity score of 91.3 and 95.4%, respectively (see Table C.1). One interesting hit from DSSTox was identified at 75% similarity to *tert*-butylbenzene: *sec*-butylbenzene. However, *sec*-butylbenzene does not

have repeated dose information at the time of assessment (a similar surrogate approach could be performed for *sec*-butylbenzene). Because of the limited number of hits (n = 2), similarity search threshold was reset to 65%. As a result, two more hits with repeated dose data within the alkylbenzene class were located: toluene (68.1%) and *n*-butylbenzene (67.7%). Finally, a total of four structural surrogates were identified: ethylbenzene (95.4%), isopropylbenzene (91.3%), toluene (68.1%), and *n*-butylbenzene (67.7%).

Toxicokinetic Data

Available information on the toxicokinetics of *tert*-butylbenzene, ethylbenzene, isopropylbenzene, toluene, and *n*-butylbenzene suggests that all five chemicals are readily absorbed into the blood following administration via different routes. These chemicals are then excreted as unchanged hydrocarbons or biotransformed products, primarily via the lungs (unchanged) or in the urine as water-soluble metabolites (Gerarde, 1959, 1960; Zahlsen et al., 1992). Zahlsen et al. (1992) stated that the highest concentration of *tert*-butylbenzene was detected in the fat of the male rat (S-D), followed by the kidneys, liver, brain, and blood on Day 1 of inhalation exposure to *tert*-butylbenzene (total exposure was 12 hours per day for 3 consecutive days). Concentrations in fat declined on Days 2 and 3 following chemical administration with very little chemical remaining 12 hours after exposure termination (see Table A.1). In contrast, concentrations of *tert*-butylbenzene showed slight declines in the kidney, liver, brain, and blood on Day 2 of administration followed by a slight increase in concentrations on Day 3 of administration (see Table A.1). Gerarde (1959, 1960) stated that the amount of alkylbenzenes exhaled via the lung was dependent on the concentration of the chemical in the blood and its vapor pressure. Consequently, chemicals with low vapor pressures such as *tert*-butylbenzene and isopropylbenzene are not efficiently excreted from blood unchanged. Chemical-specific absorption and metabolic data via the oral route are presented in Table A.2. Because absorption data for *tert*-butylbenzene were not available, a comparison of absorption between the four possible surrogates and *tert*-butylbenzene cannot be made. However, based on the absorption, distribution, and excretion information from Gerarde (1959, 1960), alkylbenzenes, in general, as a chemical class, are primarily absorbed in the blood, distributed to various tissues on the basis of blood flow and high lipid content, and are excreted primarily in the urine as water-soluble metabolites or exhaled unchanged.

Robinson and Williams (1955) examined the metabolism of *tert*-butylbenzene in rabbits. They reported that the *tert*-butylbenzene was oxidized in rabbits mainly to 2,2,-dimethyl-2-phenylethanol (66−81% of the doses; averages from the 268- and 500-mg/kg two dose groups), which was then excreted as a glucuronide in urine. A minor metabolite, 1,1-dimethylphenylacetic acid, was detected as traces, and it could be excreted as a glycine conjugate in urine. Gerarde (1959, 1960) reported that metabolism of alkylbenzenes, in general, follows a metabolic pathway that involves oxidative changes either at the beta, omega, or penultimate carbon on the side chain, forming alcohols or carboxylic acids. These alcohols and carboxylic acids are subsequently conjugated with glucuronic acid or glycine and excreted in the urine (Gerarde, 1959, 1960). These transformations most likely occur in liver microsomes; however, they may also take place in the brain, spinal cord, bone marrow, kidney, and occasionally in the adrenal glands (Gerarde, 1959, 1960; Gerarde and Ahlstron, 1966). Hydroxylation or carboxylation can occur at various methyl groups in linear and branched alkylbenzenes followed by conjugation with glycine or glucuronic acid for excretion in urine. Because of rapid absorption into blood and more efficient pulmonary elimination via oral and inhalation routes of exposure to toluene (Gerarde, 1959, 1960), it is not considered as a suitable

metabolic surrogate for *tert*-butylbenzene at this point. Based on the toxicokinetic information, ethylbenzene, *n*-butylbenzene, and isopropylbenzene are considered as metabolic surrogates. In addition, based on both structural and toxicokinetic information, these three alkylbenzenes are considered as potential surrogates.

Table A.1. Biological Concentration of *tert*-Butylbenzene in Tissues of Sprague-Dawley Male Rats Following 12-Hour Daily Exposures to 100 ppm for 1, 2, and 3 Days and After a 12-Hour Recovery Period[a]

Tissue	Time Point	Concentration (µmol/kg)
Blood	Day 1	25.5 ± 6.1
	Day 2	11.1 ± 1.8
	Day 3	15.5 ± 1.2
	Recovery Period	0.7 ± 0.2
Brain	Day 1	71.2 ± 15.0
	Day 2	31.3 ± 4.0
	Day 3	38.7 ± 3.7
	Recovery Period	ND[b]
Liver	Day 1	85.4 ± 16.1
	Day 2	26.9 ± 6.2
	Day 3	47.0 ± 4.5
	Recovery Period	2.2 ± 0.5
Kidney	Day 1	259.1 ± 25.2
	Day 2	137.5 ± 42.3
	Day 3	256.6 ± 38.7
	Recovery Period	27.9 ± 11.0
Fat	Day 1	2993 ± 642
	Day 2	1323 ± 134
	Day 3	1171 ± 134
	Recovery Period	320 ± 61

[a]Zahlsen et al. (1992).
[b]ND = None Detected.

Table A.2. Comparative Absorption Data for *tert*-Butylbenzene and Potential Surrogates

Chemical	Route	Species	Absorption	Basis	Reference
Ethylbenzene	Oral	Rabbit	73−83%	Elimination of metabolites in urine (hippuric acid, methylphenylcarbinyl glucosiduronic acid, and phenaceturic acid)	El Masry et al., 1956
Isopropylbenzene	Oral	Rat	≥70%	Elimination of metabolites in urine (2-phenyl-2-propanol and its glucuronide or sulfate conjugates, and conjugates of 2-phenyl-1,2-propanediol)	Research Triangle Institute, 1989
Toluene	Oral	Rabbit	74%	Elimination of metabolites in urine (hippuric acid)	El Masry et al., 1956
n-Butylbenzene	Oral	Rabbit	68−78%	Elimination of metabolites in urine (hippuric acid, phenylpropyl- and methylpenethyl-carbinylglucuronides, and phenaceturic acid)	El Masry et al., 1956
tert-Butylbenzene	Oral	Rabbit	66−81% (average of 3 animals)	Elimination of metabolites in urine (2,2-dimethyl-2-phenylethanol and its glucuronide conjugates, and 1,1,-dimethylphenylacetic acid and its glycine conjugates)	Robinson and Williams, 1955

Acute Lethality

Because toluene was previously ruled out as a metabolic surrogate (see above), only the acute lethality data were located for *tert*-butylbenzene, ethylbenzene, *n*-butylbenzene, and isopropylbenzene (see Table A.3). The acute toxicity of *tert*-butylbenzene, isopropylbenzene, and ethylbenzene was much higher compared to the acute oral toxicity of *n*-butylbenzene in fasted rats administered 2.5 mL of each of these hydrocarbons in 1:1 v/v olive oil (Gerarde, 1959, 1960; see Table A.3). Two other acute oral studies for *tert*-butylbenzene (Haskell Laboratory, 1987; Hazelton Laboratories, 1982) also determined a rat LD_{50} of approximately 3.5 g/kg, which is less acutely toxic than isopropylbenzene (1.4−2.91 g/kg) but more similar to ethylbenzene (3.5−5.46 g/kg). Additionally, as described in the ***"Toxicity of Alkylbenzenes in Various Tissues"*** section in the main text and in the text above, Gerarde (1959, 1960) clearly states that the toxicity of branched alkylbenzenes is higher in comparison to their single-chain counterparts via oral exposures. Based on the available LD_{50} and mortality data (see Table A.3), isopropylbenzene seems to be the most acutely toxic via the oral route.

Table A.3. Acute Toxicity of *tert*-Butylbenzene and Potential Surrogates[a]

Chemical	*n*-Butylbenzene	Ethylbenzene	Isopropylbenzene (cumene)	*tert*-Butylbenzene
Oral LD_{50} (g/kg) Oral LD_{lo} (g/kg)	NA 4.30[b,c] (rat, not specified as a LD_{50} by author; considered as a LD_{lo})	3.5[a,d] (rat); 5.46[a] (rat)	2.91[a] (rat); 1.4[d] (rat)	3.503[e] (rat); 3.517[f] (average; rat) 4.33[b,c] (not specified as a LD_{50} by author; considered as a LD_{lo})
Mortality in fasted rats following a single oral dose of 2.5 mL of each alkylbenzene in 1:1 v/v olive oil[b]	2/10	7/10	6/10	7/10

[a]HSDB (2005a,b,c), unless otherwise noted.
[b]Gerarde (1959, 1960).
[c]Dose conversion: g/kg = (mL dose × (g/mL) density) ÷ (kg body weight). For *n*-butylbenzene: 1.25 mL × 0.8601 (g/ml) ÷ 0.250 kg-bw = 4.30 g/kg.
[d]ChemIDplus (2010).
[e]Haskell Laboratory (1978).
[f]Hazelton Laboratories (1982).

Other Data

Toxicity in various tissues, acute lethality data, and toxicokinetics resulting from exposures to alkylbenzenes, in general, are described in detail in the "***Toxicity of Alkylbenzenes in Various Tissues"*** and ***"Toxicokinetics Studies"*** sections in the main document. In the endothelium, alkylbenzenes present in the blood cause irritation that might lead to various effects including gross hemorrhage. These changes are often observed in the lungs of animals exposed to alkylbenzenes via gavage, subcutaneously, or via intraperitoneal injection (Gerarde, 1959, 1960). Gerarde (1959, 1960) also states that due to the highly lipophilic nature of alkylbenzenes, these chemicals can cause central nervous system effects that might lead to sluggishness, narcosis, coma, and anesthesia. Based on toxicity manifestation in these tissues, Gerarde (1959, 1960) states that branched alkylbenzenes are more toxic than linear alkylbenzenes. This information suggests that the branched surrogate (isopropylbenzene) may be more suitable over the linear surrogates (ethylbenzene and *n*-butylbenzene).

Physicochemical properties among *tert*-butylbenzene and three potential surrogates are generally comparable (i.e., molecular weight, melting and boiling points, and log Kow). The major differences are water solubility and vapor pressure at room temperature (see Table A.4). Ethylbenzene seems to be the "outlier," while the values of these two properties are more similar among *tert*-butylbenzene, isopropylbenzene, and *n*-butylbenzene. It is noteworthy that the physicochemical properties of *tert*-butylbenzene are most similar to those of *n*-butylbenzene, but its acute toxicities are closely aligned with those of isopropylbenzene.

Genotoxicity data for isopropylbenzene indicate that there were no genotoxic effects in *Saccharomyces cerevisiae* or in *Salmonella typhimurium* (one or more of the five standard strains: TA98, TA100, TA1535, TA1537, and TA1538) as a result of exposure to isopropylbenzene (Gene-Tox, 2010). It is not clear if results were negative both in the presence

and absence of metabolic activation (±S9). Isopropylbenzene also did not induce any mutations in a mutagenicity assay in *Salmonella typhimurium* (TA98, TA100, TA1535, and TA1537) both in the presence and absence of metabolic activation (HSDB, 2005b). Genotoxic results for ethylbenzene were mixed with positive results observed in in vitro tests using human lymphocytes (sister chromatid exchange) and negative results observed in Syrian Hamster embryo cells (cell transformation; HSDB, 2005c). *tert*-Butylbenzene was negative for mutagenicity in the Ames test in five strains of *Salmonella typhimurium*, both in the presence and absence of metabolic activation, and was also negative in the mitotic gene-conversion assay, performed with and without metabolic activation. *tert*-Butylbenzene was also negative under all conditions tested in the chromosomal-aberration assay (HSDB, 2005a). Because genotoxicity data for *n*-butylbenzene were not located, a comparison between *n*-butylbenzene's genotoxic potential and the other three alkylbenzenes (isopropylbenzene, *tert*-butylbenzene, and ethylbenzene) is not feasible. However, available genotoxicity data for isopropylbenzene and *tert*-butylbenzene indicate that both these alkylbenzenes may not be genotoxic.

In conclusion, an attempt was made to derive toxicity values for *tert*-butylbenzene using ethylbenzene, *n*-butylbenzene, and isopropylbenzene (cumene) as potential surrogates. Further comparison of these potential surrogates is made based on the profiles of structural similarity, toxicokinetics, acute and tissue-specific toxicity, and genotoxicity. Table C.1 in Appendix C provides a list of potential surrogates that have a peer-reviewed toxicity value in the IRIS database, the HEAST, or the PPRTV database. The chronic oral RfDs for the three potential surrogates are generally comparable to one another, ranging from 0.05 to 0.1 mg/kg-day, and, therefore, use of any of the three potential surrogates would have resulted in a similar screening chronic p-RfD for *tert*-butylbenzene. Common target organs among the potential surrogates include kidneys and liver, with kidneys likely to be the most sensitive endpoint for *tert*-butylbenzene based on the structural information (branched vs. linear, see Table A.4).

Overall, based on weight-of-evidence of all the information presented above, isopropylbenzene is the most appropriate surrogate for *tert*-butylbenzene (high similarity score, similar toxicokinetic profile and target organs, and comparable acute toxicity and genotoxicity; see Tables A.1, A.3, A.4, and C.1). The information presented in the sections above support isopropylbenzene (cumene) as a better surrogate for *tert*-butylbenzene than either *n*-butylbenzene or ethylbenzene. Though there are data gaps in the information compiled in the main text and in the Appendix, the following factors are considered in support of using isopropylbenzene as the surrogate for *tert*-butylbenzene:

- Similar patterns in absorption, distribution, and excretion (Gerarde, 1959, 1960)
- Similar patterns in metabolic activation and elimination (Gerarde, 1959, 1960)
- Similar physicochemical properties (see Table A.4)
- Similar structure
    - Structural similarity of 91.3% using DSSTox database (www.epa.gov/dsstox)
    - Both isopropylbenzene and *tert*-butylbenzene are branched alkylbenzenes, and toxicity from branched alkylbenzenes is reported to be higher in various tissues than that of their linear counterparts (ethylbenzene and *n*-butylbenzene; Gerarde, 1959, 1960)

- Similar pattern in ototoxicity: branched alkylbenzenes did not cause ototoxicity (Gagnaire and Langlais, 2005)
- Similar patterns in acute toxicities (see Table A.3)
- Higher acute toxicity of isopropylbenzene compared to *tert*-butylbenzene (see Table A.3)

Table A.4. Comparison of Available Toxicity Data for *tert*-Butylbenzene and Potential Surrogates[a]

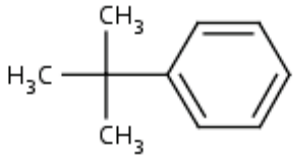
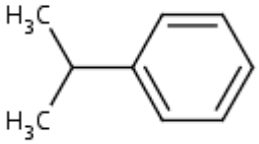
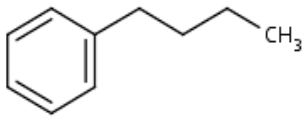
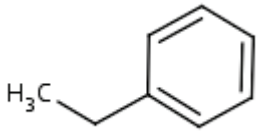
Characteristic	*tert*-Butylbenzene	Isopropylbenzene (Cumene)[b]	*n*-Butylbenzene	Ethylbenzene[b]
Structure				
CASRN	98-06-6	98-82-8	104-51-8	100-41-4
Molecular formula	C10-H14	C9-H12	C10-H14	C8-H10
Molecular weight	134.221	120.194	134.221	106.167
ChemIDplus similarity score (%)	100	NA	NA	NA
DSSTox similarity score (%)	100	91.3	67.7	95.4
Melting point (°C)	-5.78×10^{1}	-9.6×10^{1}	-8.79×10^{1}	-9.49×10^{1}
Boiling point (°C)	169.1	152.4	183.3	136.1
Vapor pressure (mm Hg at 25°C)	2.2	4.5	1.06	9.6
Water solubility (mg/L) at 25°C	29.5	61.3	11.8	169
Log Kow	4.11	3.66	4.38	3.15
pKa	NA	NA	NA	NA
Oral LD_{50} in rat (route: effect)	3503 mg/kg; 3517 mg/kg (oral exposure; see Table 2)	1400 mg/kg (oral exposure: gastritis)	NA	3500 mg/kg (oral exposure: changes in liver, kidney, ureter, bladder)
Oral LD_{50} in mice (route: effect)	NA	12,750 mg/kg (oral exposure: no effects reported)	NA	NA

Table A.4. Comparison of Available Toxicity Data for *tert*-Butylbenzene and Potential Surrogates[a]

Characteristic	*tert*-Butylbenzene	Isopropylbenzene (Cumene)[b]	*n*-Butylbenzene	Ethylbenzene[b]
Dermal LD_{50} in rabbits (route: effect)	NA	12.3 mL/kg (dermal exposure: no effects reported)	NA	17.8 mL/kg (dermal exposure: no effects reported)
Chronic oral RfD critical effect POD (source)	NA	1×10^{-1} mg/kg-day Increased average kidney weight in female rats $NOAEL_{ADJ}$: 110 mg/kg-day (U.S. EPA, 1997b)	5×10^{-2} mg/kg-day Increased incidences of hepatocellular hypertrophy in F0 and F1 parent male rats $BMDL_{10}$: 137 mg/kg-day (U.S. EPA, 2010b)	1×10^{-1} mg/kg-day Liver and kidney toxicity $NOEL_{ADJ}$: 97.1 mg/kg-day (U.S. EPA, 1991)

[a]From ChemIDplus, unless otherwise noted.
[b]From DSSTox analysis.

The summary of *IRIS Toxicological Review of Cumene* (U.S. EPA, 1997c) on dose-response (Section 6.2) is provided as an excerpt in the following (U.S. EPA, 1997b):

6.2 Dose Response

The quantitative estimates of human risk as a result of low-level chronic exposure to cumene are based on animal experiments because no human data exist.

The human dose that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime (the RfD) is 0.1 mg/kg-day. This amount is 1/1000 of the dose, adjusted for the stated schedule, at which no adverse effects were noted in female rats dosed orally with cumene over a period of about 7 mo (Wolf et al., 1956).

The overall confidence in the RfD assessment is low to medium. The confidence in the principal study is low. For purposes of quantitative assessment, the quality of the principal study (Wolf et al., 1956) is marginal because the group sizes are minimal and comprise females only, and little quantitative information is presented. The confidence in the database, judged here as medium to low, is improved from the earlier version on IRIS, principally because of the availability of inhalation developmental studies; some reproductive measures; corroboration of the critical effect by other studies, including those using oral dosing; and kinetic information. Kinetic information on oral and inhalation routes of exposure (Research Triangle Institute, 1989) justifies utilization of inhalation developmental studies performed in two species, rats and rabbits, in which no adverse results were noted. However, no 2-year chronic study is available via the oral or inhalation route. No multigeneration studies are available for this compound. Results on some male reproductive parameters were, however, documented in Cushman et al. (1995), the principal study for the RfC. The rapid metabolism and excretion of cumene in both animals and humans, coupled with the information on sperm morphology reported by Cushman et al. (1995), also indicate cumene to have a low potential for reproductive toxicity. The critical effect, altered tissue weights, was the same across routes of exposure (this was also the critical effect for the RfC) and was observed in several studies giving confidence in the consistency of this effect.

Justification for the use of a partial uncertainty factor for subchronic to chronic extrapolation was twofold: (1) the duration of the principal study (6 to 7 mo) was intermediate, between subchronic (3mo) and chronic (24 mo) duration, and (2) toxicokinetic data (Section 3) indicate that inhaled cumene and its metabolites are cleared quickly from both humans and rats, which also could indicate low potential for cumulative damage.

The daily exposure to the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime (the RfC) is 4E-1 mg/m^3. This concentration is 1/1000 of the adjusted no-effect level for significant increases (>10%) in renal and adrenal weights in rats exposed to cumene in the subchronic inhalation study of Cushman et al. (1995).

The overall confidence in the RfC assessment is medium. The RfC is based on rat subchronic inhalation studies performed with relatively large group sizes

in which thorough histopathological analyses and ancillary studies of neurotoxicity and ocular pathology were performed. The scientific quality of this evidence is high. The confidence in the database for the cumene RfC is rated as medium. Acceptable developmental studies were carried out (via inhalation route) in two species, rats and rabbits, with no adverse results noted; however, no 2-year chronic studies are available. As with the RfD database, full-scale multigeneration reproductive studies are lacking. The critical effect, altered tissue weights, is consistent across routes of exposure (altered kidney weight was also a critical effect for the RfD).

The use of a partial uncertainty factor for interspecies extrapolation is justified because species-to-species dosimetric adjustments were made and an HEC was calculated.

An area of scientific uncertainty and controversy in this assessment concerns the renal lesions in the male rats observed in the principal study. The descriptions of these lesions strongly suggest the male-specific rat nephropathic response elicited by compounds such as d-limonene and decalin (U.S. EPA, 1991a). This assessment has discounted these histopathological lesions in establishing an effect level for derivation of the RfC because EPA does not consider such lesions to be an appropriate endpoint for determining noncancer toxicity. If the male rat renal effects had not been discounted, then the RfD would have been approximately fivefold lower, because the NOAEL would be 100 ppm versus 496 ppm. What has been accepted as toxicologically relevant from the profile of renal toxicity in the principal study is the increase in female renal weight. Other repeated-dose studies with cumene also have reported increased renal weights among female rats (Wolf et al., 1956; Monsanto, 1986; Chemical Manufacturer's Association, 1989). These independent observations, coupled with the uncertainty about the progression and outcomes of these alterations (because of the absence of any true lifetime studies) further justifies considering these weight alterations as toxicologically significant.

Oral Toxicity Values

Screening Subchronic and Chronic p-RfDs

For *tert*-butylbenzene, the IRIS chronic value for isopropylbenzene (1×10^{-1} mg/kg-day) based on increased average kidney weight in female Wistar rats from a 194-day study (Wolf et al., 1956) is recommended as a screening p-RfD based on the chemical-class-specific information (e.g., metabolic profile) and overall surrogate approach presented in this document. IRIS used a NOAEL of 154 mg/kg-day (converted to 110 mg/kg-day for continuous exposure) and applied a composite UF of 1000 including a UF of 10 for interspecies extrapolation, and a UF of 10 for intraspecies variability, a partial UF of 3 to extrapolate from a less than chronic-duration (194-day study) study to a chronic-duration study, and a partial UF of 3 for database deficiencies (lack of reproductive information). Based on the current surrogate approach, it is assumed that all attributes such as critical effect, POD, and all UFs of the surrogate chemical be adopted for the chemical of concern (unless a different adverse effect was used).

Based on the surrogate analysis presented in this appendix, the IRIS chronic RfD of **1×10^{-1} mg/kg-day** for isopropylbenzene is recommended for the screening chronic p-RfD for *tert*-butylbenzene.

Given the lack of subchronic data for *tert*-butylbenzene and the uncertainty associated with the use of a surrogate approach for the derivation of toxicity values, the same value, **1×10^{-1} mg/kg-day**, is recommended for the screening subchronic p-RfD.

While studies providing specific effects for *tert*-butylbenzene following oral exposures could not be located, the information regarding metabolism, absorption, and tissue-specific toxicity provided in the Gerarde (1959, 1960) study, and the lack of ototoxicity in both *tert*-butylbenzene and isopropylbenzene (Gagnaire and Langlais, 2005), provide some confidence that the effects, or lack thereof, observed following long-term oral exposures to isopropylbenzene may also be expected following long-term oral exposures to *tert*-butylbenzene. Because the toxicity of short-chain alkylbezenes was not dependent upon the molecular weight and the actual mechanism of action is not elucidated, a molecular weight-adjustment was not applied (in general, an adjustment is not considered when the difference in molecular weights is less than 2-fold).

APPENDIX B. DATA TABLES

No data tables presented.

APPENDIX C. POTENTIAL ANALOGS FROM DSSTOX AND CHEMIDPLUS WITH AVAILABLE VALUES FROM THE IRIS DATABASE, THE HEAST, AND THE PPRTV DATABASE

Table C.1. Results of DSSTox and ChemIDplus Structure Similarity Search for *tert*-butylbenzene.

Chemical Name	Similarity Search Engine	Percent Similarity Match (DSSTox/ ChemIDplus)	IRIS Value (Chronic RfD) [Year Updated]	PPRTV Value (Chronic RfD) [Year Updated]	PPRTV Value (Subchronic RfD) [Year Updated]	HEAST Value (Subchronic RfD)
Oral exposure—RfD						
tert-Butylbenzene	DSSTox/ ChemIDplus	100/100	NA	NA[a]	NA[a]	NA
Isopropylbenzene	DSSTox	91.3	1×10^{-1} mg/kg-day (U.S. EPA, 1997b)	NA	NA	4×10^{-1} mg/kg-day (U.S. EPA, 2003)
Ethylbenzene	DSSTox	95.4	1×10^{-1} mg/kg-day (U.S. EPA, 1991)	NA[b]	5×10^{-2} mg/kg-day (U.S. EPA, 2009)	NA[b]
n-butylbenzene	DSSTox	67.7	NA	5×10^{-2} mg/kg-day (U.S. EPA, 2010b)	0.1 mg/kg-day (U.S. EPA, 2010b)	NA

[a]Surrogate approach used to develop toxicity values in this PPRTV.
[b]Value not derived because of the existing IRIS value(s).
NA = Not available.

APPENDIX D. REFERENCES

Aam, BB; Myhre, O; Fonnum, F. (2003) Transcellular signalling pathways and TNF-alpha release involved in formation of reactive oxygen species in rat alveolar macrophages exposed to *tert*-butylcyclohexane. *Arch Toxicol* 77:678−684. 598116

ACGIH (American Conference of Governmental Industrial Hygienists). (2010) 2010 TLVs and BEIs: Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: ACGIH. 594528

ATSDR (Agency for Toxic Substances and Disease Registry). (2010) Toxicological profile information sheet. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA. Available online at http://www.atsdr.cdc.gov/toxprofiles/index.asp. Accessed on 5/14/2010. 684152

CalEPA (California Environmental Protection Agency). (2000) Proposed action levels for sec-butylbenzene and tert-butylbenzene. Office of Environmental Health Hazard Assessment, Sacramento, CA. Available online at http://www.oehha.org/water/pals/sec_tertBbenz.html. Accessed on 5/14/2010. 625582

CalEPA (California Environmental Protection Agency). (2008) All OEHHA acute, 8-hour and chronic reference exposure levels (chRELs) as on December 18, 2008. Office of Environmental Health Hazard Assessment, Sacramento, CA. Available online at http://www.oehha.ca.gov/air/allrels.html. Accessed on 5/14/2010. 595416

ChemIDplus. (2010) Chemical identification file. U.S. National Library of Medicine. Available online at http://chem.sis.nlm.gov/chemidplus. Accessed on 7/6/2010. 629639

Cushman, JR; Norris, JC; Dodd, DE; et al. (1995) Subchronic inhalation toxicity and neurotoxicity assessment of cumene in Fischer 344 rats. *Int J Toxicol* 14(2):129−147. 075034

Gagnaire, F; Langlais, C. (2005) Relative ototoxicity of 21 aromatic solvents. *Arch Toxicol* 79(6):346−354. 598134

Gene-Tox. (2010) Genetic Toxicology Data Bank. National Library of Medicine, National Institutes of Health, U.S. Department of Health and Human Services, Bethesda, MD. Available online at http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?GENETOX. Accessed on 7/6/2010. 629638

Gerarde, HW. (1959) Toxicological studies on hydrocarbons. III. The biochemorphology of the phenylalkanes and phenylalkenes. *AMA Arch Ind Health* 19(4):403−418. 597515

Gerarde, HW. (1960) Toxicological effects. In: Threlfall, CJ; ed. Toxicology and biochemistry of aromatic hydrocarbons. Amsterdam, Netherlands: Elsevier Publishing Company; pp. 52−57. 628707

Gerarde, HW; Ahlstrom, DB. (1966) Toxicologic studies on hydrocarbons: XI. Influence of dose on the metabolism of mono-n-alkyl derivatives of benzene. *Toxicol Appl Pharmacol* 9:185−190.

Haskell Laboratory of Toxicology and Industrial Medicine. (1978) Oral tert butyl-benzene testing in male rats. E.I. Dupont de Nemours & Co. Newark, DE. EPA 86-870000981. Available online at http://www.ntis.gov/search/product.aspx?ABBR=OTS0514883. Accessed on 5/14/2010. 598098

Hazelton Laboratories. (1982) Initial submission: Acute oral toxicity in rats using t butyl benzene (with cover letter dated 08/24/92). Hazelton Laboratories No. 88920010733. Available online at http://www.ntis.gov/search/product.aspx?ABBR=OTS0571879. Accessed on 5/14/2010. 625141

HSDB (Hazardous Substances Data Bank). (2005a) tert-Butylbenzene. National Library of Medicine, National Institutes of Health, U.S. Department of Health and Human and Human Services, Bethesda, MD. Available online at http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+98-06-6. Last revised on December 19, 2005. Accessed on 5/14/2010. 594343

HSDB (Hazardous Substances Data Bank). (2005b) Cumene. National Library of Medicine, National Institutes of Health, U.S. Department of Health and Human and Human Services, Bethesda, MD. Available online at http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+98-82-8. Last revised on June 24, 2005. Accessed on 5/14/2010.

HSDB (Hazardous Substances Data Bank). (2005c) Ethylbenzene. National Library of Medicine, National Institutes of Health, U.S. Department of Health and Human and Human Services, Bethesda, MD. Available online at http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+100-41-4. Last revised on July 7, 2005. Accessed on 5/14/2010.

IARC (International Agency for Research on Cancer). (2000) Some industrial chemicals. IARC monographs on the evaluation of carcinogenic risks to humans, volume 77. Geneva: WHO. Available online at http://monographs.iarc.fr/ENG/Monographs/vol77/index.php. Accessed on 5/14/2010. 201837

El Masry, AM; Smith, JN; Williams, RT. (1956) Studies in detoxication. 69. The metabolism of alkylbenzenes: n-propylbenzene and n-butylbenzene with further observations on ethylbenzene. *Biochem J* 64(1):50−56.

NIOSH (National Institute for Occupational Safety and Health). (2010) NIOSH pocket guide to chemical hazards. Index of chemical abstracts service registry numbers (CAS No.). Center for Disease Control and Prevention, U.S. Department of Health, Education and Welfare, Atlanta, GA. Available online at http://www.cdc.gov/niosh/npg/npgdcas.html. 625692

NTP (National Toxicology Program). (2011) 12th Report on carcinogens. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. Available online at http://ntp.niehs.nih.gov/?objectid=03C9AF75-E1BF-FF40-DBA9EC0928DF8B15. Accessed on 11/17/2011. 737606

OSHA (Occupational Safety and Health Association). (2006) Table Z-1 limits for air contaminants: occupational safety and health standards, subpart Z, toxic and hazardous substances. U.S. Department of Labor, Washington, DC; OSHA Standard 1910.1000. Available online at http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992. Accessed on 5/14/2010. 670067

Research Triangle Institute. (1989) Metabolism, disposition and pharmacokinetics of cumene in F-344 rats following oral, IV administration or nose-only inhalation exposure. Report No. RTI/4353-01F. CMA Reference No. CU-5.0-PK-RTI.

Rivedal, E; Mikalsen, SO; Roseng, LE; et al. (1992) Effects of hydrocarbons on transformation and intercellular communication in Syrian hamster embryo cells. *Pharmacol Toxicol* 71(1):57−61. 598152

Robinson, D; Williams, RT. (1955) Studies in detoxification. 61. The metabolism of alkylbenzenes: tert-Butylbenzene. *Biochem J* 59(1):159−161.

Shell Oil Company. (1980) Toxicity studies with fine chemicals - in vitro genotoxicity studies with tertiary butyl benzene. Shell Research Limited, London, Sittingbourne Research Centre, Shell Toxicology Laboratory (Tunstall). Sittingbourne, Kent, United Kingdom. OTS0515723; 86 870001647. Available online at http://www.ntis.gov/search/product.aspx?ABBR=OTS0515723. 629644

U.S. EPA (Environmental Protection Agency). (1991) IRIS summary for ethylbenzene (CASRN 100-41-4). National Center for Environmental Assessment, Washington, DC. Available online at http://www.epa.gov/IRIS/subst/0051.htm. Accessed on 7/8/2010. 629645

U.S. EPA (Environmental Protection Agency). (1994) Chemical assessments and related activities (CARA). Office of Health and Environmental Assessment, Washington, DC; EPA/600/R-94/904. Available online at http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=60001G8L.txt. 596444

U.S. EPA (Environmental Protection Agency). (1997a) Risk assessment issue paper for: Derivation of provisional chronic RfDs for n-butylbenzene (CASRN 104-51-8), sec-butylbenzene (CASRN 135-98-8), tert-butylbenzene (CASRN 98-06-6), and n-propylbenzene (CASRN 103-65-1). National Center for Environmental Assessment, Washington, DC; EPA/97-009/6-5-97. 597097

U.S. EPA (Environmental Protection Agency). (1997b) IRIS summary for cumene. Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Last revised 4/11/2003. Available online at http://www.epa.gov/iris/subst/0306.htm. Accessed on 7/8/2010. 628708

U.S. EPA (Environmental Protection Agency). (1997c) Toxicological review of cumene (CAS No. 98-82-8). In support of the Integrated Risk Information System. National Center for Environmental Assessment, Research Triangle Park, NC. Available online at http://www.epa.gov/iris/toxreviews/0306tr.pdf. Accessed on 5/6/2011.

U.S. EPA (Environmental Protection Agency). (2003) Health effects assessment summary tables (HEAST). Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati OH for the Office of Emergency and Remedial Response, Washington, DC. Available online at http://epa-heast.ornl.gov/. Accessed on 5/14/2010. 595422

U.S. EPA (Environmental Protection Agency). (2005) Guidelines for carcinogen risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-03/001F. Federal Register 70(66):17765−17817. Available online at http://www.epa.gov/raf/publications/pdfs/CANCER_GUIDELINES_FINAL_3-25-05.PDF. Accessed on 5/14/2010. 086237

U.S. EPA (Environmental Protection Agency). (2006) 2006 Edition of the drinking water standards and health advisories. Office of Water, Washington, DC; EPA/822/R-06/013. Available online at http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf. Accessed on 5/14/2010. 091193

U.S. EPA (Environmental Protection Agency). (2009) Provisional peer-reviewed toxicity values for ethylbenzene (CASRN 100-41-4). Derivation of a subchronic oral provisional-RfD and subchronic inhalation provisional-RfC. Superfund Health Risk Technical Support Center, National Center for Environmental Assessment, Cincinnati, OH. Accessed on 7/19/2010.

U.S. EPA (Environmental Protection Agency). (2010a) Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at http://www.epa.gov/iris/. Accessed on 5/14/2010. 595423

U.S. EPA (Environmental Protection Agency). (2010b) Provisional peer reviewed toxicity value for n-butylbenzene (CASRN 104-51-8), sec-butylbenzene (CASRN 135-98-8), and tert-butylbenzene (CASRN 98-06-6). Derivation of a subchronic oral provisional-RfD and subchronic inhalation provisional-RfC. Superfund Health Risk Technical Support Center, National Center for Environmental Assessment, Cincinnati, OH. Accessed on 9/13/2010.

Wang, NCY; Zhao, QJ; Wesselkamper, SC; et al. (2012) Application of computational toxicological approaches in human health risk assessment. I. A tiered surrogate approach. *Regul Toxicol Pharmacol* 63(1):10−19. Available online at http://www.sciencedirect.com/science/article/pii/S0273230012000323. 1239453

WHO (World Health Organization). (2010) Online catalogs for the Environmental Health Criteria Series. Available online at http://www.who.int/ipcs/publications/ehc/en/. Accessed on 5/14/2010. 595424

Wolf, MA; Rowe, VK; McCollister, DD; et al. (1956) Toxicological studies of certain alkylated benzenes and benzene: Experiments on laboratory animals. *AMA Arch Ind Health* 14(4):387−398. 062279

Zahlsen, K; Eide, I; Nilsen, AM; et al. (1992) Inhalation kinetics of C6 to C10 aliphatic, aromatic and naphthenic hydrocarbons in rat after repeated exposures. *Pharmacol Toxicol* 71(2):144−149. 068948