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Provisional Peer-Reviewed Toxicity Values for

sec-Butylbenzene
(CASRN 135-98-8)

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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 *sec*-BUTYLBENZENE (CASRN 135-98-8)

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

sec-Butylbenzene is used as a solvent for coating compositions, as an organic synthesizer, a surface active agent, and a plasticizer (HSDB, 2004). The empirical formula for *sec*-butylbenzene is $C_{10}H_{14}$ (see Figure 1). A table of physicochemical properties is provided in Table 1.

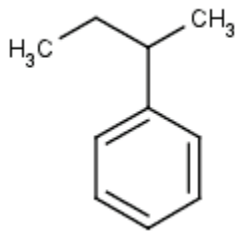


Figure 1. Structure of *sec*-Butylbenzene

Table 1. Physicochemical Properties Table for *sec*-Butylbenzene (CASRN 135-98-8)

Property (unit)	Value
Boiling point (ºC)	173.5[a]
Melting point (ºC)	-8.27×10^{1}[a]
Density (g/cm^3)	0.8580[b]
Vapor pressure (mm Hg at 25ºC)	1.75[a]
Solubility in water (mg/L at 25ºC)	17.6[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)	4.57[a]

[a]ChemIDplus (2010).
[b]HSDB (2004).

No reference dose (RfD), reference concentration (RfC), or cancer assessment for *sec*-butylbenzene is included on the EPA's 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 were reported in the HEAST (U.S. EPA, 2003). However, EPA (U.S. EPA, 1997a) did derive a chronic provisional RfD of 1×10^{-2} mg/kg-day for *sec*-butylbenzene using isopropylbenzene (cumene) as a structural analog. The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1994) does not include any health related documents for *sec*-butylbenzene. The potential carcinogenicity of the chemical was also not assessed due to lack of pertinent data. The toxicity of *sec*-butylbenzene has not been reviewed by the ATSDR (2010) or the World Health

Organization (WHO, 2010). CalEPA (2008) has not derived toxicity values for exposure to *sec*-butylbenzene but has recommended an action level of 260 µg/L for *sec*-butylbenzene in drinking water (CalEPA, 2000). This derivation was based on a subchronic rat NOAEL of 110 mg/kg-day for isopropylbenzene (similar to the structural analog approach taken by U.S. EPA, 1997a) and incorporated uncertainty factors for interspecies extrapolation, subchronic to chronic extrapolation, human variability and database deficiencies. No occupational exposure limits for *sec*-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, 1997a) does not report a cancer oral slope factor or an inhalation unit risk value for *sec*-butylbenzene. The International Agency for Research on Cancer (IARC, 2000) has not reviewed the carcinogenic potential of *sec*-butylbenzene. *sec*-Butylbenzene is not included in the *12th Report on Carcinogens* (NTP, 2011). CalEPA (2008) has not derived a quantitative estimate of carcinogenic potential for *sec*-butylbenzene.

Literature searches were conducted on sources published from 1900 through November 17, 2011, for studies relevant to the derivation of provisional toxicity values for *sec*-butylbenzene, CAS No. 135-98-8. 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 *sec*-butylbenzene, derivation of provisional toxicity values is not possible for this chemical. As a result, a surrogate 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 *sec*-butylbenzene are not presented in this document. A PPRTV document on the noncancer effects of inhalation exposure to *sec*-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.

Table 2. Summary of Potentially Relevant Data for *sec*-Butylbenzene (CASRN 135-98-8)								
Category	**Number of Male/Female, Species, Study Type, Study Duration**	**Dosimetry**	**Critical Effects**	**NOAEL**	**BMDL/ BMCL**	**LOAEL[a]**	**Reference (Comments)**	**Notes[b]**
Human								
			Oral (mg/kg-day)[a]					
None								
Animal								
			Oral (mg/kg-day)[a]					
Acute	No data, Rat	1920 mg/kg[c]	LD_{50}, was 2.24 mL/kg (1920 mg/kg); no toxic effects noted	NA	NA	NA	Carpenter et al. (1974)	
	10, Rat, sex and purity not specified; surviving animals observed for 3 weeks after dosing	4.29 g/kg-bw[c]	Eight of 10 animals died with pulmonary injury the likely cause of death; enlarged liver due to stress following biotransformation of *sec*-butylbenzene	NA	NA	NA	Gerarde (1959)	
	4, Rat, sex, duration and purity not specified	2.0 g/kg	No deaths noted; slight weight loss that was noted earlier in the study	NA	NA	NA	Dow Chemical Company (1987)	NPR
Short-term	8/0, S-D rat, gastric intubation, 5 days/week, 2 weeks followed by 10-day observation	812 mg/kg-day[d]	No deaths, changes in body-weight gain, or evidence of ototoxicity observed; use of control group not specified	812	None	None	Gagnaire and Langlais (2005)	
Subchronic	None							
Chronic	None							
Developmental	None							
Reproductive	None							
Carcinogenic	None							

[a]Not reported by the study author but determined from data.
[b]Notes: IRIS = Utilized by IRIS, date of last update; PS = Principal study, NPR = Not peer reviewed.
[c]Dosimetric conversion: g/kg = [mL dose × (g/ml) density] ÷ (kg body weight). For *sec*-butylbenzene: 1.25 mL × 0.8580 (g/ml) ÷ 0.250 (kg-bw) = 4.29 g/kg.
[d]Dosimetric conversion: mmol/kg-bw-day to mg/kg-day = 8.47 mmol/kg-bw-day × 134.22 (molecular weight) mg/mmol = 1136.8434 (Dose in mg)/kg-bw-day; final dose is 1136.8434 mg/kg-bw-day × 5 ÷ 7 = 812 mg/kg-day.
NA = Not Available; S-D = Sprague-Dawley.

HUMAN STUDIES

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

ANIMAL STUDIES

The effects of oral or inhalation exposure of animals to *sec*-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 *sec*-butylbenzene have been evaluated in three acute single-dose toxicity studies (HSDB, 2004; Gerarde, 1959; Dow Chemical Company, 1987; Carpenter et al., 1974) and one short-term repeated-dose toxicity study (Gagnaire and Langlais, 2005).

Short-term Studies

An acute oral median lethal dose (lethal dose, 50%; LD_{50}) of 2.24 mL/kg-day (1920 mg/kg) in rats for *sec*-butylbenzene is reported by Carpenter et al. (1974; as cited in ChemIDplus). This LD_{50} value was recommended by the European Chemicals Bureau with no study details available. In an acute oral toxicity study conducted by Gerarde (1959, 1960), several alkylbenzenes—including *sec*-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 *sec*-butylbenzene is 1.25 mL, or a converted dose of 4.29 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, 8 animals died from exposure to *sec*-butylbenzene. Histopathological findings, though not specific to *sec*-butylbenzene, suggest that pulmonary injury was likely the 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 *sec*-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 *sec*-butylbenzene. The dose of 4.29 g/kg is considered as a lethal dose low (LD_{lo}) for *sec*-butylbenzene.

In another acute oral toxicity study by Dow Chemical Company (1987), no mortality was observed in four rats (sex not specified) administered 2.0-g/kg *sec*-butylbenzene (purity not specified) in 10% solution in corn oil. Besides weight loss that was noted earlier in the study, no other details were provided in the report and an LD_{50} value was not reported, possibly due to lack of mortality in treated animals.

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 rats. Observations continued for 10 days following treatment. Each administered dose was 8.47 mmol/kg-day, which is converted to 812 mg/kg-day for *sec*-butylbenzene (99% pure; see Footnote C in Table 2 for dose conversion), after adjusting for continuous exposure 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 rats 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 *sec*-butylbenzene died (use of control group was not specified), and all animals appeared to gain weight normally. The study authors reported that *sec*-butylbenzene did not cause any ototoxicity in 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. Based on these results, a NOAEL of 812 mg/kg-day is identified for *sec*-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 preclude its consideration for the derivation of an oral subchronic p-RfD for *sec*-butylbenzene. In addition, the authors did not conduct a thorough toxicological evaluation of other organs to assess the possible toxicological potential of *sec*-butylbenzene at the tested dose.

Other Exposures

In a report by Shell Oil Company (1987), seven hydrocarbons, including *sec*-butylbenzene, were administered dermally to three male and three female rabbits and not classified as skin irritants as a result of the semi-occlusive path test, with the exception of 1,3-di-isopropylbenzene. However, the report did state that *sec*-butylbenzene, among a few other hydrocarbons, produced noticeable skin effects that persisted for several days after dosing but did not cause any permanent skin damage. In addition to the skin irritancy test, the study authors also conducted an eye irritancy test. The instillation of these undiluted seven hydrocarbons, including *sec*-butylbenzene, into the conjunctival sac of one eye of each of six rabbits (three male and three female rabbits) did not result in eye irritancy according to the *Official Journal of the European Communities* (EEC, 1983, as cited in Shell Oil Company, 1987). As a result, these seven hydrocarbons were not classified as eye irritants.

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Toxicokinetic	Male S-D rats, exposed to 100-ppm (549 mg/m^3)[a,b] *tert*-butylbenzene for 3 days, 12 hours/day	Accumulated rapidly and reached steady state conditions in blood, brain, liver, and kidneys; largest hydrocarbon concentrations found in the kidneys; in general, higher concentrations of aromatic hydrocarbons were found in blood compared to other hydrocarbons tested	Metabolic rate of elimination for *tert*-butylbenzene is comparatively high	Zahlsen et al. (1992)
Metabolism	Animal species and strain not specified; doses not specified	Metabolism of *sec*-butylbenzene and alkylbenzenes in general follows a metabolic pathway that involves oxidative changes either at the beta, omega, or penultimate carbons on the side-chain, forming alcohols or carboxylic acids; these alcohols and carboxylic acids subsequently conjugate with glucuronic acid and glycine, respectively, and are excreted in urine	Metabolism primarily occurs on the side-chain via the oxidative pathway followed by conjugation and excretion	HSDB (2004); Gerarde (1959)
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 *sec*-butylbenzene in 1:1 v/v olive oil (1.25 mL *sec*-butylbenzene; 4.29 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, petechial and gross hemorrhage and edema in the surrounding tissues; effects also noted in the kidneys, liver, spleen, bladder, thymus, brain, and the spinal cord; accumulation of alkylbenzenes in nerve cells resulting in signs and symptoms of central nervous system (CNS) depression such as sluggishness, stupor, coma, narcosis, and anesthesia; 8 out of 10 animals died following oral administration of *sec*-butylbenzene. Necropsy results indicated lung involvement, with severity ranging from hyperemia to gross hemorrhage, with pulmonary injury reported as potential cause of death	Toxicity manifested in the endothelial cells and CNS. Branched alkylbenzenes were reported to be more acutely toxic compared to the linear alkylbenzenes	Gerarde (1959, 1960)
Dermal irritation	New Zealand White rabbits 3/sex, exposed to 0.5-mL undiluted test material in a semi-occlusive single-application patch test (4 hours), observations made for 14 days after patch removal, purity of compound not specified	Very slight to slight inflammation seen from 24 hours up to 72 hours postdosing; all reactions cleared by 14 days	Not a skin irritant based on the test score (<2) as established in EEC (1983, as cited in Shell Oil Company, 1987)	Shell Oil Company (1987)

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Eye irritation	The instillation of undiluted *sec*-butylbenzene into the conjunctival sac of the one eye of each of six rabbits	Severe initial pain; very slight conjunctival redness and discharge	Not an eye irritant based on the test score (<2) as established in EEC (1983, as cited in Shell Oil Company, 1987)	Shell Oil Company (1987)

[a]mg/m^3 = ppm × molecular weight ÷ 24.45; HEC conversion not presented because this is an acute value.
[b]Not adjusted for continuous dosing.
[c]Dose conversion: g/kg = [mL dose × (g/mL) density] ÷ (kg body weight).

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Toxicokinetics Studies

Studies pertaining to the toxicokinetics of *sec*-butylbenzene in humans and animals were not located. Zahlsen et al. (1992) investigated the toxicokinetic properties of several alkylbenzenes, alkanes, and naphthenes in rats (see Table 3). However, a toxicokinetic study on a structurally similar alkylbenzene, *tert*-butylbenzene, was located. Male Sprague-Dawley rats exposed to 100-ppm (549 mg/m^3; dose not adjusted for continuous dosing) *tert*-butylbenzene for 12 hours/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 Day 2 and 3 following chemical administration with very little chemical remaining 12 hours after termination of exposure. In contrast, the concentrations of *tert*-butylbenzene exhibited a slight decline in the kidney, liver, brain, and blood on Day 2 of chemical administration, which was 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. These results may suggest that the metabolic rate of elimination is high for *tert*-butylbenzene. Though the authors did not directly measure the toxicokinetic properties of *sec*-butylbenzene, *tert*-butylbenzene (C10 alkylbenzene) is also a branched alkylbenzene similar to *sec*-butylbenzene (C10 alkylbenzene), thus these two isomers may share similar kinetic properties. Gerarde (1959) corroborated absorption in the blood and stated that due to the high lipophilicity ofalkylbenzenes, 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 the 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 *sec*-butylbenzene and alkylbenzenes, in general, follow a common metabolic pathway (HSDB, 2004; Gerarde, 1959, 1960) that involves oxidative changes either at the beta, omega, or penultimate carbons on the side-chain, forming alcohols or carboxylic acids. These alcohols or carboxylic acids subsequently conjugate with glucuronic acid or glycine, respectively, 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, Gerard and Ahlstrom (1966) 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. The mechanism of side-chain oxidation seems to facilitate detoxification and is the preferred pathway for alkylbenzenes, in general, which is exemplified when benzene toxicity is compared with the toxicity of 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.

While specific excretion data for *sec*-butylbenzene were not readily available, Gerarde (1959, 1960) reported on 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 being 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 rapidly eliminated from blood as compared to benzene.

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 (CNS) depression such as sluggishness, stupor, coma, narcosis, and anesthesia. The intensity and quality of these effects were described by the study author to be dependent upon 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 the 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 decreased (i.e., CNS 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 CNS effects. The rate of initiation of CNS 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 CNS 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 CNS 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

CNS effects of branched alkylbenzenes are longer lasting in contrast to the linear alkylbenzenes. The CNS 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 CNS 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) 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 (method of administration not specified) dose of 2.5 mL of *sec*-butylbenzene (purity not specified) 1:1 v/v in olive oil (1.25 mL of *sec*-butylbenzene) along with other alkylbenzenes. Following administration, 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) 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) concluded that branched-chain mono-alkylbenzenes (isopropyl-, *sec*-, *tert*-butylbenzenes) are more toxic compared with 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) 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) 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 in term of noncancer effects (the same assumption may not be true for cancer effects).

Genotoxicity Studies

No studies investigating the genotoxic effects of *sec*-butylbenzene were identified.

DERIVATION OF PROVISIONAL VALUES

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

Table 4. Summary of Screening Oral Provisional Reference Values for *sec*-Butylbenzene (CASRN 135-98-8)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UFc	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 Values for *sec*-Butylbenzene (CASRN 135-98-8)

Toxicity Type	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 RfDs (Subchronic and Chronic p-RfDs)

No chronic or subchronic toxicity data were identified for the derivation of an oral provisional RfD (p-RfD) for *sec*-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, which may be of use under certain circumstances. Please see Appendix A for details regarding the screening-level values.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

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

Table 6. Cancer WOE Descriptor for *sec*-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 *sec*-butylbenzene in humans are available.
"Likely to be Carcinogenic to Humans"	N/A	N/A	No studies pertaining to the carcinogenicity of *sec*-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 *sec*-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 the carcinogenic potential of *sec*-butylbenzene.**
"Not Likely to be Carcinogenic to Humans"	N/A	N/A	No data are available to suggest that *sec*-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 *sec*-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 *sec*-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 *sec*-butylbenzene from the 2-week study by Gagnaire and Langlais (2005). However, the lack of ototoxicity in animals following exposure to *sec*-butylbenzene, the lack of a control group, and the lack of testing at higher doses, which may have caused an effect, precludes the use of this study for the derivation of an oral subchronic p-RfD for *sec*-butylbenzene. In addition, the authors did not conduct a thorough toxicological evaluation of other organs to assess the possible toxicological potential of *sec*-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 the National Library of Medicine, ChemIDplus (http://chem.sis.nlm.nih.gov/ChemIDplus/) and then EPA DSSTox (www.epa.gov/dsstox) databases. Thirty-one possible analogs (structural surrogates) were identified using ChemIDplus (2010) with the similarity match set to ≥50%, and 27 possible analogs were identified using DSSTox with the similarity match set to ≥70%. ChemIDplus identified only one structural surrogate with repeated dose with a similarity match of 53% to *sec*-butylbenzene: isopropylbenzene. DSSTox identified three structural surrogates with repeated dose, *n*-butylbenzene ($C_{10}H_{14}$), isopropylbenzene (C_9H_{12}), and ethylbenzene (C_8H_{10}) as structurally similar to *sec*-butylbenzene with similarity score of 83.8, 81.4, and 77.7%, respectively (see Table C.1). Based on the structural information and consensus of two similarity search programs (ChemIDplus and DSSTox), isopropylbenzene is considered to be the best structural surrogate.

Toxicokinentic Data

Available information on the toxicokinetics of *sec*-butylbenzene, ethylbenzene, *n*-butylbenzene, and isopropylbenzene suggests that all four chemicals are readily absorbed into the blood following administration via different routes and excreted as unchanged hydrocarbons or biotransformed products, primarily unchanged via the lungs or in the urine as water-soluble metabolites (Gerarde, 1959). Gerarde (1959) also stated that the amount of alkylbenzene 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 *sec*-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.1. Because absorption data for *sec*-butylbenzene were not available, a comparison of absorption between the three possible surrogates and *sec*-butylbenzene cannot be made. However, based on the absorption, distribution, and excretion information from Gerarde (1959), alkylbenzenes, in general, as a chemical class, are primarily absorbed in the blood, distributed to various tissues on the basis of blood flow and lipid content, and are excreted primarily in the urine as water-soluble metabolites or exhaled unchanged.

Table A.1. Comparative Toxicokinetic Data for *sec*-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
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
sec-Butylbenzene	No data	No data	No data	No data	NA

NA = Not applicable.

While specific metabolism data for *sec*-butylbenzene could not be located, Gerarde (1959) reported that metabolism of alkylbenzenes, in general, follows a metabolic pathway that involves oxidative changes at either 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). 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. These biotransformations 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 as

well (Gerarde, 1959). Based on the toxicokinetic information, ethylbenzene, *n*-butylbenzene, and isopropylbenzene are considered as metabolic surrogates. In addition, based on the structural and toxicokinetic information, the three alkylbenzenes are considered as potential surrogates.

Acute Lethality

The acute oral toxicity of *sec*-butylbenzene, isopropylbenzene, and ethylbenzene was much higher compared with 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; see Table A.2). Additionally, as described in the ***"Toxicity of Alkylbenzenes in Various Tissues"*** section above, Gerarde (1959) 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}/LD_{lo} and mortality data (see Table A.2), isopropylbenzene seems to be the most acutely toxic via the oral route.

Table A.2. Acute Oral Toxicity of *sec*-Butylbenzene and Potential Surrogates[a]

Chemical	*n*-Butylbenzene	Ethylbenzene	Isopropylbenzene (cumene)	*sec*-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)	1.92[c,d] (rat) 4.29[b,c] (rat, not specified as a LD_{50} by author; considered as a LD_{lo}); 2.0[e]
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	8/10

[a]HSDB (2004), unless otherwise noted.
[b]Gerarde (1959).
[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]Dow Chemical Company (1987).

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 ***"Toxicokinetic Studies"*** sections of this document. In the endothelium, alkylbenzenes present in the blood cause irritation, which may lead to various effects including gross hemorrhage. These changes are often seen in the lungs of animals exposed to alkylbenzenes via gavage, subcutaneously, or i.p. (Gerarde, 1959). Gerarde (1959) also states that due to their high lipophilic nature, alkylbenzenes can cause CNS effects that can lead to sluggishness, narcosis, coma, and anesthesia. Based on toxicity manifestation in these tissues, Gerarde (1959) states that branched alkylbenzenes are more toxic compared to the 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 sec-butylbenzene and three potential surrogates are generally comparable (i.e., molecular weight, melting point, boiling point, and logKow). The major differences are water solubility and vapor pressure at room temperature (see Table A.3). Ethylbenzene seems to be the "outlier," while the values of these two properties are more similar among *sec*-butylbenzene, isopropylbenzene, and *n*-butylbenzene. It is noteworthy that the physicochemical properties of *sec*-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, 2005a). Genotoxic results for ethylbenzene were mixed with positive results seen in in vitro tests using human lymphocytes (sister chromatid exchange) and negative results seen in Syrian hamster embryo cells (cell transformation; HSDB, 2005b). Genotoxicity data for *sec*-butylbenzene and *n*-butylbenzene were not located; thus a comparison between *sec*-butylbenzene's genotoxic potential and that of the other three alkylbenzenes (isopropylbenzene, *n*-butylbenzene, and ethylbenzene) is not feasible. However, it is likely that *sec*-butylbenzene would not be genotoxic based on analogy to isopropylbenzene.

In conclusion, an attempt was made to derive toxicity values for *sec*-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 either IRIS, HEAST, or PPRTV databases. 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 *sec*-butylbenzene. Common target organs among the potential surrogates include kidneys and liver, with kidneys likely to be the most sensitive endpoint for *sec*-butylbenzene based on the structural information and critical effects (branched vs. linear; see Table A.3).

Overall, based on weight-of-evidence of all the information presented above, isopropylbenzene appears to be the most appropriate surrogate for *sec*-butylbenzene (high similarity score, similar toxicokinetic profile and target organs, and comparable acute toxicity; see Tables A.1−3 and C.1). The information presented in the sections above supports isopropylbenzene (cumene) as a better surrogate for *sec*-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 *sec*-butylbenzene:

- Similar patterns in absorption, distribution, and excretion (Gerarde, 1959)
- Similar patterns in metabolic activation and elimination (Gerarde, 1959)
- Similar physicochemical properties (see Table A.3)
- Similar structure
    - Structural similarity of 81.4% using the DSSTox database (www.epa.gov/dsstox) and 53% using ChemIDplus (2010)
    - Both isopropylbenzene and *sec*-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)
- Similar patterns in ototoxicity: branched alkylbenzenes did not cause ototoxicity (Gagnaire and Langlais, 2005)
- Similar patterns in acute toxicities (see Table A.2)
- Higher acute toxicity of isopropylbenzene compared to *sec*-butylbenzene (see Table A.2)

Table A.3. Comparison of Available Toxicity Data for *sec*-Butylbenzene and Potential Surrogates[a]

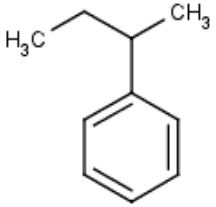
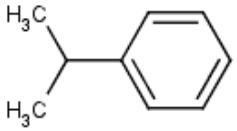
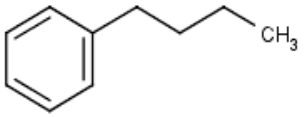
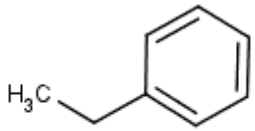
Characteristic	*sec*-Butylbenzene	Isopropylbenzene (Cumene)[b]	*n*-Butylbenzene	Ethylbenzene[b]
Structure				
CASRN	135-98-8	98-82-8	104-51-8	100-41-4
Molecular formula	C10-H14	C9-H12	C10-H14	C8-H10
Molecular weight	134.221	120.194	134.221	106.167
ChemIDplus similarity score (%)	100	NA	NA	NA
DSSTox similarity score (%)	100	81.4	83.8	77.7
Melting point (°C)	-8.27×10^{1}	-9.6×10^{1}	-8.79×10^{1}	-9.49×10^{1}
Boiling point (°C)	173.5	152.4	183.3	131.6
Vapor pressure (mm Hg at 25°C)	1.75	4.5	1.06	9.6
Water solubility (mg/L) at 25°C	17.6	61.3	11.8	169
Log Kow	4.57	3.66	4.38	3.15
pKa	NA	NA	NA	NA
Oral LD_{50} in rats (route: effect)	1920 mg/kg (oral; none)	1400 mg/kg (oral: 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.3. Comparison of Available Toxicity Data for *sec*-Butylbenzene and Potential Surrogates[a]

Characteristic	*sec*-Butylbenzene	Isopropylbenzene (Cumene)[b]	*n*-Butylbenzene	Ethylbenzene[b]
Dermal LD_{50} in rabbits (route: effect)	>16mL/kg	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 the *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):

> *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 (3 mo) 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 *sec*-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, a UF of 10 for intraspecies variability, a partial UF of 3 to extrapolate from a less than chronic (194-day study) study to a chronic duration, and a partial UF of 3 for database deficiencies (lack of reproductive information). Based on the current understanding of the 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 [surrogate] 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 *sec*-butylbenzene.

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

While studies providing specific effects for *sec*-butylbenzene following oral exposures could not be located, the information regarding metabolism, absorption, and tissue specific toxicity provided in the Gerarde (1959) study, and the lack of ototoxicity in both *sec*-butylbenzene and isopropylbenzene (Gagnaire and Langalais, 2005), provide some confidence that the observed effects, or lack thereof, following long-term oral exposures to isopropylbenzene may also be expected following long-term oral exposures to *sec*-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 are presented.

APPENDIX C. POTENTIAL SURROGATES FROM DSSTOX AND CHEMIDPLUS WITH AVAILABLE VALUES FROM IRIS, PPRTV, AND HEAST DATABASES

Table C.1. Results of DSSTox and ChemIDplus Structure Similarity Search for *sec*-Butylbenzene

Oral Exposure—RfD						
Chemical Name	**Similarity Search Engine**	**Percent Similarity Match (DSSTox/ ChemIDplus)**	**IRIS Value (Chronic RfD)**	**PPRTV Value (Chronic RfD)**	**PPRTV Value (Subchronic RfD)**	**HEAST Value (Subchronic RfD)**
sec-Butylbenzene	DSSTox/ ChemIDplus	100	NA	NA[a]	NA[a]	NA
Isopropylbenzene	DSSTox/ ChemIDplus	81.4/53.0	1×10^{-1} mg/kg-day (U.S. EPA, 1997b)	NA	NA	4×10^{-1} mg/kg-day (U.S. EPA, 2003)
Ethylbenzene	DSSTox	77.7	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	83.8	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).

Note: NA = Not available.

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