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Provisional Peer-Reviewed Toxicity Values for

n-Propylbenzene
(CASRN 103-65-1)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
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Cincinnati, OH 45268

Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
kg	kilogram
L	liter
LEL	lowest-effect level
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
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose

PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR *n*-PROPYLBENZENE (CASRN 103-65-1)

Background

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

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

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

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

Disclaimers

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

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

Questions Regarding PPRTVs

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

INTRODUCTION

n-Propylbenzene (Figure 1) is an alkyl aromatic hydrocarbon that occurs naturally in coal and petroleum.

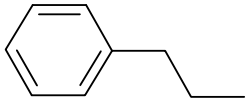

Figure 1. Structure of *n*-Propylbenzene

IRIS (U.S. EPA, 2008), the Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997a) and the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006) do not report noncancer or cancer assessments for *n*-propylbenzene. The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994) includes a Drinking Water Health Advisory for *n*-propylbenzene (U.S. EPA 1987) that characterizes the data for this compound as inadequate for risk assessment. *n*-Propylbenzene has not been assessed by the Agency for Toxic Substances and Disease Registry (ATSDR, 2008), the International Agency for Research on Cancer (IARC, 2008), or the International Programme on Chemical Safety (IPCS, 2008). The National Toxicology Program (NTP) has not evaluated the toxicity or carcinogenicity of this compound (NTP, 2008), and *n*-propylbenzene is not included in the 11th Report on Carcinogens (NTP, 2005). No occupational exposure limits have been established for *n*-propylbenzene (ACGIH, 2007; NIOSH, 2008a,b; OSHA, 2008).

To identify toxicological information pertinent to the derivation of provisional toxicity values for *n*-propylbenzene, literature searches were conducted in December 2007 using the following databases: MEDLINE, TOXLINE, DART/ETIC, BIOSIS (January 2000–December 2007), TSCATS1/2, GENETOX, CCRIS, HSDB, RTECS and Current Contents (July – December, 2007). Except where noted, the literature searches were not limited by date. An

updated literature search was conducted from December 2007 through November 2008 using PubMed. No relevant papers were identified.

REVIEW OF PERTINENT DATA

Human Studies

No data specifically relating exposure to *n*-propylbenzene with health effects in humans were located. NAS (1977) reported that in humans, *n*-propylbenzene is irritating to mucous membranes, eyes, nose, throat and skin, and that systemically it causes depression of the central nervous system, headache, anorexia, muscular weakness, incoordination, nausea, vertigo, paresthesia, mental confusion and unconsciousness. However, review of Thienes and Haley (1972), cited by NAS (1977) as the source of this information, suggests that the discussion therein was a general presentation of effects for alkylbenzenes—not effects specifically based on data for *n*-propylbenzene.

Animal Studies

Oral Exposure

With regard to oral toxicity, the information provided in the NAS (1977) summary of the *n*-propylbenzene rabbit study (Gerarde and Ahlstrom, 1966) lacks sufficient detail for risk-assessment purposes. No dose-response relationship can be determined from the 2-week ototoxicity study of Gagnaire and Langlais (2005). No other data pertaining to repeated oral exposure are available for *n*-propylbenzene.

NAS (1977) summarized the results of a 6-month oral study with *n*-propylbenzene in rabbits. The study is referenced to Gerarde and Ahlstrom (1966), but the complete citation is not provided, and efforts to identify and obtain the full reference proved unsuccessful. NAS (1977) states that

> "In a 6-month subchronic oral study (Gerarde and Ahlstrom, 1966) groups of 15 rabbits were fed propylbenzene at 0.25 and 2.5 mg/kg/day. The test animals did not differ from the controls in general appearance, body weight, organ weights, and protein function of the liver. There was a 7% decrease in red-cell count in the high-dosage group that was not significant. Hemosiderin was deposited in the spleens of the high-dosage animals, indicating red-cell destruction. There was a nonsignificant leukocyte increase in both dosage groups. Individual animals exhibited mild protein dystrophy of the liver and kidneys."

Gagnaire and Langlais (2005) tested the relative ototoxicity of 21 aromatic solvents, including *n*-propylbenzene. In their studies, groups of 7–8 young male Sprague-Dawley rats were administered 8.47 mmol/kg of chemical (in a volume of 2 mL/kg [olive oil vehicle]) by

gastric intubation for 5 days/week for a 2-week period[1]. For *n*-propylbenzene, a molar concentration of 8.47 mmol/kg is equivalent to a dose of 1018 mg/kg-day. After dosing, body weights were measured daily during the 2 weeks of treatment, then for a subsequent 10 days after the period of treatment. The behavior and general health of rats was observed on a daily basis. At the end of the 10-day recovery period, 6 rats per treatment group were chosen randomly, deeply anesthetized and perfused with buffered paraformaldehyde and glutaraldehyde. Subsequently, 3 left and 3 right cochleas were removed from the 6 chosen rats in each group and processed. Organs of Corti and basilar membranes were examined by light microscopy and scanning electron microscopy.

No treatment-related clinical signs were observed with *n*-propylbenzene. Of the 21 solvents tested, the following 8 caused histological lesions (loss of hair cells) in the organ of Corti (listed from most to least toxic based on cytocochleograms[2]): allylbenzene, ethylbenzene, styrene, *n*-propylbenzene, *p*-xylene, toluene, *trans*-β-methylstyrene and α-methylstyrene. Among the chemicals considered to be of intermediate toxicity, *n*-propylbenzene is associated with outer hair cell losses predominantly in the middle of the cochlea, with some apical loss in 4/8 animals tested and no hair loss in the basal portion.

Following an examination of octanol/water partition coefficients for the chemicals tested, Gagnaire and Langlais (2005) concluded that there was no correlation between ototoxicity and lipophilicity. Gagnaire and Langlais described the chemical structure-activity relationship SAR descriptors that contribute to ototoxicity as the following: (1) single side chain on the aromatic ring, except with *p*-xylene; (2) no branch for the side-chain; (3) number of side-chain carbon atoms of 1 to 3 (Cn-1,2,3) only; and (4) unsaturation of the side chain. Given that only one concentration was tested, a free-standing LOAEL of 1018 mg/kg-day based on histological evidence of hearing loss is identified for *n*-propylbenzene in this study.

Inhalation Exposure

No chronic, subchronic, developmental, or reproductive toxicity studies conducted by the inhalation route of exposure were located for *n*-propylbenzene.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC TOXICITY VALUES FOR *n*-PROPYLBENZENE (RfDs, RfCs)

Due to a lack of data, no chronic or subchronic RfDs or RfCs are developed. However, the Appendix of this document contains Screening Values (RfD and RfC), based on an analog treatment, that may be useful in certain instances. Please see the attached Appendix for details.

[1]The dose was selected on the basis of previous range-finding studies conducted with toluene. The chosen dose is associated with outer hair cell loss in the middle turn of the organ of Corti without causing mortality or body-weight loss.

[2] Cytocochleograms are 3-dimensional graphs based on counts of the inner hair cells (IHC) and three rows of outer hair cells (OHC) in the organ of Corti.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR *n*-PROPYLBENZENE

Weight-of-Evidence Descriptor

Under the 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), there is "*Inadequate Information to Assess the Carcinogenic Potential*" of *n*-propylbenzene; there are no human epidemiology studies, chronic toxicity studies, or carcinogenicity assays. The available mutagenicity studies with *Salmonella typhimurium* have been negative.

Quantitative Estimates of Carcinogenic Risk

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

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APPENDIX A. DERIVATION OF A SCREENING VALUE FOR *n*-PROPYLBENZENE (CASRN 103-65-1)

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for *n*-propylbenzene. 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. In the OSRTI hierarchy, Screening Values are considered to be below Tier 3, "Other (Peer-Reviewed) Toxicity Values."

Screening Values are intended for use in limited circumstances when no Tier 1, 2, or 3 values are available. Screening Values may be used, for example, to rank relative risks of individual chemicals present at a site to determine if the risk developed from the associated exposure at the specific site is likely to be a significant concern in the overall cleanup decision. Screening Values are not defensible as the primary drivers in making cleanup decisions because they are based on limited information. Questions or concerns about the appropriate use of Screening Values should be directed to the Superfund Health Risk Technical Support Center.

The free-standing LOAEL based on ototoxicity of 1018 mg/kg-day (highest dose tested) in a 2-week study (Gangnaire and Langlais, 2005) could serve as a basis for development of a subchronic screening p-RfD. A composite UF of 10,000 would be required (10 for intra- and 10 for interspecies extrapolation, 10 for LOAEL to NOAEL extrapolation and 10 for database deficiencies (no developmental or reproductive studies). This would provide a subchronic screening p-RfD of 0.1 or 1E-01 mg/kg-day. Because of the large composite uncertainty factor (UF) and inherent loss in confidence, a stronger case can be made for using the current IRIS values for ethylbenzene toxicity, as a surrogate for *n*-propylbenzene. Although the screening chronic RfD based on the IRIS value, derived by analogy to ethylbenzene, is identical to the proposed screening subchronic p-RfD with a composite UF of 10,000, use of ethylbenzene as a surrogate is better supported.

To evaluate the possibility of deriving toxicity values for *n*-propylbenzene on the basis of structural analogs, selective information on the toxicity of cumene (isopropylbenzene) and ethylbenzene based on structural similarity are presented in the following sections. Comparison of these compounds is provided on the basis of toxicokinetics, acute lethality, parenteral exposure, neurotoxicity and genotoxicity**.**

Toxicokinetics

The available information on the absorption and elimination of *n*-propylbenzene, ethylbenzene and cumene suggest that all three chemicals are readily absorbed and rapidly excreted, primarily in the urine (Theienes and Haley, 1972; El Masry et al., 1956, Senczuk and Litewka, 1976, Bardodej and Bardodejova, 1970; Gromiec and Piotrowski, 1984; Research Triangle Institute, 1989). Table 1 presents a comparison of the available absorption data.

Table 1. Comparative Absorption Data for *n*-Propylbenzene and Analogs

Chemical	Route	Species	Absorption	Basis	Reference
Ethylbenzene	Oral	Rabbit	73-83 %	Elimination of metabolites in urine	El Masry et al., 1956
	Inhalation	Human	49-64%	Retention in lungs	Bardodej and Bardodejova, 1970; Gromiec and Piotrowski, 1984
n-Propylbenzene	Oral	Rabbit	62%	Elimination of metabolites in urine	El Masry et al., 1956
	Inhalation	No data	No data	No data	No data
Cumene (Isopropyl benzene)	Oral	Rat	≥70%	Elimination of metabolites in urine	Research Triangle Institute, 1989
	Inhalation	Rat	≥70%	Elimination of metabolites in urine	Research Triangle Institute, 1989
		Human	50%	Retention in lungs	Senczuk and Litewka, 1976

The metabolism of *n*-propylbenzene has been studied in rats and rabbits. El Masry et al. (1956) fed *n*-propylbenzene to rabbits (3 mmol/kg [361 mg/kg] for a total of 13.8 grams/rabbit) and collected the urine for 24 hours after dosing. Based on the administered dose, 15% was excreted in the urine as hippuric acid and 47% was excreted in the urine as conjugates of glucuronic acid (glucuronides of ethylphenyl carbinol and benzylmethylcarbionol). In a similar protocol with ethylbenzene, 31% of the administered dose (also 3 mmol/kg [318 mg/kg]) was excreted in the urine as hippuric acid, 32% was excreted as conjugates of glucuronic acid, and 10–20% was excreted in the urine as phenaceturic acid.

Using microsomes isolated from male rabbits, Sato and Nakajima (1979) determined the rate of metabolism of various solvents in lung and liver tissue. Table 2 summarizes the results for *n*-propylbenzene, ethylbenzene and cumene.

Table 2. Mean Rates of Metabolism *In Vitro* in Tissues Isolated from Five Male Rabbits[a]

	Rate of Metabolism					
	nmol/g-10 min		µmol/organ-10 min		nmol/nmol cytp450-10 min	
Substrate	Liver	Lung	Liver	Lung	Liver	Lung
Ethylbenzene	453.0	680.3	34.4	5.3	11.7	200.1
n-Propylbenzene	740.2	1187.6	56.2	9.2	19.1	349.3
Cumene	1021.1	12,436.2	77.6	11.1	26.4	422.4

[a]Sato and Nakajima, 1979

Pyykko et al. (1987) demonstrated that various aromatic hydrocarbons induce pulmonary and hepatic enzymes following a single i.p. injection (5 mmol/kg) of each solvent. Table 3 summarizes the significant results for *n*-propylbenzene, ethylbenzene and cumene.

Table 3. Induction or Depression of Pulmonary and Liver Enzymes in Microsomes Isolated from Male Rats[a]

	Significantly Increased or Decreased Enzymes Relative to Controls					
	Ethylbenzene		*n*-Propylbenzene		Cumene	
Enzyme	**Liver**	**Lung**	**Liver**	**Lung**	**Liver**	**Lung**
Cytochrome P450	Yes increase	Yes decrease	Yes increase	Yes decrease	Yes increase	Yes decrease
Aryl hydrocarbon hydroxylase	Yes increase	Yes decrease	Yes increase	No change	Yes increase	No change
7-Ethoxycumarin-O-deethylase	Yes increase	Yes decrease	Yes increase	Yes decrease	Yes increase	No change
Cytochrome b5	No change	No change	No change	No change	Yes increase	No change
NADPH cytochrome c reductase	Yes increase	No change	Yes increase	No change	Yes increase	No change

[a]Pyykko et al., 1987

Further studies (Backes et al., 1993; Yuan et al., 1995) conducted with male rats injected intraperitoneally with various aromatic hydrocarbons demonstrate that the effects of the various hydrocarbons on the different isozymes of cytochrome p450 and p450 mRNA are complicated. Both *n*-propylbenzene and ethylbenzene have a similar protein induction pattern: both substrates induced p4502B1 and -2B2 but suppressed -2C11 in rat liver (Backes et al., 1993). However, the pattern of mRNA induction is different for *n*-propylbenzene and ethylbenzene and does not correlate with the observed effects of these chemicals on induction of the enzymes (Yuan et al., 1995). mRNA associated with p4502B1 is not elevated for any hydrocarbon tested and mRNA associated with p4502B2 is elevated relative to controls only for the larger hydrocarbons, including ethylbenzene and *n*-propylbenzene. P450C11 mRNA is not suppressed by *n*-propylbenzene or any other hydrocarbon tested except for ethylbenzene.

Sato and Nakajima (1979) report a human blood:air partition coefficient of 47 for propylbenzene measured using preserved human blood containing 13% by volume (v/v) of blood preserving solution (2.2 g sodium citrate, 0.8 g citric acid and 2.2 g glucose in 100 mL). Blood:air partition coefficients of 28.4 and 37.0 were measured in the same system for ethylbenzene and cumene, respectively.

Acute Lethality

Table 4 presents acute oral and inhalation toxicity values for *n*-propylbenzene, ethylbenzene and cumene. When exposure is by the oral route, ethylbenzene and cumene are clearly more acutely toxic to rats than *n*-propylbenzene. However, the relative acute toxicity of the three analogs is not strictly comparable for inhalation exposure due to a lack of studies that use the same species and exposure duration.

Table 4. Acute Toxicity of *n*-Propylbenzene and Possible Analogs[a]

Chemical	Ethylbenzene	*n*-Propylbenzene	Cumene
Oral LD_{50} (mg/kg-day)	3500[b], rat	6040, rat	1400[b], rat
Mortality in fasted rats following single gavage dose of 2.5 ml in olive oil[c]	7/10	3/10	6/10
Inhalation LC_{50} (ppm)	4000 (4 hr)[d], mouse	65,000 (2 hr), rat	8000 (4 hr)[e], rat

[a]ChemIDPlus (2008) unless noted otherwise
[b]Wolf et al., 1956
[c]Gerarde, 1959
[d]Smyth et al. 1962
[e]Gerarde, 1960; ChemIDplus incorrectly cites this value as an LClo

Parenteral Exposure

Six groups of Wistar rats (40 males/group) weighing 125–150 grams each were given daily subcutaneous injections of olive oil (control), benzene, toluene, ethylbenzene, *n*-propylbenzene, or *n*-butylbenzene (all chemicals were 99% pure) for a period of 2 weeks (Gerarde, 1956). The dose for each chemical was 1 mL/kg in an equal volume of olive oil, and injections were given in a different area of skin each day. Assuming the densities shown in Table 5 (below), the doses for *n*-propylbenzene and ethylbenzene were 862 and 867 mg/kg-day, respectively. Groups of 10 animals per chemical were sacrificed at weekly intervals during exposure and at 10-day intervals over a 3-week recovery period. The following observations were made for each animal: appearance, behavior, activity, and food/water consumption, stool appearance, body weight, fur and skin appearance, irritation of subcutaneous tissues at site of injection, hematology (peripheral leukocyte count, microhematocrit, total femoral marrow nucleated cell count) and bone marrow biochemistry (total femoral marrow RNA and DNA). A gross and microscopic examination of tissues and internal organs, thymus and spleen weight and an examination of site of injection tissue as well as a gross and microscopic examination of bone marrow was also conducted.

The authors considered the responses observed following treatment with all chemicals—except benzene—to be similar and, therefore, grouped them together as *n*-alkylbenzenes for the purposes of presentation of results and discussion (Gerarde, 1956). Rats exposed to *n*-propylbenzene, ethylbenzene and the other *n*-alkylbenzenes had 5% mortality and diminished activity (attributed to CNS depression) but were considered to be normal in appearance. The *n*-alkylbenzenes were considered to be more irritating than benzene and caused induration of subcutaneous tissue at the sites of injection. The *n*-alkylbenzenes had no effect on body-weight gain relative to controls throughout the treatment and recovery periods. The *n*-alkylbenzenes had no effect on hematocrit, leukocyte count, or the femoral bone marrow nucleated cell population during any period of treatment or recovery. Rats treated with *n*-alkylbenzenes had slightly elevated femoral marrow DNA and RNA relative to controls during the exposure period. The authors considered elevated nucleic acids to be indicative of hyperplastic marrow resulting from inflammatory response to the injected materials. The study authors contend that *n*-alkylbenzenes caused subcutaneous irritation, but they did not report treatment-related pathological changes in other tissues or organs (specifics not reported other than for spleen and thymus). These results

suggest that the toxic effects caused by *n*-propylbenzene and ethylbenzene (and other *n*-alkylbenzenes) are qualitatively similar.

Neurotoxicity

The acute neurobehavioral toxicity of 6 different alkylbenzenes was evaluated by a functional observational battery (FOB) (Tegeris and Balster, 1994). Groups of adult male Charles River/Swiss mice (8/group) were exposed by whole-body inhalation for 20 minutes to benzene, toluene, ethylbenzene, *n*-propylbenzene, m-xylene, or cumene over a range of 3 concentrations (2000, 8000 or 14,000 ppm for *n*-propylbenzene; 2000, 4000 or 8000 for cumene and ethylbenzene). Two additional groups were used as air-exposed controls. In order to compare the results of alkylbenzene exposure with the known effects of pentobarbital, a separate group of 8 mice was injected intraperitoneally with pentobarbital (each mouse tested sequentially with 0, 5, 10, 20, 30 or 40 mg/kg). The authors point out that the purpose of their study was to make qualitative—rather than quantitative—comparisons between the chemicals tested with pentobarbital, a known CNS depressant. Therefore, strict quantitative comparisons between the chemicals are not supported by their results. That said, general comparisons are possible for ranges of concentrations as follows.

All of the alkylbenzenes tested and pentobarbital exhibited nearly identical profiles of effects at a concentration range of 2000–8000 ppm when the individual measures of the FOB are taken into account (Tegeris and Balster, 1994). Relative to air-exposed controls, these effects include changes in posture, decreased arousal and rearing, increased ease of handling, disturbances in gait, mobility and righting reflex, decreased forelimb grip strength, increased landing foot splay, and impaired psychomotor coordination. Results for *n*-propylbenzene-exposed rats are statistically different from controls for 15/23 assessed endpoints. Detailed results for 6/23 assessed endpoints are presented for each of the chemicals tested in the report. Based on the reported results, the LOAEL for *n*-propylbenzene in the study is 2000 ppm (lowest dose tested) for statistically significant decreases in rearing effect in mobility (during exposure), righting reflex and forelimb grip strength, and a signficant increase in hindlimb foot splay, relative to controls. Other endpoints may have achieved statistical significance at this concentration, but because they are not reported individually for each chemical, the dose-response details are not discernable. Of the two remaining endpoints reported in detail for each chemical (inverted screen test of motor coordination, touch response), a dose-related statistical difference from controls was achieved at the 8000- and 14,000-ppm concentrations, but not at 2000 ppm, for *n*-propylbenzene. Similar dose-response patterns (i.e., similar shapes of dose-response curves and nearly identical exposure concentrations that were statistically significant for the endpoints discussed above with regard to *n*-propylbenzene) were observed for cumene and ethylbenzene, with LOAEL values of 2000 ppm for each of those chemicals. Similar results were also obtained for pentobarbital in terms of the direction of response and general shape of the dose-response curve, suggesting that these findings might be generally applicable to CNS depressants.

n-Methyl-D-aspartate (NMDA) receptors are ionotropic receptors that have been studied as targets of CNS depression. Using recombinant NMDA receptors expressed in *Xenopus* oocytes, Cruz et al. (2000) tested the inhibition of these receptors by commonly abused inhalant solvents—including *n*-propylbenzene—to determine whether a common mechanism of action mediated through the NMDA receptor was possible. All of the solvents tested—including *n*-propylbenzene—caused a reversible inhibition of NMDA-induced membrane currents that was dose- and subunit-dependent. The median inhibition concentrations (IC_{50}) for *n*-propylbenzene and ethylbenzene, corrected for solvent evaporation, are 0.35 and 0.17 mM, respectively. Cumene is not tested in this study. The results of this study are congruent with the observation that *n*-propylbenzene is a CNS depressant that, along with some other abused inhalants, displays pharmacological selectivity for specific NMDA receptors, but this do not provide sufficient evidence to conclude that a common mechanism of action is appropriate for the solvents tested. However, this study does provide a basis for the CNS effect using ethylbenzene as the surrogate for the derivation of an RfD—provided that the CNS effect is the most sensitive endpoint.

Genotoxicity

n-Propylbenzene, ethylbenzene and cumene each were not found to be mutagenic in Ames tests conducted with *Salmonella typhimurium*—regardless of the presence or absence of metabolic activation (Florin et al., 1980; Jensen et al., 1988; Dean et al. 1985; Degirmenci et al. 2000, Kubo et al. 2002; Nestmann et al. 1980; NTP 1986, 1999; Lawlor and Wagner, 1987). No further tests of genotoxicity have been reported for *n*-propylbenzene. A fairly complete battery of *in vitro* and *in vivo* genotoxicity tests, in addition to those reported above, have been conducted for cumene and ethylbenzene, with predominantly negative results (ATSDR, 2007; U.S. EPA, 1997b).

Ethylbenzene (C_8H_{10}) and cumene (C_9H_{12}) are structurally similar to *n*-propylbenzene, but ethylbenzene appears to be the more appropriate analog for *n*-propylbenzene (Table 5).

Table 5. Structures and Physical/Chemical Properties of *n*-Propylbenzene and Possible Analogs[a]

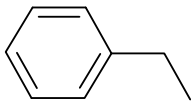
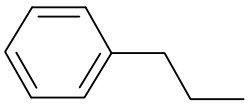
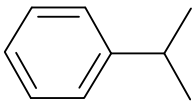
Chemical	**Ethylbenzene**	***n*-Propylbenzene**	**Cumene**
Structure			
CASRN	100-41-4	103-65-1	98-82-8
ChemID Plus Similarity Search[b]	56%	–	<50%
Molecular formula	C_8H_{10}	C_9H_{12}	C_9H_{12}
Molecular weight	106.16	120.19	120.19
Melting point (ºC)	-94.9	-99.5	-96.03
Boiling point (ºC)	136.1	159.2	152.39
Vapor Pressure (mmHg)	9.6 @ 25 ºC	3.42 @ 25 ºC	4.5 @ 25 ºC
Henry's Law Constant (atm-m^3/mole)	0.00788 @ 25 ºC	0.0105 @ 25 ºC	0.0115 @ 25 ºC
Water solubility (g/L)	169 @ 25 ºC	52.2 @ 25 ºC	61.3 @ 25 ºC

Table 5. Structures and Physical/Chemical Properties of *n*-Propylbenzene and Possible Analogs[a]

Chemical	Ethylbenzene	*n*-Propylbenzene	Cumene
Specific gravity/density	0.8670 @20 ºC/4 ºC	0.8620 @ 20 ºC/4 ºC	0.8620 @ 20 ºC/4 ºC
Log K_{ow}	3.15 @ 25 ºC	3.69 @ 25 ºC	3.66

[a]ChemIDPlus (2008)
[b]The ChemID Plus Similarity Search function characterizes the similarity of compounds. In this case, it was used to determine the similarity of ethylbenzene and Cumene to *n*-propylbenzene. Note that 100% indicates an exact match; 56% is not high, but it is high enough to suggest that some structural-related property can be applied using SAR analysis. The low similarity score (≤50%) for cumene suggests that cumene is not a strong surrogate candidate.

The scope of information available in support of using either cumene or ethylbenzene as an analog for *n*-propylbenzene is limited. However, based on information presented in the previous sections, the following factors can be considered.

Factors supporting the use of ethylbenzene as an analog for *n*-propylbenzene:

- Similar patterns of gastrointestinal and pulmonary absorption and elimination of metabolites in the urine (Table 1).
- Similar, but not identical, patterns of metabolism (El Masry et al., 1956) and pulmonary and liver metabolic enzyme induction (Pyykko et al., 1987; Sato and Nakajima, 1979; Backes et al., 1993).
- A similar pattern of ototoxicity (Gagnaire and Langlais, 2005). In addition, the ototoxicity of 21 solvents was not related to lipophilicity, suggesting that structural—rather than physical/chemical properties—have a greater influence on this critical endpoint.
- A similar pattern of neurological effects (Tegeris and Balster, 1994; Cruz et al., 2000). However, these findings appear to be broadly applicable to CNS depressants, and, therefore, are too general to provide strong support for use of ethylbenzene as a surrogate for *n*-propylbenzene.
- Ethylbenzene is more toxic than *n*-propylbenzene with regard to acute oral toxicity (Table 4) and ototoxicity (Gagnaire and Langlais, 2005); therefore, using ethylbenzene as a surrogate would likely be protective of potential *n*-propylbenzene toxicity.
- Structural similarity = 56%

Factors inconsistent with the use of cumene as an analog for *n*-propylbenzene:

- Branched chain structure.
- No ototoxicity because of the branched chain structure (Gagnaire and Langlais, 2005).

Taken together, the above factors support the selection of ethylbenzene over cumene as the basis for toxicity screening values for *n*-propylbenzene. Further considerations are discussed with regard to the derivation of oral and inhalation values below.

Oral Toxicity Values

Screening subchronic RfD and screening chronic RfD

For *n*-propylbenzene, the IRIS chronic RfD for ethylbenzene (1E-01 or 0.1 mg/kg-day), derived in June 1991 and based on liver and kidney toxicity in a subchronic rat study (Wolf et al., 1956), is recommended as a screening RfD based on the surrogate analysis presented here. IRIS used a NOEL of 136 mg/kg-day (converted to 97.1 mg/kg-day) and applied a composite UF of 1000 including 10 for interspecies- and 10 for intraspecies extrapolation and 10 to extrapolate from subchronic to chronic exposure duration.

Based on the analysis of structure-activity relationships presented here, **the IRIS chronic RfD of 1E-01 or 0.1 mg/kg-day for ethylbenzene is recommended for the screening chronic RfD for *n*-propylbenzene.** Also, as indicated earlier, using a 2-week LOAEL of 1080 mg/kg-day for ototoxicity induced by n-propylbenzene with the application of a composite UF of 10,000 would give an identical value.

Given the lack of data on n-propylbenzene and the uncertainty associated with the use of a surrogate for the derivation of the toxicity values, the same value, 1E-01 or 0.1 mg/kg-day, is recommended for the screening subchronic RfD.

While the Gerarde and Ahlstrom (1966) study cited by NAS (1977) suggests the possibility of mild liver and kidney effects attributable to *n*-propylbenzene following repeated oral exposure, the study cannot be located for detailed scrutiny. The similarities between ethylbenzene and *n*-propylbenzene observed in short-term studies (e.g., Gagnaire and Langlais, 2005) and the suggestion of liver or kidney toxicity tentatively identified in the Gerarde and Ahlstrom (1966) study cited by NAS (1977) raise confidence that these effects would also be observed following longer-term exposures, as they are with ethylbenzene.

Inhalation Toxicity Values

Inhalation values are based on using ethylbenzene as a surrogate.

For ethylbenzene, IRIS provides a chronic RfC of 1 or 1E+0 mg/m^3 (100 ppm) based on Andrews et al. (1981) and Hardin et al. (1981) on developmental toxicity. IRIS chose a composite UF of 300 (10 for intra- and 3 for interspecies extrapolation and 10 for database deficiencies (lack of multigenerational reproductive and chronic studies). **Based on the argument by analogy presented here, the chronic screening value RfC of 1 or 1E+0 mg/m^3 is recommended for *n*-propylbenzene.**

Because the IRIS RfC (for ethylbenzene) is based on developmental studies, the same value is recommended as a screening subchronic RfC: 1 or 1E+0 mg/m^3.

The ototoxicity observed in rats by Gagnaire and Langlais (2005) was investigated further in a subchronic rat study using ethylbenzene by the inhalation route of exposure (Gagnaire et al., 2007). Given that the ototoxicity of ethylbenzene was shown to be

quantitatively greater, but qualitatively similar to that shown by *n*-propylbenzene following short-term oral exposure (Gagnaire and Langlais, 2005), it is probable that a similar result would be obtained following inhalation exposure if *n*-propylbenzene had been tested in parallel with ethylbenzene.

The current IRIS RfC of 1 mg/m^3 for ethylbenzene is based on developmental toxicity studies (Andrew et al., 1981; Hardin et al., 1981). Subsequent developmental toxicity studies support the results of these earlier studies. The subchronic ototoxicity study by Gagnaire et al. (2007) suggests that ototoxicity may be the most sensitive endpoint for inhalation exposure to ethylbenzene. However, at this time, the best available information supports utilization of the existing IRIS values.