

# Provisional Peer-Reviewed Toxicity Values for *p*-Isopropyltoluene (CASRN 99-87-6)



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*p*-Isopropyltoluene  
(CASRN 99-87-6)

Center for Public Health and Environmental Assessment  
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Questions regarding the contents of this PPRTV document may be directed to the U.S. EPA Office of Research and Development (ORD) Center for Public Health and Environmental Assessment (CPHEA) website at <https://ecomments.epa.gov/pprtv>.

## TABLE OF CONTENTS

COMMONLY USED ABBREVIATIONS AND ACRONYMS .....	v
BACKGROUND .....	1
QUALITY ASSURANCE .....	1
DISCLAIMERS .....	2
QUESTIONS REGARDING PPRTVs .....	2
1. INTRODUCTION .....	3
2. REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER) .....	7
2.1. HUMAN STUDIES .....	11
2.2. ANIMAL STUDIES .....	11
2.2.1. Oral Exposures .....	11
2.2.2. Inhalation Exposures .....	15
2.3. OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS) .....	15
2.3.1. Genotoxicity .....	16
2.3.2. Supporting Animal Studies .....	20
2.3.3. Mode-of-Action/Mechanistic Studies .....	32
2.3.4. Metabolism/Toxicokinetic Studies .....	32
3. DERIVATION OF PROVISIONAL VALUES .....	35
3.1. DERIVATION OF ORAL REFERENCE DOSES .....	35
3.2. DERIVATION OF INHALATION REFERENCE CONCENTRATIONS .....	35
3.3. SUMMARY OF NONCANCER PROVISIONAL REFERENCE VALUES .....	35
3.4. CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR .....	36
3.5. DERIVATION OF PROVISIONAL CANCER RISK ESTIMATES .....	37
APPENDIX A. NONCANCER SCREENING PROVISIONAL VALUES .....	38
APPENDIX B. DATA TABLES .....	90
APPENDIX C. BENCHMARK DOSE MODELING RESULTS .....	99
APPENDIX D. PARAMETERS OF TOOLS USED FOR READ-ACROSS .....	115
APPENDIX E. REFERENCES .....	117

## COMMONLY USED ABBREVIATIONS AND ACRONYMS

$\alpha$ 2u-g	alpha 2u-globulin	IVF	in vitro fertilization
ACGIH	American Conference of Governmental Industrial Hygienists	LC <sub>50</sub>	median lethal concentration
AIC	Akaike's information criterion	LD <sub>50</sub>	median lethal dose
ALD	approximate lethal dosage	LOAEL	lowest-observed-adverse-effect level
ALT	alanine aminotransferase	MN	micronuclei
AR	androgen receptor	MNPCE	micronucleated polychromatic erythrocyte
AST	aspartate aminotransferase	MOA	mode of action
atm	atmosphere	MTD	maximum tolerated dose
ATSDR	Agency for Toxic Substances and Disease Registry	NAG	<i>N</i> -acetyl- $\beta$ -D-glucosaminidase
BMC	benchmark concentration	NCI	National Cancer Institute
BMCL	benchmark concentration lower confidence limit	NOAEL	no-observed-adverse-effect level
BMD	benchmark dose	NTP	National Toxicology Program
BMDL	benchmark dose lower confidence limit	NZW	New Zealand White (rabbit breed)
BMDS	Benchmark Dose Software	OCT	ornithine carbamoyl transferase
BMR	benchmark response	ORD	Office of Research and Development
BUN	blood urea nitrogen	PBPK	physiologically based pharmacokinetic
BW	body weight	PCNA	proliferating cell nuclear antigen
CA	chromosomal aberration	PND	postnatal day
CAS	Chemical Abstracts Service	POD	point of departure
CASRN	Chemical Abstracts Service Registry Number	POD <sub>ADJ</sub>	duration adjusted POD
CBI	covalent binding index	QSAR	quantitative structure-activity relationship
CHO	Chinese hamster ovary (cell line cells)	RBC	red blood cell
CL	confidence limit	RDS	replicative DNA synthesis
CNS	central nervous system	RfC	inhalation reference concentration
CPHEA	Center for Public Health and Environmental Assessment	RfD	oral reference dose
CPN	chronic progressive nephropathy	RGDR	regional gas dose ratio
CYP	cytochrome P450	RNA	ribonucleic acid
DAF	dosimetric adjustment factor	SAR	structure-activity relationship
DEN	diethylnitrosamine	SCE	sister chromatid exchange
DMSO	dimethyl sulfoxide	SD	standard deviation
DNA	deoxyribonucleic acid	SDH	sorbitol dehydrogenase
EPA	Environmental Protection Agency	SE	standard error
ER	estrogen receptor	SGOT	glutamic oxaloacetic transaminase, also known as AST
FDA	Food and Drug Administration	SGPT	glutamic pyruvic transaminase, also known as ALT
FEV <sub>1</sub>	forced expiratory volume of 1 second	SSD	systemic scleroderma
GD	gestation day	TCA	trichloroacetic acid
GDH	glutamate dehydrogenase	TCE	trichloroethylene
GGT	$\gamma$ -glutamyl transferase	TWA	time-weighted average
GSH	glutathione	UF	uncertainty factor
GST	glutathione S transferase	UF <sub>A</sub>	interspecies uncertainty factor
Hb/g A	animal blood gas partition coefficient	UF <sub>C</sub>	composite uncertainty factor
Hb/g H	human blood gas partition coefficient	UF <sub>D</sub>	database uncertainty factor
HEC	human equivalent concentration	UF <sub>H</sub>	intraspecies uncertainty factor
HED	human equivalent dose	UF <sub>L</sub>	LOAEL-to-NOAEL uncertainty factor
i.p.	intraperitoneal	UF <sub>S</sub>	subchronic-to-chronic uncertainty factor
IRIS	Integrated Risk Information System	U.S.	United States of America
		WBC	white blood cell

Abbreviations and acronyms not listed on this page are defined upon first use in the PPRTV assessment.

## PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR *p*-ISOPROPYLTOLUENE (CASRN 99-87-6)

### BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund program. PPRTVs are derived after a review of the relevant scientific literature using established U.S. Environmental Protection Agency (U.S. EPA) guidance on human health toxicity value derivations.

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.

Currently available PPRTV assessments can be accessed on the U.S. EPA's PPRTV website at <https://www.epa.gov/pprtv>. PPRTV assessments are eligible to be updated on a 5-year cycle and revised as appropriate to incorporate new data or methodologies that might impact the toxicity values or affect the characterization of chemical's potential for causing toxicologically relevant human-health effects. Questions regarding nomination of chemicals for update can be sent to the appropriate U.S. EPA eComments Chemical Safety website at <https://ecomments.epa.gov/chemicalsafety/>.

### QUALITY ASSURANCE

This work was conducted under the U.S. EPA Quality Assurance (QA) program to ensure data are of known and acceptable quality to support their intended use. Surveillance of the work by the assessment managers and programmatic scientific leads ensured adherence to QA processes and criteria, as well as quick and effective resolution of any problems. The QA manager, assessment managers, and programmatic scientific leads have determined under the QA program that this work meets all U.S. EPA quality requirements. This PPRTV assessment was written with guidance from the CPHEA Program Quality Assurance Project Plan (PQAPP), the QAPP titled *Program Quality Assurance Project Plan (PQAPP) for the Provisional Peer-Reviewed Toxicity Values (PPRTVs) and Related Assessments/Documents (L-CPAD-0032718-QP)*, and the PPRTV assessment development contractor QAPP titled *Quality Assurance Project Plan—Preparation of Provisional Toxicity Value (PTV) Documents (L-CPAD-0031971-QP)*. As part of the QA system, a quality product review is done prior to management clearance. A Technical Systems Audit may be performed at the discretion of the QA staff.

All PPRTV assessments receive internal peer review by at least two CPHEA scientists and an independent external peer review by at least three scientific experts. The reviews focus on whether all studies have been correctly selected, interpreted, and adequately described for the purposes of deriving a provisional reference value. The reviews also cover quantitative and qualitative aspects of the provisional value development and address whether uncertainties associated with the assessment have been adequately characterized.

## **DISCLAIMERS**

The PPRTV document provides toxicity values and information about the toxicologically relevant 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. 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.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

## **QUESTIONS REGARDING PPRTVs**

Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA ORD CPHEA website at <https://ecomments.epa.gov/pprtv>.

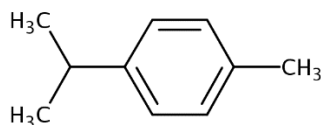
## 1. INTRODUCTION

*p*-Isopropyltoluene, CASRN 99-87-6, is a naturally occurring monoterpene also known as *p*-cymene. Its structure consists of a benzene ring, substituted with one methyl group and one isopropyl group in the *para*- (1 and 4) positions on the aromatic ring. *p*-Isopropyltoluene is the most common isomer; the other geometric isomers are *o*-isopropyltoluene (CASRN 527-84-4) and *m*-isopropyltoluene (CASRN 535-77-3), with alkyl groups substituted in the *ortho*- and *meta*- positions, respectively ([NLM, 2022a, c](#); [U.S. EPA, 2011d](#)).

*p*-Isopropyltoluene is preregistered with Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program ([ECHA, 2022](#)) and is listed on the U.S. EPA's Toxic Substances Control Act (TSCA) public inventory ([U.S. EPA, 2024c](#)). *p*-Isopropyltoluene is identified as a plant metabolite and human urinary metabolite ([NLM, 2022b](#)). It has a sweet aromatic, weak citrus odor, and is used to mask and improve the odor of products.

*p*-Isopropyltoluene is also used in lacquers and varnishes as a thinner and in solvents as a starting material and heat-transfer fluid ([NLM, 2022b](#)). *p*-Isopropyltoluene occurs naturally in foods including butter, carrots, nutmeg, orange juice, oregano, raspberries, and lemon oil, as well as a in number of essential oils ([FFHPVC, 2005](#)).

The empirical formula for *p*-isopropyltoluene is C<sub>10</sub>H<sub>14</sub>. The chemical structure is shown in Figure 1. Table 1 summarizes the physicochemical properties for *p*-isopropyltoluene. *p*-Isopropyltoluene is a colorless, transparent liquid. Its low water solubility and high vapor pressure indicate that this substance is hydrophobic and volatile and will exist predominantly in the vapor phase in air. Additionally, volatilization from water surfaces or moist soil surfaces is expected, based upon an estimated Henry's law constant of  $1.13 \times 10^{-2}$  atm·m<sup>3</sup>/mole at 25°C. In the atmosphere, *p*-isopropyltoluene has an estimated half-life of 1 day, calculated from an estimated rate constant of  $1.45 \times 10^{-11}$  cm<sup>3</sup>/molecule-second at 25°C for reaction with photochemically produced hydroxyl radicals ([NLM, 2022b](#); [Atkinson and Arey, 2003](#)). The estimated soil adsorption coefficient (K<sub>oc</sub>) for *p*-isopropyltoluene indicates moderate potential for mobility in soil; therefore, *p*-isopropyltoluene has the potential for migration into groundwater ([U.S. EPA, 2012b](#)). *p*-Isopropyltoluene is not expected to undergo hydrolysis due to its lack of hydrolysable functional groups.



**Figure 1. *p*-Isopropyltoluene (CASRN 99-87-6) Chemical Structure**

Property (unit)	Value <sup>a</sup>
Physical state	Liquid <sup>b</sup>
Boiling point (°C)	177
Melting point (°C)	-68.2
Density (g/cm <sup>3</sup> at 20°C)	0.8573 <sup>b</sup>
Vapor pressure (mm Hg at 25°C)	0.772
pH (unitless)	NA
Acid dissociation constant (pKa) (unitless)	NA
Solubility in water (mg/L at 25°C)	23.2 (reported as $1.73 \times 10^{-4}$ mol/L)
Octanol-water partition coefficient (log K <sub>ow</sub> )	4.10
Henry's law constant (atm-m <sup>3</sup> /mol at 25°C)	$7.94 \times 10^{-3}$ (predicted)
Soil adsorption coefficient K <sub>oc</sub> (L/kg)	$2.78 \times 10^3$ (predicted)
Atmospheric OH rate constant (cm <sup>3</sup> /molecule-sec at 25°C)	$1.51 \times 10^{-11}$
Atmospheric half-life (d)	1 <sup>b</sup>
Relative vapor density (air = 1)	4.62 <sup>b</sup>
Molecular weight (g/mol)	134.222
Flash point (°C)	47.2 (reported as 117°F open cup and closed cup) <sup>b</sup>

<sup>a</sup>Unless otherwise noted, average values were extracted from the U.S. EPA CompTox Chemicals Dashboard (<https://comptox.epa.gov/dashboard/chemical/details/DTXSID3026645>. Accessed May 21, 2024); [U.S. EPA \(2024a\)](#). Values are experimental unless otherwise specified.

<sup>b</sup>[NLM \(2022b\)](#); Values are experimental unless otherwise specified.

NA = not applicable; U.S. EPA = U.S. Environmental Protection Agency.

A summary of available toxicity values for *p*-isopropyltoluene from the U.S. EPA and other agencies/organizations is provided in Table 2.

Source (parameter) <sup>a,b</sup>	Value (applicability)	Notes	Reference <sup>c</sup>
<b>Noncancer</b>			
IRIS	NV	NA	<a href="#">U.S. EPA (2024b)</a>
HEAST	NV	NA	<a href="#">U.S. EPA (2011c)</a>
DWSHA	NV	NA	<a href="#">U.S. EPA (2018a)</a>
ATSDR	NV	NA	<a href="#">ATSDR (2021)</a>
WHO (safety evaluation)	No safety concern at the estimated intake levels of approximately 1,100 µg/person in Europe and 470 µg/person in the United States	Expected to be metabolized to innocuous products	<a href="#">WHO (2022, 2006)</a>

**Table 2. Summary of Available Toxicity Values and Qualitative Conclusions Regarding Carcinogenicity for *p*-Isopropyltoluene (CASRN 99-87-6)**

Source (parameter) <sup>a,b</sup>	Value (applicability)	Notes	Reference <sup>c</sup>
CalEPA	NV	NA	<a href="#">CalEPA (2022, 2020)</a>
OSHA	NV	NA	<a href="#">OSHA (2021a, 2021b, 2021c)</a>
NIOSH	NV	NA	<a href="#">NIOSH (2018)</a>
ACGIH	NV	NA	<a href="#">ACGIH (2021)</a>
TCEQ (RfD)	0.1 mg/kg-d	Basis for RfD not specified; value developed with TCEQ's protocol	<a href="#">TCEQ (2021, 2015)</a>
DOE (PAC)	PAC 1: 120 mg/m <sup>3</sup> PAC 2: 1,300 mg/m <sup>3</sup> PAC 3: 1,900 mg/m <sup>3</sup>	PAC-1 based on TEEL, PAC-2 based on unspecified rat 300-min TC <sub>Lo</sub> , PAC-3 based on unspecified rat 240-min LC <sub>Lo</sub>	<a href="#">DOE (2018)</a>
USAPHC (air-MEG)	1-h critical: 500 mg/m <sup>3</sup> 1-h marginal: 500 mg/m <sup>3</sup> 1-h negligible: 250 mg/m <sup>3</sup>	Based on TEELs	<a href="#">U.S. APHC (2013)</a>
<b>Cancer</b>			
IRIS	NV	NA	<a href="#">U.S. EPA (2024b)</a>
HEAST	NV	NA	<a href="#">U.S. EPA (2011c)</a>
DWSHA	NV	NA	<a href="#">U.S. EPA (2018a)</a>
NTP	NV	NA	<a href="#">NTP (2021)</a>
IARC	NV	NA	<a href="#">IARC (2021)</a>
CalEPA	NV	NA	<a href="#">CalEPA (2022, 2020)</a>
ACGIH	NV	NA	<a href="#">ACGIH (2021)</a>

<sup>a</sup>Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; DOE = U.S. Department of Energy; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; TCEQ = Texas Commission of Environmental Quality; USAPHC = U.S. Army Public Health Command; WHO = World Health Organization.

<sup>b</sup>Parameters: LC<sub>Lo</sub> = lowest reported lethal concentration; MEG = military exposure guideline; PAC = protective action criteria; RfD = reference dose; TC<sub>Lo</sub> = toxic concentration lowest; TEEL = temporary emergency exposure limit.

<sup>c</sup>Reference date is the publication date for the database and not the date the source was accessed.

NA = not applicable; NV = not available.

Non-date-limited literature searches were conducted in June 2019 and updated most recently in November 2023 for studies pertinent to understanding potential human health hazards of *p*-isopropyltoluene, CASRN 99-87-6. Searches were conducted using the U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches

the following databases: PubMed, TOXLINE<sup>1</sup> (including TSCATS1), Scopus, and Web of Science. The National Technical Reports Library (NTRL) was searched for government reports from 2020 through December 2022<sup>2</sup>. The following resources were searched outside of HERO for health-related values: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (CalEPA), Defense Technical Information Center (DTIC), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), European Chemicals Agency (ECHA), the U.S. EPA Chemical Data Access Tool (CDAT), the U.S. EPA ChemView, the U.S. EPA Integrated Risk Information System (IRIS), the U.S. EPA Health Effects Assessment Summary Tables (HEAST), the U.S. EPA Office of Water (OW), International Agency for Research on Cancer (IARC), the U.S. EPA TSCATS2/TSCATS8e, the U.S. EPA High Production Volume (HPV), Chemicals via International Programme on Chemical Safety (IPCS) INCHEM, Japan Existing Chemical Data Base (JECDB), Organisation for Economic Co-operation and Development (OECD) Screening Information Data Sets (SIDS), OECD International Uniform Chemical Information Database (IUCLID), OECD HPV, National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), Occupational Safety and Health Administration (OSHA), and World Health Organization (WHO).

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<sup>1</sup>TOXLINE was retired in December 2019. Searches of this database were conducted through July 2019.

<sup>2</sup>NTRL was a subset of TOXLINE until December 2019 when TOXLINE was discontinued. Searches of NTRL were conducted starting in 2020 to ensure that references were not missed due to delays in importing items into the database.

## 2. REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide overviews of the relevant noncancer and cancer evidence bases, respectively, for *p*-isopropyltoluene and include all potentially relevant subchronic, and chronic studies, as well as reproductive and developmental toxicity studies. These tables include studies for which no-observed-adverse-effect levels (NOAELs)/lowest-observed-adverse-effect levels (LOAELs) could be identified (the principal study is identified in bold). All NOAELs/LOAELs were identified by the U.S. EPA unless noted otherwise. The phrase “statistical significance” and term “significant,” used throughout the document, indicate a *p*-value of < 0.05 unless otherwise specified.

Table 3A. Summary of Potentially Relevant Noncancer Data for <i>p</i> -Isopropyltoluene (CASRN 99-87-6)							
Category <sup>a</sup>	Number of Male/Female, Strain Species, Study Type, Reported Doses, Study Duration	Dosimetry <sup>b</sup>	Critical Effects	NOAEL <sup>b</sup>	LOAEL <sup>b</sup>	Reference (comments)	Notes <sup>c</sup>
<b>Human</b>							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m <sup>3</sup> )							
ND							
<b>Animal:</b>							
1. Oral (mg/kg-d)							
Short-term	ND						
Subchronic	10 M/10 F, Sprague Dawley (CrI:CD) rat (gavage administration)  F: 2 wk prior to mating, continued through mating (up to 2 wk), gestation, and lactation until sacrifice on PND 13 (~63 d) M: 2 wk pre-mating and continued through mating (up to 2 wk) and postmating until sacrifice (~35 d)	0, 50, 100, 200	Biologically significant (>10%) and dose-related increases in liver weights (absolute and relative) in P <sub>0</sub> female rats at 50 and 100 mg/kg-d.  Corroborative evidence of liver toxicity included: biologically significant increases in absolute and relative liver weights in P <sub>0</sub> males at 200 mg/kg-d; dose-related increases in ALP in P <sub>0</sub> rats (statistically significant at 100 mg/kg-day in females and 200 mg/kg-day in males); increased hepatocyte hypertrophy in P <sub>0</sub> males and females mostly at ≥100 mg/kg-d.  Other effects occurring mostly at ≥200 mg/kg-d included decreased hindlimb grip strength and increased BUN and kidney lesions in P <sub>0</sub> males.	NA	50	<a href="#">ECHA (2019b)</a> ; <a href="#">Symrise (2018)</a>	NPR, PS
Chronic	ND						

**Table 3A. Summary of Potentially Relevant Noncancer Data for *p*-Isopropyltoluene (CASRN 99-87-6)**

Category <sup>a</sup>	Number of Male/Female, Strain Species, Study Type, Reported Doses, Study Duration	Dosimetry <sup>b</sup>	Critical Effects	NOAEL <sup>b</sup>	LOAEL <sup>b</sup>	Reference (comments)	Notes <sup>c</sup>
Reproductive/ Developmental	10 M/10 F, Sprague Dawley (CrI:CD) rat (gavage administration)  F: 2 wk prior to mating, continued through mating (up to 2 wk), gestation, and lactation until sacrifice on PND 13 (~63 d) M: 2 wk pre mating and continued through mating (up to 2 wk) and postmating until sacrifice (~35 d)	0, 50, 100, 200	Reproductive: decreased fertility index and degenerative lesions in the testes and epididymides of P <sub>0</sub> male rats at ≥100 mg/kg-d (sperm retention, reduced luminal sperm, and/or cribriform changes).	50	100	<a href="#">ECHA (2019b)</a> ; <a href="#">Symrise (2018)</a>	NPR, PS
			Alterations in estrous cyclicity, male reproductive organ weight changes and additional male reproductive histopathology in P <sub>0</sub> rats at 200 mg/kg-d.  Developmental: marginally significant (≥4.5%) decreases in F <sub>1</sub> female body weights on PND 1 at 50 and 100 mg/kg-d.  Decreased F <sub>1</sub> offspring survival (i.e., postimplantation survival index and live birth index) and decreased F <sub>1</sub> male body weights on PND 1 at 100 mg/kg-d.	NA	50 <sup>d</sup>		
<b>2. Inhalation (mg/m<sup>3</sup>)</b>							
ND							

<sup>a</sup>Duration categories are defined as follows: acute = exposure for ≤24 hours; short term = repeated exposure for 24 hours to ≤30 days; long-term (subchronic) = repeated exposure for >30 days ≤10% life span for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% life span for humans (>90 days to 2 years in typically used laboratory animal species) ([U.S. EPA, 2002](#)).

<sup>b</sup>Dosimetry: Doses are presented as ADDs (mg/kg-day) for oral noncancer effects.

<sup>c</sup>Notes: NPR = not peer-reviewed; PS = principal study.

<sup>d</sup>Tentative LOAEL based on marginally significant decreases in F<sub>1</sub> female body weights on PND 1 (≥5% is considered biologically significant for this health effect).

ADD = adjusted daily dose; ALP = alkaline phosphatase; BUN = blood urea nitrogen; F = female(s); HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; M = male(s); NA = not applicable; ND = no data; NOAEL = no-observed-adverse-effect level; PND = postnatal day.

<b>Table 3B. Summary of Potentially Relevant Cancer Data for <i>p</i>-Isopropyltoluene (CASRN 99-87-6)</b>					
<b>Category</b>	<b>Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration</b>	<b>Dosimetry</b>	<b>Critical Effects</b>	<b>Reference (comments)</b>	<b>Notes<sup>b</sup></b>
<b>Human</b>					
		<b>1. Oral (mg/kg-d)</b>			
ND					
		<b>2. Inhalation (mg/m<sup>3</sup>)</b>			
ND					
<b>Animal</b>					
		<b>1. Oral (mg/kg-d)</b>			
ND					
		<b>2. Inhalation (mg/m<sup>3</sup>)</b>			
ND					

ND = no data.

## 2.1. HUMAN STUDIES

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

## 2.2. ANIMAL STUDIES

### 2.2.1. Oral Exposures

The effects of oral exposure of animals to *p*-isopropyltoluene were evaluated in a combined repeated-dose systemic and reproductive/developmental toxicity study in rats exposed for subchronic duration ([ECHA, 2019b](#); [Symrise, 2018](#)). Three short-term oral studies in rodents exposed to *p*-isopropyltoluene were also identified that had significant reporting limitations (very few details on methods and results; see Table 4B) [([Li et al., 2020](#); [DuPont, 1992](#)); Stel'makh et al. (1983) as cited in [ECHA \(1986\)](#)]. As such, these studies were considered supplemental and summarized in Section 2.3.

#### *Subchronic Studies (Including Combined Reproductive and Developmental Screening)* [Symrise \(2018\)](#)

[Symrise \(2018\)](#) is non peer-reviewed, Good Laboratory Practice (GLP)-compliant OECD guideline 422 (combined repeated-dose, systemic toxicity study with a reproductive/developmental toxicity screening test) TSCA study in rats that was summarized in ChemView and reported in [ECHA \(2019b\)](#). A combination of these documents was used to generate the summary of this OECD 422 guideline study below. Details on methods of endpoint assessment and results were limited in some cases and most data were provided qualitatively.

Commercially obtained Sprague Dawley (CrI:CD) rats (10 sex/group), 11–13 weeks old, with initial body weights of 332–434 g (male) and 235–299 g (female) at study initiation, were administered *p*-isopropyltoluene (purity not reported) in corn oil daily, via gavage, at doses of 0 (vehicle control), 50, 100, or 200 mg/kg-day. For parental (P<sub>0</sub>) males, dosing began 2 weeks pre-mating and continued through mating (up to 2 weeks) and post-mating until sacrifice, for a total of ~35 days. P<sub>0</sub> females were dosed 2 weeks prior to mating, and dosing continued through mating (up to 2 weeks), gestation, and lactation until sacrifice on postnatal day (PND) 13, for a total of ~63 days. Homogeneity, stability, and confirmation of doses of the test substance under the storage conditions used in the study were analytically verified.

Rats were observed twice daily during the administration period for mortality and general condition. Clinical signs of toxicity and body weights were evaluated in P<sub>0</sub> males once per week until termination, in P<sub>0</sub> females once per week from initiation of exposure through mating, and in mated females on gestation days (GDs) 0, 7, 14, and 20 and PNDs 1, 4, 7, and 14. Additionally, daily observations of maternal behavior were recorded from GD 18 to PND 13. Food intake was measured throughout the study. Functional observational battery (FOB) tests (sensory reactivity, grip strength, and locomotor activity) were performed in five rats per sex per group during the last week of administration in males and on PND 8 in females. Blood drawn at terminal necropsy from five rats per sex per group was used for hematology evaluation (indices were not specified; blood from an additional five rats per sex per group was used for coagulation evaluation) and serum clinical chemistry evaluation (parameters were not specified). Additional blood was drawn at study termination in up to 10 per sex per group for thyroid hormone analysis (serum thyroxine [T<sub>4</sub>] and thyroid-stimulating hormone [TSH]). Postmortem macroscopic examinations conducted on all P<sub>0</sub> animals included external and internal examinations focusing on reproductive system organs. Organs weights were measured in up to five males per group and up to five lactating females per group. Females that failed to deliver a litter were euthanized on GD 25 (organs were not weighed in females that failed to deliver a litter). Microscopic pathology was conducted on

all P<sub>0</sub> animals surviving until study termination. Livers were examined for all females, including those from nonpregnant females that were euthanized during the gestation period. Very few details were provided on the specific organs weighed and tissues that were examined microscopically.

Assessment of reproductive endpoints included determinations of the mating and fertility indices of males and females, sperm parameters, length of estrous cycle, number of days to copulation, conception rate, numbers of pregnant dams, implantation index, gestation period, gestation index, corpora lutea, implantations, pre- and postimplantation loss, birth indices, and litter size. Reproductive parameters also included gross pathology of reproductive organs (including organ weights) and histopathology of reproductive tissues. Developmental endpoints included sex ratio, viability index, number of live pups on Days 1, 4, 7, 11, and 13, postimplantation survival, pup body weight, and examination of pups at sacrifice on PND 13 for gross abnormalities. Blood from F<sub>1</sub> female pups (up to two per litter) was collected on PND 4 and blood from F<sub>1</sub> males and females (up to two per litter) was collected on PND 13 for thyroid hormone analysis (T<sub>4</sub> and TSH). Thyroid glands from one randomly selected male and female pup per litter were collected for histopathological examination.

No treatment-related mortalities were reported at doses up to 200 mg/kg-day for P<sub>0</sub> males and 100 mg/kg-day for P<sub>0</sub> females; one (nonpregnant) female in the 200-mg/kg-day group was euthanized on GD 24 in extremis. Microscopic examination of the euthanized female revealed lesions in the liver and adrenal glands (micro/macro vesicular vacuolation), kidney (bilateral tubular dilation and vacuolation in the cortex and bilateral tubular necrosis with degeneration/regeneration in the papilla) and lymphoid tissues (decreased cellularity or necrosis/apoptosis in the thymus, mesenteric lymph node, splenic white pulp, and Peyer's patch/gut-associated lymphoid tissue, and atrophy of the splenic red pulp). Additionally, females that failed to become pregnant were euthanized early on GD 25, including 1/10 in the control and 50-mg/kg-day groups, 6/10 in the 100-mg/kg-day group, and 10/10 in the 200-mg/kg-day group. No other general signs of toxicity were seen in males or females from any group during observations.

The FOB showed a dose-related, statistically significant decrease in hindlimb grip strength (35%) at Week 5 in P<sub>0</sub> males in the 200-mg/kg-day group (see Table B-1). Decreases (18–30%) in forelimb strength were also observed in treated P<sub>0</sub> males but the changes were not dose-related or statistically significant. All other FOB observations of treated groups (including females) were comparable to the control group (data were not provided). Body weights, body-weight changes, and food consumption in P<sub>0</sub> males were similar to controls at all dose levels (data were not provided). Body weights, body-weight changes, and food consumption in P<sub>0</sub> females of all dose groups during premating and mating periods and during gestation and lactation in dams treated with 50 and 100 mg/kg-day were similar to controls (data were not provided). Females treated with 200 mg/kg-day could not be evaluated for body weight, body-weight change, or food consumption during gestation and lactation due to lack of pregnancy.

Statistically significant changes in hematology and clinical chemistry measures are shown in Table B-2. Observed changes in reported hematological parameters for P<sub>0</sub> males at  $\geq 100$  mg/kg-day (increased reticulocytes, red blood cell distribution width [RDW], and prothrombin time [PT]) lacked a dose-response relationship and/or were of unknown toxicological significance. No hematology results were provided for P<sub>0</sub> female rats. Clinical chemistry measures in P<sub>0</sub> male rats showed statistically significant increases in alkaline phosphatase (ALP) (45%) and blood urea nitrogen (BUN) (50%) at 200 mg/kg-day. Significant

increases in ALP were also observed in P<sub>0</sub> females at 100 mg/kg-day (79%). The changes in ALP and BUN levels in rats showed a dose-response relationship. Females in the 200-mg/kg-day group were not evaluated for clinical chemistry since they were euthanized due to nonpregnancy. All other observed changes in reported clinical chemistry parameters in P<sub>0</sub> males and females were not dose-related and/or were of unknown toxicological significance (see Table B-2). T<sub>4</sub> values in P<sub>0</sub> males were decreased (44 and 63%) compared to controls at 100 and 200 mg/kg-day, respectively, at the end of the study (no other details were provided). There were no corresponding thyroid weight changes or histopathological findings in the thyroid gland, and TSH values were generally below the level of detection in P<sub>0</sub> males and females (data were not provided); therefore, the toxicological significance of the T<sub>4</sub> changes was unclear. Changes in T<sub>4</sub> levels in females were not noted.

The data for selected organ weights (percent difference to controls) are summarized in Table B-3. Any discussion of relative organ weights is based on changes with respect to body weight unless otherwise noted. Dose-related, biologically significant (>10%) increases in liver weights were reported in both male and female rats. In P<sub>0</sub> males, absolute and relative liver weights were biologically and statistically significantly increased in the 200-mg/kg-day group (27 and 41% higher than controls, respectively). In P<sub>0</sub> females, absolute and relative liver weights were biologically and/or statistically significantly increased at 50 and 100 mg/kg-day (14–26% higher than controls). Liver weight data for females at 200 mg/kg-day were unavailable. Statistically significant decreases in absolute and/or relative reproductive organ weights (testis, epididymis, and prostate) were reported in the P<sub>0</sub> males at 200 mg/kg-day (data for other dose groups were not reported for the testis or the epididymides). Other organ weight changes, including kidney weights in males, were not considered treatment-related; however, quantitative data were not provided.

No gross changes were reported in P<sub>0</sub> females. Gross pathological findings were observed in two P<sub>0</sub> males at 200 mg/kg-day: one with unilateral small testis and one with bilateral small testes, both seen in conjunction with germ cell degeneration/depletion. A single male also exhibited a small prostate and another male exhibited small levator ani/bulbocavernosus (LABC) muscle complex.

Histopathological findings in the liver included minimal hepatocellular hypertrophy in 2/5 high-dose P<sub>0</sub> males and 1/6 and 1/10 P<sub>0</sub> females in the low- and high-dose groups, respectively (see Table B-4). This liver lesion was not observed in the controls. Focal hepatocellular necrosis and inflammatory cell infiltrates were reportedly sporadic in the dosed P<sub>0</sub> animals or occurred at similar incidences in controls (data were not provided). These findings were not considered treatment-related (but rather a background incidence). Kidney lesions included increased incidence of minimal to slight hyaline droplet accumulation (three of five rats) and minimal tubular epithelial vacuolation (two of five animals) in P<sub>0</sub> males in the high-dose group compared to one of five and zero of five controls, respectively) (see Table B-4). Minimal tubular basophilia was found only in treated P<sub>0</sub> males (one of five rats for all dose groups). Testicular and epididymal lesions were reported in male P<sub>0</sub> rats mostly at ≥100 mg/kg-day but not in the controls (see Table B-5). At 100 mg/kg-day, minimal spermatid retention (7/10) was observed in the testes and minimal-to-slight reduced luminal sperm (2/10) and slight cribriform changes (1/10) were observed in the epididymides. Male reproductive tract effects observed at 200 mg/kg-day included minimal-to-slight spermatid retention (9/10) and minimal-to-moderate germ cell degeneration/depletion (7/10) in the testis, and slight-to-markedly reduced luminal sperm (10/10), sperm with minimal-to-slight cribriform

changes (5/10), and minimal-to-moderate luminal cell debris (9/10) in the epididymides. Additionally, unilateral or bilateral seminiferous tubular atrophy (with or without luminal cell debris and reduced sperm) was observed in 1/10 males at 50 and 100 mg/kg-day (severity was not reported; therefore, data were not summarized in Table B-5).

Changes in estrous cyclicity were observed in P<sub>0</sub> females during the pre-mating period. The number of females with regular cycles decreased (4/10 compared to 6/10 in controls) and the number of females with at least one irregular cycle increased (6/10 compared to 4/10 in controls) at the highest dose (200 mg/kg-day) (see Table B-6). The mean cycle duration and number of cycles were reportedly comparable to controls in all treatment groups (data were not provided). Select fertility and reproductive parameters are shown in Table B-7. There were effects on fertility in P<sub>0</sub> females at doses  $\geq 100$  mg/kg-day, with no pregnant females in the 200-mg/kg-day group. The numbers of pregnant animals were 9/10, 9/10, 4/10, and 0/10 in the control, 50-, 100-, and 200-mg/kg-day groups, respectively. There were no statistically significant differences in the number of mated females, mean number of days to mating, gestation length, corpora lutea, implantations, or preimplantation loss compared to controls.

F<sub>1</sub> offspring survival was affectedly demonstrated by a reduction in postimplantation survival index and live birth index in the 100-mg/kg-day group compared to controls (see Table B-7); the effects on live birth index were statistically significant. Only one of four litters had 100% viability in the 100 mg/kg-day group, compared to all the litters (nine of nine) having 100% viability in the control group. Viability indices in litters in the 50- and 100-mg/kg-day group were comparable with controls on PNDs 4, 7, and 13. Dose-related decreases in mean offspring body weights occurred in females at 50 and 100 mg/kg-day on PND 1 compared to controls. The decrease at the lowest dose (50 mg/kg-day) was marginally significant ( $\geq 4.5\%$ ;  $\geq 5\%$  is considered biologically significant for this effect). Correspondingly, decreased offspring body weight was observed in males (10%) on PND 1 but only at the highest dose tested (100 mg/kg-day). Minimal changes in body weight ( $< 5\%$ ) were observed on mean offspring body weights on PND 4, 7, 11, or 13. No significant changes on sex ratio, thyroid/parathyroid gland weights, or histopathological findings in offspring of the 50- or 100-mg/kg-day groups, or on T<sub>4</sub> or TSH in F<sub>1</sub> females on PND 4 or T<sub>4</sub> levels in F<sub>1</sub> males on PND 13 were reported (data were not provided). The following clinical observations were made in offspring: thin, cold to touch, partially absent appendages, little or no milk in stomach, swollen, twisted, encrustation, ulceration, dark color, and pallor. The [ECHA \(2020b\)](#) report stated that “gross pathological findings were not considered test material-related because they occurred only in the control group, occurred in the control group in similar incidence, did not occur in a treatment-related manner, were of short duration and/or were considered to be a common finding of young pups in a laboratory situation.” Due to the lack of quantitative data on incidence and severity, the significance of these observations is unclear.

Despite reporting deficiencies (including lack of details on methods of endpoint assessment and presentation of results) that to some extent limit interpretation of results, the [ECHA \(2019b\)](#)/[Symrise \(2018\)](#) study provided sufficient information to identify sensitive health effects associated with repeated-dose oral exposure to *p*-isopropyltoluene. A systemic lowest-observed-adverse-effect level (LOAEL) of 50 mg/kg-day is identified from this study based on biologically significant increases ( $\geq 10\%$ ) in absolute and relative liver weights in P<sub>0</sub> female rats. A systemic no-observed-adverse-effect level (NOAEL) cannot be determined because the liver weight changes occurred at the lowest dose. Increases ( $\geq 10\%$ ) in liver weights were also

observed in P<sub>0</sub> male rats and were accompanied by dose-related increases in serum ALP levels and some evidence of hepatocyte hypertrophy in both sexes mostly at doses  $\geq 100$  mg/kg-day.

A reproductive NOAEL value of 50 mg/kg-day and LOAEL value of 100 mg/kg-day is determined based on decreased fertility index and degenerative lesions in the testes and epididymides of P<sub>0</sub> male rats (i.e., sperm retention, reduced luminal sperm, and cribriform changes). At the highest dose (200 mg/kg-day), changes in estrous cyclicity and effects on male reproductive organ weights and histopathology were found. For developmental effects, a tentative LOAEL of 50 mg/kg-day (lowest dose tested) is identified based on a dose-related and marginally significant decrease ( $\geq 4.5\%$ ) in the body weights of F<sub>1</sub> females on PND 1. A developmental NOAEL cannot be identified. Significant reductions in F<sub>1</sub> male body weights on PND 1 ( $\geq 5\%$ ) and offspring survival (decreased postimplantation survival index and live birth index) also occurred at 100 mg/kg-day.

Other possible treatment-related effects include decreases in hindlimb grip strength, kidney lesions (tubular epithelial vacuolation, hyaline droplet accumulation, and tubular basophilia) and increased BUN levels reported in P<sub>0</sub> male rats mostly at doses  $\geq 200$  mg/kg-day. As mentioned above, there is some uncertainty in the identified health effects and associated effects levels due to the reporting deficiencies in the [ECHA \(2019b\)](#) study. The administered doses of 0, 50, 100, and 200 mg/kg-day correspond to human equivalent doses (HEDs) of 0, 14, 28.1, and 56.2 mg/kg-day in P<sub>0</sub> males and 0, 13, 25.6, and 51.2 mg/kg-day in P<sub>0</sub> females<sup>3</sup>.

### **Chronic Studies**

No chronic oral studies were identified for *p*-isopropyltoluene.

### **2.2.2. Inhalation Exposures**

No inhalation studies suitable for use in risk assessment were located. One short-term study in rats ([Lam et al., 1996](#)) and two subchronic studies in dogs ([DuPont, 1992](#)) were identified for *p*-isopropyltoluene exposure via inhalation. The studies had outstanding design and reporting limitations (e.g., small number of test animals, limited relevant endpoints evaluated, and/or few details on methods and results; see Table 4B). As such, these studies were considered supplemental and are summarized in Section 2.3.

### **2.3. OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)**

Other studies that examined *p*-isopropyltoluene but were not appropriate for the selection of a point of departure (POD) are described here. These studies are not adequate for the determination of provisional reference values but may provide supportive data supplementing a weight-of-evidence (WOE) approach. These include genotoxicity, metabolism/toxicokinetic, and acute-duration studies, studies using routes of exposure other than the oral or inhalation route, and short-term and subchronic oral studies with significant design and reporting limitations that

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<sup>3</sup>Administered doses were converted to HEDs by multiplying by a dosimetric adjustment factor (DAF) of 0.281 for males and 0.256 for females, calculated as follows:  $DAF = (BW_a^{1/4} \div BW_h^{1/4})$ , where  $BW_a$  = animal body weight, and  $BW_h$  = human body weight. The study reported initial body weights of 0.332–0.434 and 0.235–0.299 kg for Sprague Dawley male and female rats, respectively. In the absence of data for study-specific time-weighted average (TWA) or final body weights in the animals, the upper end of the reported initial body weight for rats in this study was used for males (0.434 kg) and females (0.299 kg) given that the initial body weights are higher than the recommended default values for males and females Sprague Dawley rats in a subchronic study (0.267 and 0.204 kg, respectively) ([U.S. EPA, 1988](#)). For humans, the reference value of 70 kg was used for body weight, as recommended by [U.S. EPA \(1988\)](#).

are considered inadequate for the derivation of toxicity values (see Section 2.3.2 for more details).

### 2.3.1. Genotoxicity

Table 4A provides an overview of genotoxicity studies of *p*-isopropyltoluene. The limited data available from in vitro and in vivo animal model systems suggest that *p*-isopropyltoluene is not genotoxic. Genotoxicity data in human model systems are mostly lacking. The chemical was negative for mutagenicity in both plate incorporation and preincubation tests in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, *Escherichia coli* WP2uvrA, and Chinese hamster lung fibroblasts (CHL/V9) cells, both in the presence and absence of rat liver S9 metabolic activation (ECHA, 2020a, 2018). Two other studies also reported that the chemical was negative for mutagenicity in bacteria (*S. typhimurium* strains TA98 and TA100, and *E. coli* Sd-4-73); both studies provided insufficient study details [Szybalski (1958) as cited in FFHPVC (2005); (Rockwell and Raw, 1979)]. *p*-Isopropyltoluene did not induce chromosomal aberrations (CAs) in human peripheral lymphocytes (ECHA, 2017) or Chinese hamster ovary (CHO) cells (ECHA, 2019a) in the presence or absence of rat liver S9 metabolic activation.

Table 4A. Summary of *p*-Isopropyltoluene Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested <sup>a</sup>	Results Without Activation <sup>b</sup>	Results With Activation <sup>b</sup>	Comments	References
<b>Genotoxicity studies in prokaryotic organisms</b>						
Mutation	<i>Salmonella typhimurium</i> TA98, TA100, TA1535, TA1537 and <i>Escherichia coli</i> WP2 uvrA, with and without liver microsomal metabolic activation  TA98: 0 or 3–5,000 µg/plate; all other strains: 0 or 10–5,000 µg/plate	5,000 µg/plate	–	–	Plate incorporation and preincubation tests. No evidence of mutagenicity in any of the strains of <i>S. typhimurium</i> or <i>E. coli</i> tested with or without S9 activation.  Cytotoxicity at the highest concentration.	<a href="#">ECHA (2020a)</a>
Mutation	<i>S. typhimurium</i> TA98 and TA100	ND	NDr	–	Plate incorporation assay. No evidence of mutagenicity reported in any of the strains tested with S9 activation (data not provided).  Limited details were provided. Doses were not explicitly stated. Cytotoxicity was not evaluated or not reported. Only two strains of <i>S. typhimurium</i> were tested.  The test substance in this study is identified as “cymene;” it is not specified if it is <i>p</i> -cymene.	<a href="#">Rockwell and Raw (1979)</a>
Mutation	<i>S. typhimurium</i> TA98 and TA100	0.05–100 µL/plate	NDr	–	Plate incorporation assay. No evidence of mutagenicity reported in any of the strains tested with 24-h urinary extracts of Sprague Dawley rats ( <i>n</i> = 2) that were administered 0.5 mL of undiluted <i>p</i> -isopropyltoluene via gavage in the presence of S9 activation.  The test substance in this study is identified as “cymene;” it is not specified if it is <i>p</i> -cymene.	<a href="#">Rockwell and Raw (1979)</a>

Table 4A. Summary of *p*-Isopropyltoluene Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested <sup>a</sup>	Results Without Activation <sup>b</sup>	Results With Activation <sup>b</sup>	Comments	References
Mutation	<i>E. coli</i> Sd-4-73, 0.01–0.025 mL or small crystals of <i>p</i> -cymene (applied to paper disk and then placed on agar)	0.025 mL or small crystals of <i>p</i> -cymene	–	NDr	Paper-disk method. No evidence of mutagenicity.  Use of positive controls is unclear. Limited details are available in a secondary source.	Szybalski (1958) as cited in <a href="#">FFHPVC (2005)</a>
<b>Genotoxicity studies in mammalian cells—in vitro</b>						
Mutation	CHL/V79 (Chinese hamster lung fibroblasts) tested for 4 h with (0, 5, 10, 20, 40, 50, 60, 70, 80 µg/mL) and without S9 rat liver fraction (0, 1.25, 2.5, 5, 10, 20, 30, 40, 50 µg/mL)	50 µg/mL	–	–	No evidence of mutagenicity in any test condition.  Precipitation was observed at 40 µg/mL and precipitation and excessive toxicity were observed at 50 µg/mL without metabolic activation. Excessive cytotoxicity was observed at 60 µg/mL with metabolic activation. For the experiment without metabolic activation, the plates were discarded at 50 µg/mL due to excessive toxicity and precipitate. The experiments without metabolic activation were not plated starting at 60 µg/mL after Day 0 due to excessive toxicity.	<a href="#">ECHA (2018)</a>
CA	Human peripheral lymphocytes; cells tested with or without activation by S9 hepatic microsomal fraction (0, 10–80 µg/mL) for 4 h and without metabolic activation (0, 20–160 µg/mL) for 24 h	160 µg/mL	–	–	No increase in CAs in any test condition.  No cytotoxicity was seen. The main study used doses determined to be noncytotoxic, based on a preliminary test.	<a href="#">ECHA (2017)</a>

Table 4A. Summary of *p*-Isopropyltoluene Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested <sup>a</sup>	Results Without Activation <sup>b</sup>	Results With Activation <sup>b</sup>	Comments	References
CA	CHO cells, with (0, 24–225 µg/mL) and without (0, 7.0–200 µg/mL) activation by S9 rat liver fraction	225 µg/mL	–	–	No increase in CAs in any test condition. A statistically significant increase in CAs was observed at 156 µg/mL with metabolic activation compared to vehicle control but was within the historical control range. There was no statistically significant increase compared to untreated control cells.  Cytotoxicity at 200 µg/mL without metabolic activation and at 225 µg/mL with metabolic activation.	<a href="#">ECHA (2019a)</a>

<sup>a</sup>Lowest effective dose for positive results; highest dose tested for negative results.

<sup>b</sup>– = negative.

CA = chromosomal aberration; CHO = Chinese hamster ovary; ND = no data; NDr = not determined.

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

### 2.3.2. Supporting Animal Studies

Table 4B provides an overview of other supporting studies on *p*-isopropyltoluene. Studies on acute lethality of *p*-isopropyltoluene indicate low acute toxicity in animals following oral, inhalation, dermal, and intraperitoneal (i.p.) routes. The median lethal dose (LD<sub>50</sub>) in rats ranged from 2,460 to 4,750 mg/kg ([DuPont, 1992](#); [Jenner et al., 1964](#); [Mellon Institute, 1951](#)). No effect on motor activity was observed in mice following a single oral dose of 40 mg/kg ([Siqueira Quintans et al., 2013](#)). An analgesic effect (i.e., increased reaction time on the hot plate test) was noted in mice exposed to 40 mg/kg ([Siqueira Quintans et al., 2013](#)). Three short-term studies available in rodents exposed via the oral route had outstanding reporting limitations (very few details on methods and results; see Table 4B for more details). A Russian study noted reduced mobility in mice at a reported dose of 1,650 mg/kg-day for 24–28 days [Stel'makh et al. (1983) as cited in [ECHA \(1986\)](#)]. Another short-term oral study in rats reported no effects on mortality or gross or microscopic pathology (unspecified) with *p*-isopropyltoluene exposures of 510 mg/kg-day, 5 days/week for 2 weeks ([DuPont, 1992](#)). The third short-term oral study exposed male mice to low doses of *p*-isopropyltoluene (3 and 7 mg/kg-d) or 10–40 mg/kg-day of the volatile oil of *Chenopodium ambrosioides* L. (containing *p*-isopropyltoluene [24.25%]) for 27 days ([Li et al., 2020](#)). The study reported significant increases in relative liver weights, serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and morphological changes in mouse liver, heart, and kidney with exposure to the volatile oil but no significant effects were noted with *p*-isopropyltoluene exposure alone.

<b>Table 4B. Other Studies</b>				
<b>Test</b>	<b>Materials and Methods</b>	<b>Results</b>	<b>Conclusions</b>	<b>References</b>
<b>Supporting studies in animals following oral exposure</b>				
Acute (oral)	Osborne-Mendel rats (10/sex/group) were administered a single dose of <i>p</i> -isopropyltoluene via gavage and observed for 2 wk. The doses tested were not provided.	Clinical signs included depression after dosing, coma, bloody lacrimation, diarrhea, irritation, and scrawny appearance.	Rat LD <sub>50</sub> (95% CI) = 4,750 (3,720–6,060) mg/kg.	<a href="#">Jenner et al. (1964)</a>
Acute (oral)	In an acute oral toxicity of <i>p</i> -isopropyltoluene, white rats (strain, sex, and number per group not specified) were administered a single dose ranging from 1,100 to 6,750 mg/kg via gavage. Mortality, clinical signs, gross necropsy, and histopathology were evaluated.	Gross and microscopic evidence of gastritis and liver damage (not further described) were observed.	Rat LD <sub>50</sub> = 3,000 mg/kg (approximate).	<a href="#">DuPont (1992)</a>
Acute (oral)	Rats (five per group; strain and sex not specified) were administered single oral doses (1,880–3,230 mg/kg) of <i>p</i> -isopropyltoluene.	Mortality occurred (incidence of deaths was not reported).	Rat LD <sub>50</sub> = 2,460 mg/kg.	<a href="#">Mellon Institute (1951)</a>
Acute (oral)	Male Swiss mice (eight per group) were administered single doses of 0, 20, or 40 mg/kg <i>p</i> -isopropyltoluene via gavage. Motor activity was evaluated after administration using a rotarod test. Additional tests evaluated the protective effect on pain.	No effect on motor performance in the rotarod test was observed. Significantly increased latency time (licking and jump parameters) was reported in a hot plate test at 40 mg/kg <i>p</i> -isopropyltoluene.	An analgesic effect was noted at 40 mg/kg. Motor performance was not affected.	<a href="#">Siqueira Quintans et al. (2013)</a>
Short-term (oral)	Groups of six rats (strain and sex not specified) were administered <i>p</i> -isopropyltoluene at a dose of 510 mg/kg-d via an unspecified oral route for 5 d/wk for 2 wk. Rats were sacrificed 11 d following the final dose.	No mortality occurred. No gross or microscopic pathology was observed.	The study has data reporting limitations (lack of details on experimental procedures and results).	<a href="#">DuPont (1992)</a>

<b>Table 4B. Other Studies</b>				
<b>Test</b>	<b>Materials and Methods</b>	<b>Results</b>	<b>Conclusions</b>	<b>References</b>
Short-term (oral)	Mice (strain, sex, and number not specified) were administered <i>p</i> -isopropyltoluene (purity not reported) at 0.22 mg/kg-d, via gavage, for 4 d; doses were increased by a factor of 1.5 every 4 d for a total of 24–28 d. Endpoints evaluated were not specified.	Reduced mobility was observed at a reported dose of 1,650 mg/kg-d.	The study has data reporting limitations (lack of details on experimental procedures and results). Also, original study is in Russian.	Stel'makh et al. (1983) as cited in <a href="#">ECHA (1986)</a>
Short-term (oral)	Male Kunming mice (10/group) were administered <i>p</i> -isopropyltoluene (purity not reported) at 3 and 7 mg/kg-d (exact method of administration not specified) or <i>Chenopodium ambrosioides</i> L. volatile oil (containing <i>p</i> -isopropyltoluene [24.25%]) at 10, 25, and 40 mg/kg-d for 27 d. Endpoints evaluated included body weight, serum enzymes levels (ALT and AST), and liver, thymus, heart, and kidney weights and histopathology.	Significant increases in relative liver weights, serum ALT and ALP levels, and morphological changes in liver, heart and kidney were reported with exposure to the volatile oil but no effects were noted with <i>p</i> -isopropyltoluene exposure alone.	The study evaluated few relevant endpoints and lacked details regarding compound administration, methods and results for statistical analysis, and presentation of histopathological findings (quantitative data were not provided and representative images were difficult to interpret).	<a href="#">Li et al. (2020)</a>
<b>Supporting studies in animals following inhalation exposure</b>				
Acute (inhalation)	Rats, guinea pigs, and mice were exposed to <i>p</i> -isopropyltoluene at an atmospheric concentration of 9.7 mg/L (9,700 mg/m <sup>3</sup> ) for 5 h and observed for up to 1 d.	Mortality was observed in mice, but not in rats or guinea pigs. Transient clonic convulsions reported within 15 min in rats and 90 min in guinea pigs. Necropsy in mice revealed hyperemic lungs, mottled liver, and pale kidneys.	Mouse LC <sub>Lo</sub> <9,700 mg/m <sup>3</sup> Rat and guinea pig LC <sub>50</sub> >9,700 mg/m <sup>3</sup>	MacDonald (1962a, b) as cited in <a href="#">FFHPVC (2005)</a>

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Short-term (inhalation)	Male Long-Evans rats (7–12/group) were exposed whole body to <i>p</i> -isopropyltoluene (purity >99%) as a vapor via inhalation at concentrations of 0, 50, or 250 ppm (v/v) (equivalent to 0, 270, or 1,370 mg/m <sup>3</sup> , respectively) for 6 h/d, 5 d/wk, for 4 wk followed by an 8-wk untreated period. Endpoints evaluated include mortality, clinical signs, body weight, and brain weight (dissected into regions—forebrain [whole brain without cerebellum] and cerebellum—and weighed separately). Brain homogenates and synaptosomes were prepared and analyzed for neurotransmitters (NA, DA, and 5-HT), and an aliquot of each was reserved for determination of enzyme activities (LDH, AchE, and BuChE) and protein analysis. Neurotransmitters and enzymes were compared either to forebrain weight (total) or relative to synaptosomal protein.	No effects on body weight or brain weight (whole brain, cerebellum, or forebrain) were observed. There were no effects on enzyme activities, protein synthesis, or neurotransmitter concentrations in the whole brain, forebrain, or cerebellum. Statistically significant decreases were observed in relative (to forebrain weight) synaptosomal protein yield and total amount of forebrain synaptosomal protein at $\geq 270$ mg/m <sup>3</sup> . Statistically significant increases were observed in the enzyme activity relative to synaptosomal protein (defined as 1 $\mu$ M min <sup>-1</sup> /mg synaptosomal protein) of LDH, AchE, and BuChE. No effect was observed on total (forebrain) enzyme activity of LDH, AchE, or BuChE, or relative (to LDH) synaptosomal concentrations of NA or DA. Relative (to LDH) concentrations of 5-HT were reduced (nonsignificantly) at both concentrations. NA and DA concentrations were significantly increased, relative (to synaptosomal protein concentration), whereas no effect was observed on total NA or DA (forebrain) concentrations. 5-HT concentrations (relative to synaptosomal protein) were increased (nonsignificantly), whereas total 5-HT concentrations were decreased.	This study evaluated few relevant endpoints. <i>p</i> -Isopropyltoluene exposure did not have effects on mortality, clinical signs, body weights, or brain weights. The synaptosomal protein, enzyme activity, and neurotransmitter data from this study suggest that the density and total number of synapses is reduced by <i>p</i> -isopropyltoluene.	<a href="#">Lam et al. (1996)</a>

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Subchronic (inhalation)	Dogs (four total; breed and sex not specified) were exposed 6 h/d, 5 d/wk to mean <i>p</i> -isopropyltoluene vapor concentrations of 75 ppm for 1 mo, then to 100 ppm for 6 wk. Endpoints evaluated included blood pressure, respiration pulse rates, body temperatures, mortality, body weights, hematology, clinical chemistry, and urinalysis. Measurements were compared to baseline values established prior to exposure. At sacrifice, animals were subjected to gross and microscopic examinations.	No mortality was observed, but one dog was removed from the study on Day 12 due to an illness unrelated to exposure (no other details were provided). Pulse pressure was consistently decreased in the three remaining dogs. Changes in other blood pressure endpoints were variable. Marked increases in respiration rate were observed within the first week of exposure in two dogs at 75 ppm, and in the third dog at 100 ppm. Respiration changes were attributed to the external temperature and humidity during the summer months. Hemoglobin concentrations were decreased in all three animals in the absence of changes in RBC counts. Animals did not become severely anemic. No changes in the other endpoints evaluated were reported.	The study included a small number of animals and provided few details on experimental procedures and results. There was limited evidence of effects on blood pressure and hematological changes.	<a href="#">DuPont (1992)</a>
Subchronic (inhalation)	Dogs (four total; breed and sex not specified) were exposed 6 h/d, 5 d/wk to mean <i>p</i> -isopropyltoluene vapor concentrations of 50 ppm for 40 exposures, 74 ppm for 24 exposures, and 160 ppm for 28 exposures. Endpoints evaluated included blood pressure, respiration pulse rates, body temperatures, mortality, body weights, hematology, clinical chemistry, and urinalysis. Measurements were compared to baseline values established prior to exposure. At sacrifice, animals were subjected to gross and microscopic examinations.	No mortalities occurred. Diastolic and pulse pressure showed a downward trend in three of four animals and systolic pressure was reduced in four of four animals. Effects were significant at 50 ppm in one dog and at 160 ppm in three dogs. No changes in respiration were observed. Decreased hemoglobin levels, increased percentages of eosinophils, and elevated blood urea levels were observed in one animal. A filarial infestation was identified in this animal during postmortem examinations. These changes and the observed congestion of the lungs and zones of fibrosis in the kidney were attributed to the infestation.	The study included a small number of animals and provided few details on experimental procedures and results. There was limited evidence of effects on blood pressure and hematological changes.	<a href="#">DuPont (1992)</a>

Table 4B. Other Studies				
Test	Materials and Methods	Results	Conclusions	References
<b>Supporting studies in animals via other routes</b>				
Acute (i.p.)	Male albino Swiss mice (eight per group) were administered a single dose of <i>p</i> -isopropyltoluene via i.p. injection at doses of 0, 25, 50, and 100 mg/kg. Animals were observed for clinical signs and behavioral screening 4 h after the injection. <i>p</i> -Isopropyltoluene was also evaluated for effects preventing pain and inflammation.	CNS depression, based on reduced spontaneous activity, analgesia, and sedation, was observed at 50 and 100 mg/kg. Reduced urination and defecation were noted at 100 mg/kg. Reaction time to the hot plate test was significantly increased in all dose groups for up to 1 h and lasting longer at higher doses (up to 2 h at 100 mg/kg).	<i>p</i> -Isopropyltoluene induced clinical signs of CNS depressive behaviors.	<a href="#">Bonjardim et al. (2012)</a>
Acute (i.p.)	Male Swiss mice (six per group) were administered <i>p</i> -isopropyltoluene as a single i.p. injection of 0, 25, 50, or 100 mg/kg. Animals were sacrificed after 1.5 h and whole brains were collected and prepared for immunofluorescence c-Fos staining. The focus of the study was preventive effects of <i>p</i> -isopropyltoluene on pain and inflammation.	Histopathology immunofluorescence of the periaqueductal grey brain region showed significantly increased c-Fos-positive cells at all doses, compared to vehicle control.	<i>p</i> -Isopropyltoluene increased c-Fos staining in the periaqueductal grey brain region.	<a href="#">Santana et al. (2015)</a>
Acute (i.p.)	Male Swiss albino mice (five per group) were administered single doses of 800 $\mu$ L/kg (equivalent to 680 mg/kg using a density of 0.85 g/mL) <i>p</i> -isopropyltoluene via i.p. injection. At 24 h after the dose, animals were sacrificed. Endpoints evaluated include clinical chemistry (serum ALT). No other standard toxicological endpoints were evaluated.	No effect on serum ALT was observed.	Limited data indicated no effects on ALT in mice at a dose of 680 mg/kg.	<a href="#">Mansour et al. (2001)</a>

<b>Table 4B. Other Studies</b>				
<b>Test</b>	<b>Materials and Methods</b>	<b>Results</b>	<b>Conclusions</b>	<b>References</b>
Acute (i.p.)	Male albino Swiss mice (six to eight per group) were administered a single dose of 200 mg/kg <i>p</i> -isopropyltoluene via i.p. injection. Motor activity was evaluated using a rotarod test. Additional tests evaluated the protective effect on pain induction (acetic acid-induced writhing and formalin-induced pain tests; 50, 100, and 200 mg/kg i.p.).	No effect on motor performance was observed.  Treatment with <i>p</i> -isopropyltoluene produced significant antinociceptive effects and inhibition of licking response to injected paw.	Significant antinociceptive effects in mice at a dose of 200 mg/kg but no changes on motor performance.	<a href="#">Quintans-Júnior et al. (2013)</a>
Acute (i.p.)	Male Swiss mice (eight per group) were administered single doses of 0, 25, 50, or 100 mg/kg <i>p</i> -isopropyltoluene via i.p. injection. Motor activity was evaluated at 0.5, 1, and 2 h after administration using a rotarod test. Additional tests evaluated the protective effect on orofacial pain (formalin, capsaicin, and glutamate tests; 0, 25, 50, or 100 mg/kg).	No effect on motor performance was observed. Treatment with <i>p</i> -isopropyltoluene produced significant antinociceptive effects at all doses.	Significant antinociceptive effects in mice at $\geq 25$ mg/kg but not changes on motor performance up to doses of 100 mg/kg.	<a href="#">Santana et al. (2011)</a>
Acute (dermal)	In an unpublished acute toxicity study summarized in a secondary source, rabbits were dermally exposed to <i>p</i> -isopropyltoluene.	Unpublished study where insufficient data were reported in the secondary source.	Rabbit LD <sub>50</sub> $\geq 5,000$ mg/kg.	Moreno (1973) as cited in <a href="#">FFHPVC (2005)</a>
<b>MOA/Mechanistic Studies</b>				
Cytotoxicity	Human THP-1 monocytes were exposed to <i>p</i> -isopropyltoluene concentrations of 1, 10, 100, and 1,000 ng/mL for 24 h. Cell viability was determined using an MTT assay.	Viability was reduced by 40% in the 1,000 ng/mL group. No effects on viability were observed at concentrations $\leq 100$ ng/mL.	<i>p</i> -Isopropyltoluene was cytotoxic in a human monocyte cell line at high exposure levels (1,000 ng/mL).	<a href="#">Kavoosi and Teixeira da Silva (2012)</a>

<b>Table 4B. Other Studies</b>				
<b>Test</b>	<b>Materials and Methods</b>	<b>Results</b>	<b>Conclusions</b>	<b>References</b>
Cytotoxicity	Murine macrophage cells (RAW 264.7) were exposed to <i>p</i> -isopropyltoluene concentrations ranging from 0 to 428.65 µg/mL for up to 18 h. Cell viability was assessed using an MTT assay.	No cytotoxicity was observed at <i>p</i> -isopropyltoluene concentrations up to 428.65 µg/mL.	<i>p</i> -Isopropyltoluene was not cytotoxic to RAW 264.7 cells at concentrations up to 428.65 µg/mL.	<a href="#">Zhong et al. (2013)</a>
Nerve excitability	Sciatic nerves, isolated from Wistar rats (both sexes), were mounted in moist chambers and stimulated to record baseline CAPs. When a stable CAP peak-to-peak amplitude was achieved for at least 30 min, nerves were exposed to a solution containing <i>p</i> -isopropyltoluene (analytical-grade) at 1.79 mg/mL for 180 min followed by a washout recovery period of 180 min. Throughout the experiment, rheobase, chronaxie, peak-to-peak amplitude, and conduction velocity of CAP components were recorded.	Treatment with <i>p</i> -isopropyltoluene had no significant effect on electrophysiological parameters of sciatic nerve CAP.	<i>p</i> -Isopropyltoluene did not affect nerve excitability in an ex vivo nerve conduction test in rat sciatic nerves.	<a href="#">Barbosa et al. (2017)</a>
<b>Metabolism/Toxicokinetic Studies</b>				
Dermal absorption	0.1 mL of [ <sup>14</sup> C]- <i>p</i> -isopropyltoluene was applied to the shaved skin of male albino mice (five to nine per group) for 15–60 min. Urine was collected for 72 h and radioactivity was measured.	The rate of skin absorption remained constant throughout the exposure duration (32 nmol/cm <sup>2</sup> /min).	<i>p</i> -Isopropyltoluene was readily absorbed through intact mouse skin.	<a href="#">Wepierre et al. (1968)</a>

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Metabolism/ toxicokinetics	Two male albino rats (strain not reported) were administered a purified diet containing 1% neomycin sulfate for 7 d and control urine was obtained for analysis on Days 5–7. Rats were then given 100 mg/kg <i>p</i> -isopropyltoluene as a single gavage dose and urine was collected for 48 h and analyzed for phenolic metabolites. Samples were incubated with $\beta$ -glucuronidase (type H-1 containing sulfatase) for hydrolysis prior to detection.	Phenolic metabolites, such as 5-isopropyl-2-methylphenol (carvacrol) and 2-isopropyl-5-methylphenol (thymol), were not detected following administration of <i>p</i> -isopropyltoluene. Administration of purified diet containing neomycin sulfate reduced the amount of phenolic compounds typically found in rat urine.	The absence of detectable phenolic metabolites indicates that ring hydroxylation did not occur.	<a href="#">Bakke and Scheline (1970)</a>
Metabolism/ toxicokinetics	Three bushtail possums were administered <i>p</i> -isopropyltoluene over a period of 10 d (administered in bread at varying volumes; dose not provided). Urine and feces were collected for analysis during dosing.	Urinary metabolites included <i>p</i> -isopropylbenzoic acid and <i>p</i> -cresol. Trace amounts of <i>p</i> -isopropyltoluene were detected in feces. Data were not provided for control animals; therefore, the source of urinary <i>p</i> -cresol could not be conclusively attributed to <i>p</i> -isopropyltoluene administration.	Dealkylation of the isopropyl group to form <i>p</i> -cresol is unlikely and this metabolite is not reported in any other study.	<a href="#">Southwell et al. (1980)</a>
Metabolism/ toxicokinetics	A single male Japanese white rabbit was administered <i>p</i> -isopropyltoluene as a single gavage dose at 670 mg/kg. Urine was collected daily for 3 d after chemical administration and stored at 0–5°C until time of analysis. Samples were incubated with $\beta$ -glucuronidase-arylsulfatase for hydrolysis prior to detection.	Within 72 h after administration, 20% of the administered dose was eliminated in the urine as neutral or acidic metabolites. The main metabolites identified in the urine were 2- <i>p</i> -tolylpropan-1-ol and 2- <i>p</i> -tolylpropan-2-ol (50 and 28%, respectively, of the neutral metabolites). In total, seven metabolites were identified.	Hydroxylation at the three possible aliphatic sites of <i>p</i> -isopropyltoluene contributes to the metabolite formation in this species. However, the methyl group oxidation makes a minor contribution compared with that shown by hydroxylation of the isopropyl group. No ring hydroxylation was observed.	<a href="#">Ishida et al. (1981)</a>

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Metabolism/ toxicokinetics	Male Wistar rats and Dunkin Hartley guinea pigs were administered <i>p</i> -isopropyltoluene orally or by inhalation at a dose of 100 mg/kg (two to three per group). Urine was collected for 48 h. Samples were incubated with a glucuronidase and sulfatase preparation for hydrolysis prior to detection.	Within 48 h after oral administration, approximately 70–80% of the administered dose (60–70% following inhalation) was excreted in the form of extractable metabolites in the urine. Similar urinary metabolites were identified in both species but in different quantities.	Oxidation of both the methyl and isopropyl groups of <i>p</i> -isopropyltoluene contributed to the metabolite formation in both species. No ring-hydroxylation of <i>p</i> -isopropyltoluene was detected in rats, but trace amounts of the ring hydroxylation metabolite, 5-isopropyl-2-methylphenol (carvacrol), were detected in the urine in guinea pigs and only occurred <i>ortho</i> - to the methyl group.	<a href="#">Walde et al. (1983)</a>
Metabolism/ toxicokinetics	Four rabbits (two per sex) were given <i>p</i> -isopropyltoluene orally at a dose of 1,000 mg/kg. Urine was collected 3 d after dosing. The study was designed to identify the stereochemistry of <i>p</i> -isopropyltoluene metabolites. Samples were incubated with a glucuronidase and sulfatase preparation for hydrolysis prior to detection.	Different hydroxylated and carboxylated metabolites were recovered in the urine. Four were optically active, and three were optically inactive.	The enzymatic oxidation of <i>p</i> -isopropyltoluene occurred stereoselectively.	<a href="#">Matsumoto et al. (1992)</a>
Metabolism/ toxicokinetics	A variety of species (rat, brushtail possum, and greater glider [six per group] and ringtail possum [three per group]) were administered <i>p</i> -isopropyltoluene orally at doses equivalent to 50 and 200 mg/kg. Urine and feces were collected for 48 h. Control samples were taken prior to dosing. Samples were incubated with $\beta$ -glucuronidase-arylsulfatase for hydrolysis prior to detection.	The fraction of dose recovered within 48 h ranged from 52 to 74%. Differences were observed between species in the urinary metabolic disposition of <i>p</i> -isopropyltoluene. The rat excreted metabolites containing all degrees of oxidation (one to four oxygen atoms added) but predominantly a monooxygenated metabolite. The brushtail possum excreted metabolites with two to four oxygens and the greater glider and ringtail possum excreted metabolites containing three or four oxygen atoms. A conjugation reaction with glycine, glucuronic acid, or glutathione was observed in the rat and brushtail possum. No parent compound or metabolites were detected in feces.	All species exhibited a complex metabolic pattern with extensive oxidation of the methyl and isopropyl groups of <i>p</i> -isopropyltoluene.	<a href="#">Boyle et al. (1999)</a>

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Metabolism/ toxicokinetics	In vitro metabolism of <i>p</i> -isopropyltoluene was evaluated using liver microsomes obtained from Wistar rats, brushtail possums, and koalas. Microsomes were also obtained from possums exposed to mixed terpenes prior to sacrifice.	The primary metabolite in each species was <i>p</i> -isopropylbenzyl alcohol (84, 73, and 89% of total metabolites using rat, possum, and koala microsomes, respectively). Other metabolites, each accounting for <10% of the total, included 2- <i>p</i> -tolylpropan-2-ol (or <i>p</i> , $\alpha$ , $\alpha$ -trimethylbenzylalcohol), <i>p</i> -isopropylbenzoic acid, 2- <i>p</i> -(hydroxymethyl)phenyl-2-propan-2-ol, 2- <i>p</i> -tolylpropan-1,2-diol, and 2- <i>p</i> -(hydroxymethyl)phenyl-propan-1-ol. No phenolic metabolites were detected. Kinetic analysis revealed the following rank order for intrinsic clearance ( $Cl_{int}$ ): terpene-treated possum ( $128 \mu\text{L}/\text{mg protein}^{-1} \text{min}^{-1}$ ) > control possum ( $107 \mu\text{L}/\text{mg protein}^{-1} \text{min}^{-1}$ ) > koala ( $69 \mu\text{L}/\text{mg protein}^{-1} \text{min}^{-1}$ ) > rat ( $38 \mu\text{L}/\text{mg protein}^{-1} \text{min}^{-1}$ ).	In vitro metabolism occurred at the same sites of oxidation as observed in the in vivo studies in the same species (i.e., hydroxylation of the methyl and isopropyl substituents without ring hydroxylation). Metabolic capacity (measured as $Cl_{int}$ ) was increased in possums that were pretreated with terpenes, suggesting induction of metabolic enzymes. Metabolism was greater in possums and koalas, compared to rats.	<a href="#">Pass et al. (2002)</a>

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Metabolism/ toxicokinetics	<p>In vitro incubation of <i>p</i>-isopropyltoluene (purity 99%) with human recombinant CYP enzymes followed by GC-MS analysis.</p> <p>A single volunteer swallowed 35 tablets containing 1% tea tree oil and a concentration of 0.5–12% <i>p</i>-isopropyltoluene among other monoterpenes (dose not further described). Ingestion occurred over a 2-h period. Blood was collected 10 min after the ingestion period, and urine samples were taken at 60 min during the ingestion period and 10 and 25 min postingestion.</p>	<p>In the in vitro study, 2-isopropyl-5-methylphenol (thymol), <i>p</i>-isopropylbenzyl alcohol, and <i>p</i>-isopropylbenzaldehyde were identified in the extract. In the human study, thymol was recovered from both blood and urine as glucuronide or sulfate conjugate, while other monoterpenes were detected in urine.</p>	<p>One predicted metabolite from an in vitro study (thymol) was found in human blood and urine following oral dosing with tea tree oil containing <i>p</i>-isopropyltoluene.</p>	<p><a href="#">Meesters et al. (2009)</a></p>

<sup>a</sup>Values in the study report were given in ppm. Values in mg/m<sup>3</sup> = exposure in ppm × MW of *p*-isopropyltoluene ÷ 24.45. The MW of *p*-isopropyltoluene is 134.222 g/mol ([U.S. EPA, 2022a](#)).

AchE = acetylcholinesterase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BuChE = butyrylcholinesterase; CAP = compound action potential; CI = confidence interval; CNS= central nervous system; CYP = cytochrome P450; DA = dopamine; 5-HT = 5-hydroxytryptamine; GC = gas chromatography; i.p. = intraperitoneal; LC<sub>50</sub> = median lethal concentration; LC<sub>Lo</sub> = lowest reported lethal concentration; LD<sub>50</sub> = median lethal dose; LDH = lactate dehydrogenase; MOA = mode-of-action; MS = mass spectrometry; MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; MW = molecular weight; NA = noradrenaline; RBC = red blood cell.

In an unpublished, acute inhalation study, summarized in secondary sources, mice, rats, and guinea pigs were evaluated for acute lethality following a 5-hour exposure to a concentration of 9,700 mg/m<sup>3</sup> [MacDonald, (1962a, b) as cited in [FFHPVC \(2005\)](#)]. No mortality was observed in rats or guinea pigs; however, transient clonic convulsions were reported within 15 minutes in rats and 90 minutes in guinea pigs. The lowest lethal concentration (LC<sub>Lo</sub>) in mice was <9,700 mg/m<sup>3</sup> as all three mice died.

A 4-week inhalation study in male rats exposed to *p*-isopropyltoluene at concentrations up to 1,370 mg/m<sup>3</sup> showed no effects on mortality, clinical signs, body weight, or whole brain, cerebellum, or forebrain weight ([Lam et al., 1996](#)). Statistically significant decreases in relative (to forebrain weight) synaptosomal protein yield and total amount of forebrain synaptosomal protein were observed at ≥270 mg/m<sup>3</sup>. No effect was observed on total forebrain lactate dehydrogenase (LDH), acetylcholinesterase (AChE), or butyrylcholinesterase (BuChE) activities or noradrenaline (NA) or dopamine (DA) concentrations; however, enzyme activities and concentrations of DA and NA relative to synaptosomal protein were significantly increased at ≥270 mg/m<sup>3</sup>. In addition, total forebrain 5-hydroxytryptamine (5-HT) concentrations were decreased at 1,370 mg/m<sup>3</sup>, and 5-HT concentrations relative to synaptosomal protein were increased (nonsignificantly). These findings suggest that the density and total number of synapses is reduced by *p*-isopropyltoluene, leading to changes in neurotransmitter concentrations ([Lam et al., 1996](#)). Subchronic inhalation studies in dogs suggest effects on blood pressure and hematological changes; however, the evidence was limited ([DuPont, 1992](#)).

Several acute-duration studies by other routes are also described in Table 4B. In an unpublished study cited in a secondary source, the rabbit dermal LD<sub>50</sub> was ≥5,000 mg/kg according to Moreno (1973) as cited in [FFHPVC \(2005\)](#) (no additional details regarding this study were available). Several acute i.p. studies examined neurological changes in mice. Reduced spontaneous activity, analgesia (i.e., increased reaction time on the hot plate test), and reduced urination and defecation were observed at doses of 50–100 mg/kg ([Bonjardim et al., 2012](#)). Increased c-Fos expression in the brain periaqueductal grey region ([Santana et al., 2015](#)) and antinociceptive effects ([Quintans-Júnior et al., 2013](#); [Santana et al., 2011](#)) were reported at doses ≥25 mg/kg; however, no effects were observed on motor performance up to doses of 200 mg/kg ([Quintans-Júnior et al., 2013](#); [Santana et al., 2011](#)). No effects on serum ALT levels were observed in mice administered a single i.p. dose of 680 mg/kg ([Mansour et al., 2001](#)).

### 2.3.3. Mode-of-Action/Mechanistic Studies

Few noncancer mechanistic studies were identified. *p*-Isopropyltoluene was not cytotoxic to murine macrophage cells (RAW 264.7) ([Zhong et al., 2013](#)), but was cytotoxic to human THP-1 monocytes at high exposure concentrations ([Kavoosi and Teixeira da Silva, 2012](#)). *p*-Isopropyltoluene did not affect nerve excitability in sciatic nerves isolated from Wistar rats ([Barbosa et al., 2017](#)).

### 2.3.4. Metabolism/Toxicokinetic Studies

Studies in animals (rats, rabbits, guinea pigs, and marsupials [possum, greater glider, and koala]) have shown that *p*-isopropyltoluene is well absorbed from the gastrointestinal tract, widely distributed in the body, metabolized, and excreted mainly in the urine ([Boyle et al., 1999](#); [Matsumoto et al., 1992](#); [Walde et al., 1983](#); [Ishida et al., 1981](#)). Dermal absorption was also demonstrated in mice ([Wepierre et al., 1968](#)). No in vivo human or animal studies reporting

distribution of *p*-isopropyltoluene were identified; however, based on a log  $K_{ow}$  (octanol-water partition coefficient) value  $>4$  (see Table 1), *p*-isopropyltoluene is expected to accumulate in fatty tissues. The metabolism studies in laboratory animals summarized in Table 4B demonstrate that *p*-isopropyltoluene undergoes extensive oxidation of the methyl substituent and isopropyl side-chain to yield polar oxygenated metabolites (see Figure 2). The primary metabolites include monohydric alcohols, diols, mono- and dicarboxylic acids, and hydroxy acids. These metabolites are either excreted unchanged in the urine or undergo conjugation with glucuronic acid and/or glycine, followed by excretion in the urine. Ring-hydroxylation was not observed in in vivo animal studies ([Boyle et al., 1999](#); [Matsumoto et al., 1992](#); [Walde et al., 1983](#); [Ishida et al., 1981](#); [Bakke and Scheline, 1970](#)), with the single exception of trace amounts of 5-isopropyl-2-methylphenol (carvacrol) found in the urine of guinea pigs ([Walde et al., 1983](#)). There are limited data in humans. An in vitro study using human recombinant cytochrome P450 (CYP) enzymes identified 2-isopropyl-5-methylphenol (thymol) as a metabolite in addition to *p*-isopropylbenzyl alcohol, 2-*p*-tolylpropan-2-ol (or *p*, $\alpha$ , $\alpha$ -trimethylbenzylalcohol), and *p*-isopropylbenzylaldehyde (quantitative data were not presented) ([Meesters et al., 2009](#)). An in vitro study using liver microsomes obtained from rats or marsupials (possum and koala) reported the same sites of oxidation as observed in the in vivo studies discussed above (i.e., hydroxylation of the methyl and isopropyl substituents without ring hydroxylation) and noted the absence of phenolic metabolites ([Pass et al., 2002](#)). [Southwell et al. \(1980\)](#) reported *p*-cresol as a metabolite of *p*-isopropyltoluene in bushtail possums; however, this is a poorly reported study with significant limitations. Dealkylation of the isopropyl group to form *p*-cresol is unlikely, and this metabolite is not reported in any other study. In addition, endogenous *p*-cresol is produced via the digestion of tyrosine (from food proteins) in the intestine. Free *p*-cresol formed in this way is absorbed from the intestine and eliminated in the urine as conjugates ([IPCS, 1995](#)).



### 3. DERIVATION OF PROVISIONAL VALUES

#### 3.1. DERIVATION OF ORAL REFERENCE DOSES

The database of repeated-dose oral exposure studies for *p*-isopropyltoluene adequate for quantitative dose-response analysis consists of a non-peer-reviewed, repeated-dose systemic toxicity study that included a reproductive/developmental toxicity screening test in rats ([Symrise, 2018](#)). This study was insufficient to support deriving a provisional toxicity value given its non-peer-reviewed status, reporting limitations in assessment methods, and most data were reported qualitatively from a secondary source. However, this study provides sufficient data to develop screening subchronic and chronic provisional reference dose (p-RfD) values (see Appendix A).

#### 3.2. DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No adequate repeated-dose studies (including subchronic or chronic studies) were located regarding toxicity of *p*-isopropyltoluene to humans or animals via inhalation exposure. Due to the limited inhalation toxicity data for *p*-isopropyltoluene, subchronic and chronic provisional reference concentrations (p-RfCs) were not derived using chemical-specific information. Instead, screening subchronic and chronic p-RfCs are derived in Appendix A using an alternative analogue approach.

#### 3.3. SUMMARY OF NONCANCER PROVISIONAL REFERENCE VALUES

The noncancer screening provisional reference values for *p*-isopropyltoluene are summarized in Table 5.

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

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD (HED/HEC)	UF <sub>C</sub>	Principal Study
Screening subchronic p-RfD (mg/kg-d)	Rat/F	Increased ALP	$4 \times 10^{-2}$	BMDL	3.6	100	<a href="#">Symrise (2018)</a>
Screening chronic p-RfD (mg/kg-d)	Rat/F	Increased ALP	$4 \times 10^{-3}$	BMDL	3.6	1,000	<a href="#">Symrise (2018)</a>
Screening subchronic p-RfC (mg/m <sup>3</sup> )	Rat/M	Impaired motor coordination (decreased rotarod performance)	$1 \times 10^{-1}$	NOAEL	39 (based on analogue POD <sup>a</sup> )	300	Korsak et al. (1994) as cited in <a href="#">U.S. EPA (2009)</a> ; and <a href="#">U.S. EPA (2003)</a>
Screening chronic p-RfC (mg/m <sup>3</sup> )	Rat/M	Impaired motor coordination (decreased rotarod performance)	$4 \times 10^{-2}$	NOAEL	39 (based on analogue POD <sup>a</sup> )	1,000	Korsak et al. (1994) as cited in <a href="#">U.S. EPA (2009)</a> ; and <a href="#">U.S. EPA (2003)</a>

<sup>a</sup>Xylene (mixed isomers) was selected as a suitable source analogue for *p*-isopropyltoluene as described in Appendix A.

ALP = alkaline phosphatase; BMDL = benchmark dose lower confidence limit; F = female; HEC = human equivalent concentration; HED = human equivalent dose; M = male; NOAEL = no-observed-adverse-effect level; POD = point of departure p-RfC = provisional reference concentration; p-RfD = provisional reference dose; UF<sub>C</sub> = composite uncertainty factor.

### 3.4. CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

No oral or inhalation studies have been conducted to assess the carcinogenicity of *p*-isopropyltoluene. Limited data suggest that the chemical is not genotoxic (see Section 2.3). Under the U.S. EPA Cancer Guidelines ([U.S. EPA, 2005](#)), there is “*Inadequate Information to Assess the Carcinogenic Potential*” of *p*-isopropyltoluene by oral or inhalation exposure (see Table 6).

<b>Possible WOE Descriptor</b>	<b>Designation</b>	<b>Route of Entry (oral, inhalation, or both)</b>	<b>Comments</b>
<i>“Carcinogenic to Humans”</i>	NA	NA	The available data do not support this descriptor.
<i>“Likely to be Carcinogenic to Humans”</i>	NA	NA	The available data do not support this descriptor.
<i>“Suggestive Evidence of Carcinogenic Potential”</i>	NA	NA	The available data do not support this descriptor.
<b><i>“Inadequate Information to Assess Carcinogenic Potential”</i></b>	<b>Selected</b>	<b>Both</b>	<b>No adequate information is available to assess the carcinogenic potential of <i>p</i>-isopropyltoluene by the inhalation or oral routes of exposure.</b>
<i>“Not Likely to be Carcinogenic to Humans”</i>	NA	NA	The available data do not support this descriptor.

NA = not applicable; WOE = weight-of-evidence.

### 3.5. DERIVATION OF PROVISIONAL CANCER RISK ESTIMATES

The absence of data indicating a tumorigenic effect precludes development of cancer risk estimates for *p*-isopropyltoluene (see Table 7).

<b>Toxicity Type</b>	<b>Species/Sex</b>	<b>Tumor Type</b>	<b>Cancer Value</b>	<b>Principal Study</b>
p-OSF (mg/kg-d) <sup>-1</sup>	NDr			
p-IUR (mg/m <sup>3</sup> ) <sup>-1</sup>	NDr			

NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

## APPENDIX A. NONCANCER SCREENING PROVISIONAL VALUES

Due to the lack of evidence described in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) assessment, it is inappropriate to derive provisional toxicity values for *p*-isopropyltoluene because the limited database on the toxicity of *p*-isopropyltoluene is insufficient to support direct derivation. However, some information is available for this chemical, which although insufficient to support deriving a provisional toxicity value under current guidelines, may be of use to risk assessors. In such cases, the Center for Public Health and Environmental Assessment (CPHEA) 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 provisional reference values 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 could be 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 CPHEA.

Screening subchronic and chronic provisional reference doses (p-RfDs) were derived for *p*-isopropyltoluene as described below. For inhalation, an alternative analogue approach was utilized to derive screening subchronic and chronic provisional reference concentration (p-RfC) values.

### ORAL NONCANCER TOXICITY VALUES

As discussed in the main body of the report, the database of repeated-dose oral studies for *p*-isopropyltoluene adequate for quantitative dose-response analysis consists of a non-peer-reviewed repeated-dose systemic toxicity study that included a reproductive/developmental toxicity screening test in rats ([Symrise, 2018](#)). Other studies that examined *p*-isopropyltoluene but are not appropriate for the selection of a point of departure (POD) are described in Section 2.3. These include short-term oral studies with significant design and reporting limitations, as well as genotoxicity, metabolism/toxicokinetic, and acute studies and studies using routes of exposure other than the oral or inhalation route.

The [ECHA \(2019b\)/Symrise \(2018\)](#) study is insufficient to derive p-RfD values because of its non-peer-reviewed status and uncertainties surrounding reporting deficiencies (limited details on methods and results for some endpoints and most data were reported qualitatively from a secondary source). However, the study adhered to Good Laboratory Practice (GLP) and Organisation for Economic Co-operation and Development (OECD) test guidelines, evaluated a wide range of relevant toxicity endpoints (including body weight, food consumption, clinical observations, functional observational battery [FOB], hematology, clinical chemistry, organ weight, and histopathology) and provided sufficient information to identify toxicologically relevant health effects and associated dose-response relationships for deriving screening-level p-RfD values (see study summary in Section 2.2.1 for more details).

The [ECHA \(2019b\)/Symrise \(2018\)](#) study identified the liver as a sensitive target of toxicity following subchronic oral exposure in rats. [ECHA \(2019b\)/Symrise \(2018\)](#) reported dose-related and biologically significant (>10%) increases in absolute and relative<sup>4</sup> liver weight at 50 and 100 mg/kg-day in P<sub>0</sub> female rats exposed for ~63 days (50 mg/kg-day was the lowest dose tested) that were the basis for the systemic lowest-observed-adverse-effect level (LOAEL) value (LOAEL = 50 mg/kg-day; a no-observed-adverse-effect level [NOAEL] could not be determined). These findings are supported by increases (≥10%) in absolute and relative liver weights in P<sub>0</sub> male rats at 200 mg/kg-day, statistically significant and dose-related increases in serum alkaline phosphatase (ALP) levels (a biomarker of hepatobiliary injury) in P<sub>0</sub> males and females at ≥100 mg/kg-day, and low incidence of hepatocyte hypertrophy (10–40%) in both sexes at ≥50 mg/kg-day. The data across organ weights, serum chemistry, and histopathology provide coherent evidence of liver toxicity following oral exposure to *p*-isopropyltoluene in rats.

Effects on the reproductive system and developing offspring were also reported in the [ECHA \(2019b\)/Symrise \(2018\)](#) study. A reproductive NOAEL of 50 mg/kg-day and a LOAEL of 100 mg/kg-day were identified based on decreased fertility index (40 and 0% at 100 and 200 mg/kg-day, respectively, compared to 90% for controls) and degenerative male reproductive lesions in the testes and epididymides of P<sub>0</sub> rats (i.e., increased minimal sperm retention and minimal-to-slight reduced luminal sperm and sperm with slight cribriform changes, respectively). These effects were accompanied by changes in estrous cyclicity (decreased number of females with regular cycles and increased number of females with irregular cycles), male reproductive organ weights (statistically significant decreases in absolute and/or relative testes, epididymides, and prostate weights), and male histopathology (increased minimal-to-slight spermatid retention and minimal-to-moderate germ cell degeneration/depletion in the testis, and slight-to-markedly reduced luminal sperm, sperm with minimal-to-slight cribriform changes, and minimal-to-moderate luminal cell debris in the epididymides) at the highest dose (200 mg/kg-day). A tentative LOAEL of 50 mg/kg-day (lowest dose tested; a NOAEL could not be determined) for developmental effects was based on marginally significant (≥4.5%; ≥5% is considered biologically significant) decreases in the body weights of female offspring on postnatal day (PND) 1. The findings were dose-related, consistent with reductions in male offspring body weights (–10%) on PND 1, and coherent with effects on offspring survival (reductions in postimplantation survival index and live birth index) occurring at 100 mg/kg-day, which provide support for the biological significance of the reductions in female F<sub>1</sub> body weights. Furthermore, reduced birth weight has been associated with toxicologically relevant effects such as neonatal and postnatal mortality, coronary heart disease, arterial hypertension, chronic renal insufficiency, and diabetes mellitus in humans ([Barker, 2007](#); [Reyes and Mañalich, 2005](#)).

Kidney lesions occurred in P<sub>0</sub> male rats in the [ECHA \(2019b\)/Symrise \(2018\)](#) study, including increases in minimal tubular epithelium vacuolation (two of five rats at 200 mg/kg-day compared to zero of five rats in the controls), minimal-to-slight hyaline droplets accumulation (one of five and three of five rats at 50 and 200 mg/kg-day, respectively, compared to one of five rats in the controls), and minimal tubular basophilia (one of five rats in all dose groups compared to zero of five rats in the controls). Additionally, statistically significant increases in blood urea nitrogen (BUN) levels occurred in males at the highest dose (200 mg/kg-day). In

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<sup>4</sup>Any discussion of relative organ weights is based on changes with respect to body weight unless otherwise noted.

general, the increases in the incidence and severity of the kidney lesions were relatively minor and lacked dose-response correspondence. Therefore, the biological significance of these lesions and accompanying clinical chemistry changes (increased BUN levels) in male rats occurring mostly at the highest dose in the [ECHA \(2019b\)/Symrise \(2018\)](#) study are unclear.

Statically significant decreases in hindlimb grip strength were observed in P<sub>0</sub> male rats at the highest dose (200 mg/kg-day) ([ECHA, 2019b](#); [Symrise, 2018](#)), but there was no corroborative evidence of neurotoxicity from other FOB assays evaluating grip strength (forelimb grip), sensory reactivity, and locomotor activity. Several acute/short-term supplemental studies reported neurological effects associated with *p*-isopropyltoluene exposure that included reduced mobility at 1,650 mg/kg-day for 24–28 days [Stel'makh et al. (1983) as cited in [ECHA \(1986\)](#)] and analgesic effects (i.e., increased reaction time on the hot plate test) after a dose of 40 mg/kg in mouse studies with oral exposure ([Siqueira Quintans et al., 2013](#)); transient clonic convulsions in rats and guinea pigs after a single inhalation exposure at 9,700 mg/m<sup>3</sup> [MacDonald, (1962a, b) as cited in [FFHPVC \(2005\)](#)]; and reduced spontaneous activity, analgesia, reduced urination and defecation, and antinociceptive effects in acute intraperitoneal (i.p.) studies in mice at doses of 25–200 mg/kg ([Quintans-Júnior et al., 2013](#); [Bonjardim et al., 2012](#); [Santana et al., 2011](#)). The significance of these findings and association with potential neurological effects (decreases in hindlimb grip strength) observed after repeated-dose exposure to *p*-isopropyltoluene in the [ECHA \(2019b\)/Symrise \(2018\)](#) study is unclear.

Overall, coherent evidence of liver toxicity based on organ weights, clinical chemistry, and histopathology effects was identified in P<sub>0</sub> rats at doses ≥50 mg/kg-day after subchronic exposure ([ECHA, 2019b](#); [Symrise, 2018](#)). Similarly, developmental effects were observed at ≥50 mg/kg-day in the [ECHA \(2019b\)/Symrise \(2018\)](#) study that included marginally significant reductions in body weight and survival of F<sub>1</sub> rats. There is also evidence of reproductive effects in P<sub>0</sub> rats, involving alterations in fertility index, estrous cyclicity, and male reproductive organ weights and histopathology at ≥100 mg/kg-day. As such, liver, developmental, and reproductive effects were considered further for the derivation of screening p-RfDs. Other treatment-related effects that occurred only in P<sub>0</sub> male rats (i.e., kidney lesions, increased BUN, and decreased hindlimb grip strength) in the [ECHA \(2019b\)/Symrise \(2018\)](#) study were not considered for dose-response analysis due to the limitations in the database for *p*-isopropyltoluene, which prevent further evaluation of the biological significance of these effects in animals.

### **Derivation of a Screening Subchronic Provisional Reference Dose**

Data for liver, developmental, and reproductive effects in rats from the [ECHA \(2019b\)/Symrise \(2018\)](#) study were considered for modeling using the U.S. Environmental Protection Agency (U.S. EPA) Benchmark Dose Software (BMDS, Version 3.3). As mentioned previously, despite the non-peer-reviewed status and data reporting limitations, the [ECHA \(2019b\)/Symrise \(2018\)](#) study used an adequate design (repeated-dose systemic study in rats with reproductive/developmental screening test according to GLP/OECD 422 guidelines), included multiple doses and a comprehensive array of toxicity endpoints, and identified sensitive health effects that are suitable for the derivation of the screening subchronic p-RfD. Increased liver weights (≥10%) in P<sub>0</sub> female rats observed at the lowest dose could not be modeled due to the lack of quantitative data on this endpoint (only percent change relative to controls was provided) but the LOAEL of 50 mg/kg-day was considered as a candidate POD. Dose-related increases in ALP in both male and P<sub>0</sub> female rats were modeled as continuous data using a

standard benchmark response (BMR) of 1 standard deviation (SD). Increased liver weights ( $\geq 10\%$ ) in P<sub>0</sub> male rats and increased hepatocyte hypertrophy in P<sub>0</sub> male and female rats were not considered for dose-response analysis since these effects were mostly observed at the highest dose (200 mg/kg-day) and there were more sensitive markers of liver toxicity available (i.e., increased liver weights in females and increased ALP in males and females at  $\geq 50$  mg/kg-day).

For developmental effects, dose-related decreases in body weights in F<sub>1</sub> females on PND 1 were modeled as continuous data using a BMR of 5% relative deviation (RD) because a 5% change in markers of growth/development in gestational studies (e.g., fetal weight) is considered a minimally biologically significant response level (U.S. EPA, 2012b). Significant decreases ( $\geq 5\%$ ) in body weights of F<sub>1</sub> males on PND 1 and in F<sub>1</sub> offspring survival (postimplantation survival index and live birth index) were only observed at 100 mg/kg-day; therefore, these endpoints were not considered for dose-response analysis.

For reproductive effects, the changes in percent fertility index observed at  $\geq 100$  mg/kg-day were considered for dose-response analysis by estimating the increased incidence of nonpregnant P<sub>0</sub> female rats over the total mated P<sub>0</sub> females (1/10, 1/10, 6/10, and 9/9 at 0, 50, 100, and 200 mg/kg-day, respectively); however, the data were not ultimately selected for BMD modeling because the response rate (60%) at the lowest dose group with increased incidence over the control (100 mg/kg-day) is much higher than the standard BMR of 10% extra risk used for dichotomous data. Similarly, the increased incidence in testicular spermatid retention in P<sub>0</sub> male rats at  $\geq 100$  mg/kg-day was not considered amenable for BMD modeling because of the steep dose-repose curve (response rate at 100 mg/kg-day was 70%). As such, the NOAEL of 50 mg/kg-day for these endpoints was considered for POD candidate comparisons. For other dose-related male degenerative lesions (i.e., epididymal reduced luminal sperm and sperm with cribriform changes in P<sub>0</sub> males at  $\geq 100$  mg/kg-day), the incidence data were evaluated as dichotomous data using a standard BMR of 10% extra risk. Other reproductive effects occurring only at the highest dose (200 mg/kg-day) were not amenable for BMDS modeling (i.e., changes in estrous cyclicity, decreased male reproductive organ weights, and increased incidence in testicular germ cell degeneration/depletion and epididymal luminal cell debris) and were not considered for POD candidate derivation due to the presence of more sensitive endpoints.

Prior to modeling the selected liver, developmental and reproductive endpoints, exposure doses used in ECHA (2019b)/Symrise (2018) study were converted to human equivalent doses (HEDs)<sup>5</sup>. In *Recommended Use of Body Weight<sup>3/4</sup> as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011e), the Agency endorses body-weight scaling to the

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<sup>5</sup>Administered doses were converted to HEDs by multiplying by a dosimetric adjustment factor (DAF) of 0.281 for males and 0.256 for females, calculated as follows:  $DAF = (BW_a^{1/4} \div BW_h^{1/4})$ , where  $BW_a$  = animal body weight, and  $BW_h$  = human body weight. The study reported initial body weights of 0.332–0.434 and 0.235–0.299 kg for Sprague Dawley male and female rats, respectively. In the absence of data for study-specific time-weighted average (TWA) or final body weights in the animals, the upper end of the reported initial body weight for rats in this study was used for males (0.434 kg) and females (0.299 kg) given that the initial body weights are higher than the recommended default values for males and females Sprague Dawley rats in a subchronic study (0.267 and 0.204 kg, respectively) (U.S. EPA, 1988). For humans, the reference value of 70 kg was used for body weight, as recommended by U.S. EPA (1988).

3/4 power (i.e.,  $BW^{3/4}$ ) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for deriving an RfD from effects that are not portal-of-entry effects or effects resulting from direct exposure of neonatal or juvenile animals. In the [ECHA \(2019b\)](#)/[Symrise \(2018\)](#) study, the observed decreases in body weight in female offspring resulted from exposure of the P<sub>0</sub> female rats; there was no direct exposure of neonates in this study. As such, HEDs for all the endpoints evaluated, including developmental effects, were calculated using a dosimetric adjustment factor (DAF) of 0.256 for P<sub>0</sub> female rats.

Table A-1 shows the data for liver, developmental, and reproductive endpoints that were considered for dose-response assessment and Table A-2 summarizes the BMD modeling results and provides candidate PODs for the derivation of the screening subchronic p-RfD. Details of model fit for each data set are presented in Appendix C. Candidate PODs that could not be evaluated via BMDS analysis (i.e., liver weights and fertility index in P<sub>0</sub> rats) are presented as NOAEL/LOAEL values.

<b>Table A-1. Data for Sensitive Liver and Reproductive Effects in P<sub>0</sub> Rats and Developmental Effects in F<sub>1</sub> Offspring<sup>a</sup></b>				
	<b>P<sub>0</sub> Females: exposed ~63 Days [HED] (mg/kg-d)<sup>b</sup></b>			
	<b>0 (control)</b>	<b>50 [13]</b>	<b>100 [25.6]</b>	<b>200 [51.2]<sup>c</sup></b>
<i>Number of animals</i>	5	5	4	0
ALP (U/L) <sup>d</sup>	151 ± 19.8 <sup>c</sup>	210 ± 70.9 (+39%)	270 ± 119.1* (+79%)	NA
Liver weight relative to body weight (%) <sup>e</sup>	–	14	22*	NA
Absolute liver weight (%) <sup>e</sup>	–	16	26*	NA
<i>Number of mated females</i>	10	10	10	9
Increased incidence of nonpregnant females <sup>f</sup>	1	1	6	9
<b>P<sub>0</sub> Males: exposed ~35 [HED] (mg/kg-d)<sup>b</sup></b>				
	<b>0 (control)</b>	<b>50 [14]</b>	<b>100 [28.1]</b>	<b>200 [56.2]</b>
<i>Number of animals</i>	5	5	5	5
ALP (U/L) <sup>d</sup>	160 ± 23.5	166 ± 43.5 (+4%)	184 ± 22.8 (+15%)	232 ± 61.4* (+45%)
<i>Number of animals</i>	10	10	10	10
Spermatid retention in the testes <sup>f</sup>	0	0	7*	9*
Reduced luminal sperm in the epididymides <sup>f</sup>	0	0	2	10*
Sperm with cribriform changes in the epididymides <sup>f</sup>	0	0	1	5*
<b>F<sub>1</sub> Offspring: exposed during gestation and lactation until PND 13 [HED] (mg/kg-d)<sup>b</sup></b>				
	<b>0 (control)</b>	<b>50 [13]</b>	<b>100 [25.6]</b>	<b>200 [51.2]<sup>c</sup></b>
<i>Number of pregnant females</i>	9	9	4	0
Decreased F <sub>1</sub> female body weight on PND 1 <sup>d</sup>	6.6 ± 0.66	6.3 ± 0.84 (–4.5%)	6.0 ± 0.3 (–9.1%)	NA

<sup>a</sup>Symrise (2018).

<sup>b</sup>ADDs (mg/kg-day) were reported by the study authors; calculated HEDs appear in brackets.

<sup>c</sup>Data for females exposed to 200 mg/kg-day were not collected due to failure to become pregnant.

<sup>d</sup>Data represent mean ± SD. Value in parentheses is % change relative to control =  $([\text{treatment mean} - \text{control mean}] \div \text{control mean}) \times 100$ .

<sup>e</sup>Data represent percent difference relative to controls [actual measurement data for control and treatment groups were not available in the study report (ECHA, 2019b)].

<sup>f</sup>Data represent number of animals showing changes.

\*Significantly different from control ( $p < 0.05$ ) as reported by the study authors.

– = reported in ECHA as not test item-related; ALP = alkaline phosphatase; ECHA = European Chemicals Agency; HED = human equivalent dose; NA = not available; SD = standard deviation.

**Table A-2. Comparison of Candidate POD Values in Sprague Dawley Rats Exposed to *p*-Isopropyltoluene via Subchronic Gavage Exposure (~35–63 Days) or During Gestation and Lactation until Postnatal Day 13<sup>a</sup>**

Endpoint	Best-Fitting Model	BMR	BMDL (HED) (mg/kg-d)	POD type	POD (HED) (mg/kg-d)
Increased absolute and relative liver weight in P <sub>0</sub> female rats	Data not amenable for BMD modeling <sup>b</sup>			LOAEL	13
<b>Increased ALP in P<sub>0</sub> female rats</b>	<b>Exponential (degree 3)</b>	<b>1 SD from control (1SD)</b>	<b>3.6</b>	<b>BMDL</b>	<b>3.6</b>
Increased ALP in P <sub>0</sub> male rats	Linear	1 SD from control (1SD)	18	BMDL	18
Increased incidence of nonpregnant P <sub>0</sub> female rats	Data not amenable for BMD modeling <sup>c</sup>			NOAEL	13
Increased incidence of spermatid retention in the testes of P <sub>0</sub> male rats	Data not amenable for BMD modeling <sup>c</sup>			NOAEL	14
Increased incidence of reduced luminal sperm in the epididymides of P <sub>0</sub> male rats	Log-logistic	10% extra risk	20	BMDL	20
Increased incidence of sperm with cribriform changes in the epididymides of P <sub>0</sub> male rats	Multistage (degree 3)	10% extra risk	14	BMDL	14
Decreased F <sub>1</sub> female body weight on PND 1	Linear	5% RD from control (0.05 RD)	7.1	BMDL	7.1

<sup>a</sup>[Symrise \(2018\)](#).

<sup>b</sup>Data were not considered amenable for BMD modeling due to the lack of quantitative data on mean liver weights and variance.

<sup>c</sup>Data were not considered amenable for BMD modeling since the response rates (60–70%) at the lowest dose group (100 mg/kg-day) with increased incidence over the controls is much higher than the standard BMR used for dichotomous data (10% extra risk).

BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; BMR = benchmark response; HED = human equivalent dose; LOAEL = lowest-adverse-effect level; PND = postnatal day 1; POD = point of departure; RD = relative deviation; SD = standard deviation.

The benchmark dose lower confidence limit with one standard deviation (BMDL<sub>1SD</sub>) (HED) of 3.6 mg/kg-day for increased ALP in P<sub>0</sub> female rats exposed ~63 days ([ECHA, 2019b](#); [Symrise, 2018](#)) provides the lowest candidate POD for liver effects. A freestanding LOAEL (HED) of 13 mg/kg-day for increased liver weights in P<sub>0</sub> female rats is also available but the changes (16 and 14% for absolute and relative liver weights, respectively) at the identified

LOAEL (HED) were close to the minimally biologically significant response level (10%). Therefore, it is likely that the POD for increased ALP, which is 70% lower, is protective of the POD for increased liver weights. Further, these endpoints are coherent and reliable markers of liver toxicity occurring in the same species and sex. In particular, increased ALP is associated with obstruction of hepatic bile flow and damage to the biliary epithelial cells ([EMEA, 2008](#); [Boone et al., 2005](#)). Additionally, there is higher confidence in the POD estimate for increased ALP based on the availability of quantitative data (mean  $\pm$  SD) for this endpoint for BMD modeling. As mentioned above, data for liver weights in P<sub>0</sub> rats from the [Symrise \(2018\)](#) study were only available as percent change relative to controls from the [ECHA \(2019b\)](#) report. Finally, the POD for increased ALP in P<sub>0</sub> female rats (BMDL<sub>1SD</sub> [HED] of 3.6 mg/kg-day) is protective of the lowest PODs derived for developmental effects (a benchmark dose lower confidence limit with 5% relative deviation [BMDL<sub>0.05RD</sub>] [HED] of 7.1 mg/kg-day for decreased F<sub>1</sub> female body weights on PND 1) and reproductive effects (a NOAEL [HED] of 13 mg/kg-day for increased incidence of nonpregnant P<sub>0</sub> females). **Altogether, the evidence suggests that the liver is a primary target for *p*-isopropyltoluene via oral exposure and the BMDL<sub>1SD</sub> (HED) of 3.6 mg/kg-day for increased ALP in P<sub>0</sub> female rats exposed ~63 days ([ECHA, 2019b](#); [Symrise, 2018](#)) is selected as the most sensitive POD for the derivation of the screening subchronic p-RfD.**

The screening subchronic p-RfD for *p*-isopropyltoluene is derived by applying a composite uncertainty factor (UF<sub>C</sub>) of 100 (reflecting an interspecies uncertainty factor [UF<sub>A</sub>] of 3, a database uncertainty factor [UF<sub>D</sub>] of 3, and an intraspecies uncertainty factor [UF<sub>H</sub>] of 10) to the selected POD of 3.6 mg/kg-day.

$$\begin{aligned}
 \text{Screening Subchronic p-RfD} &= \text{POD (HED)} \div \text{UF}_C \\
 &= 3.6 \text{ mg/kg-day} \div 100 \\
 &= \mathbf{4 \times 10^{-2} \text{ mg/kg-day}}
 \end{aligned}$$

Table A-3 summarizes the uncertainty factors for the screening subchronic p-RfD for *p*-isopropyltoluene.

Table A-3. Uncertainty Factors for the Screening Subchronic p-RfD for <i>p</i> -Isopropyltoluene (CASRN 99-87-6)		
UF	Value	Justification
UF <sub>A</sub>	3	A UF <sub>A</sub> of 3 (10 <sup>0.5</sup> ) is applied to account for uncertainty associated with extrapolating from animals to humans when cross-species dosimetric adjustment (HED calculation) is performed.
UF <sub>D</sub>	3	A UF <sub>D</sub> of 3 is applied to account for deficiencies and uncertainties in the database. The oral database of relevant studies for <i>p</i> -isopropyltoluene includes a non-peer-reviewed, repeated-dose systemic toxicity study with a reproductive/developmental toxicity screening test (ECHA, 2019b; Symrise, 2018). The study had data reporting limitations but adhered to GLP and OECD test guidelines, evaluated a wide range of relevant toxicity endpoints (including body weight, food consumption, clinical observations, FOB, hematology, serum chemistry, organ weights, histopathology, and reproductive and developmental endpoints [mating and fertility indices, reproductive parameters, sperm evaluations, estrous cycle, histopathology of reproductive organs, and offspring viability, body weight, gross abnormalities, and thyroid hormone levels]) and provided sufficient information to identify toxicologically relevant health effects and associated dose-response relationships. The lack of teratogenic studies examining potential effects in utero and multigenerational reproductive studies represent a significant limitation in the database for <i>p</i> -isopropyltoluene.
UF <sub>H</sub>	10	A UF <sub>H</sub> of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of <i>p</i> -isopropyltoluene in humans.
UF <sub>L</sub>	1	A UF <sub>L</sub> is applied because the POD is a BMDL.
UF <sub>S</sub>	1	A UF <sub>S</sub> of 1 is applied because the POD was derived from a study of suitable duration (35–63 days) for a subchronic value.
UF <sub>C</sub>	100	Composite UF = UF <sub>A</sub> × UF <sub>D</sub> × UF <sub>H</sub> × UF <sub>L</sub> × UF <sub>S</sub> .

BMDL = benchmark dose lower confidence limit; FOB = functional observational battery; GLP = Good Laboratory Practice; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; OECD = Organisation of Economic Co-operation and Development; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor; UF<sub>A</sub> = interspecies uncertainty factor; UF<sub>C</sub> = composite uncertainty factor; UF<sub>D</sub> = database uncertainty factor; UF<sub>H</sub> = intraspecies uncertainty factor; UF<sub>L</sub> = LOAEL-to-NOAEL uncertainty factor; UF<sub>S</sub> = subchronic-to-chronic uncertainty factor.

### Derivation of Screening Chronic Provisional Reference Dose

No chronic studies are available for *p*-isopropyltoluene via any exposure route. Therefore, the POD (BMDL<sub>1SD</sub> [HED]) of 3.6 mg/kg-day used for the derivation of the screening subchronic p-RfD based on increased ALP in P<sub>0</sub> female rats exposed for ~63 days (ECHA, 2019b; Symrise, 2018) is also selected for the derivation of the chronic p-RfD. The rationale for the selection of this POD is provided in the section above (Derivation of a Screening Subchronic Provisional Reference Dose). The screening chronic p-RfD is derived by applying a UF<sub>C</sub> of 1,000 to the selected POD of 3.6 mg/kg-day. The UF<sub>C</sub> of 1,000 was derived by applying a UF<sub>A</sub> of 3, a UF<sub>D</sub> of 3, a UF<sub>H</sub> of 10, and a subchronic-to-chronic uncertainty factor (UF<sub>S</sub>) of 10.

$$\begin{aligned}
 \text{Screening Chronic p-RfD} &= \text{POD (HED)} \div \text{UF}_C \\
 &= 3.6 \text{ mg/kg-day} \div 1,000 \\
 &= \mathbf{4 \times 10^{-3} \text{ mg/kg-day}}
 \end{aligned}$$

Table A-4 summarizes the uncertainty factors for the screening subchronic p-RfD for *p*-isopropyltoluene.

**Table A-4. Uncertainty Factors for the Screening Chronic p-RfD for *p*-Isopropyltoluene (CASRN 99-87-6)**

UF	Value	Justification
UF <sub>A</sub>	3	A UF <sub>A</sub> of 3 (10 <sup>0.5</sup> ) is applied to account for uncertainty associated with extrapolating from animals to humans when cross-species dosimetric adjustment (HED calculation) is performed.
UF <sub>D</sub>	3	A UF <sub>D</sub> of 3 is applied to account for deficiencies and uncertainties in the database. The oral database of relevant studies for <i>p</i> -isopropyltoluene includes a non-peer-reviewed, repeated-dose systemic toxicity study with a reproductive/developmental toxicity screening test ( <a href="#">ECHA, 2019b</a> ; <a href="#">Symrise, 2018</a> ). The study had data reporting limitations but adhered to GLP and OECD test guidelines, evaluated a wide range of relevant toxicity endpoints (including body weight, food consumption, clinical observations, FOB, hematology, serum chemistry, organ weights, histopathology, and reproductive and developmental endpoints [mating and fertility indices, reproductive parameters, sperm evaluations, estrous cycle, histopathology of reproductive organs, and offspring viability, body weight, gross abnormalities and thyroid hormone levels]) and provided sufficient information to identify toxicologically relevant health effects and associated dose-response relationships. The lack of teratogenic studies examining potential effects in utero and multigenerational reproductive studies represent a significant limitation in the database for <i>p</i> -isopropyltoluene. Additionally, the lack of chronic studies, which is accounted by applying a UF <sub>S</sub> of 10, represents a limitation in the database for <i>p</i> -isopropyltoluene.
UF <sub>H</sub>	10	A UF <sub>H</sub> of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of <i>p</i> -isopropyltoluene in humans.
UF <sub>L</sub>	1	A UF <sub>L</sub> is applied because the POD is a BMDL.
UF <sub>S</sub>	10	A UF <sub>S</sub> of 10 is applied because the POD was derived from a study of subchronic duration (35–63 days) for a chronic value.
UF <sub>C</sub>	1,000	Composite UF = UF <sub>A</sub> × UF <sub>D</sub> × UF <sub>H</sub> × UF <sub>L</sub> × UF <sub>S</sub> .

BMDL = benchmark dose lower confidence limit; FOB = functional observational battery; GLP = Good Laboratory Practice; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; OECD = Organisation of Economic Co-operation and Development; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor; UF<sub>A</sub> = interspecies uncertainty factor; UF<sub>C</sub> = composite uncertainty factor; UF<sub>D</sub> = database uncertainty factor; UF<sub>H</sub> = intraspecies uncertainty factor; UF<sub>L</sub> = LOAEL-to-NOAEL uncertainty factor; UF<sub>S</sub> = subchronic-to-chronic uncertainty factor.

## INHALATION NONCANCER TOXICITY VALUES

As discussed in the main body of the report, no repeated-dose inhalation studies adequate for quantitative dose-response analysis are available for *p*-isopropyltoluene. Instead, an alternative analogue approach was taken to support the derivation of inhalation noncancer toxicity values.

## APPLICATION OF AN ALTERNATIVE ANALOGUE APPROACH (METHODS)

The analogue approach allows for the use of data from related compounds to calculate screening values when data for the target chemical are limited or unavailable. Details regarding searches and methods for analogue analysis are adapted from [Wang et al. \(2012\)](#) and [Lizarraga et al. \(2023\)](#) and chemical-specific parameters of read-across tools can be found in Appendix D. Candidate analogues are identified on the basis of three similarity categories (structure, toxicokinetics [metabolism], and toxicodynamics [toxicity and mode of action; MOA]) to facilitate the final source analogue selection. The analogue approach may or may not be route-

specific or applicable to multiple routes of exposure. All information is considered together as part of the final weight-of-evidence (WOE) approach to select the most suitable source analogue.

In this assessment, an expanded analogue identification approach was utilized to collect an augmented set of candidate analogues for the target chemical. As described below, this approach applies a variety of tools and methods for identifying candidate analogues that are similar to the target chemical based on structural features; metabolic relationships; or related toxic effects and mechanisms of action. The application of a variety of different tools and methods to identify candidate analogues minimizes the impact of limitations of any individual tool or method on the pool of chemicals included, chemical fragments considered, and methods for assessing similarity. Further, the inclusion of techniques to identify analogues based on metabolism and toxicity or bioactivity expands the pool of candidates beyond those based exclusively on structural similarity. The specific tools described below used for the expanded analogue searches were selected because they are publicly available, supported by U.S. and OECD agencies, updated regularly, and widely used.

To identify structurally-related compounds, an initial pool of analogues is identified using automated tools, including ChemIDplus<sup>6</sup> (NLM, 2022a), the CompTox Chemicals Dashboard<sup>7</sup> (U.S. EPA, 2022a), and the OECD Quantitative Structure-Activity Relationship (QSAR) Toolbox<sup>8</sup> (NLM, 2022a). Additional analogues identified as ChemIDplus-related substances, mixtures, and CompTox “related substances”<sup>9</sup> are also considered. CompTox General Read-Across (GenRA)<sup>10</sup> analogues are collected using the methods deployed on the publicly available GenRA Beta version, which may include Morgan fingerprints, Torsion fingerprints, ToxPrints and the use of ToxCast, Tox21, and ToxRef data (Patlewicz and Shah, 2023). For compounds that have very few analogues identified by structural similarity using a similarity threshold of 0.8 or 80%, substructure searches may be performed in the QSAR Toolbox, or similarity searches may be rerun using a reduced similarity threshold (e.g., <80%). Structural

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<sup>6</sup>ChemIDplus is a free, web search system that provides access to the structure and nomenclature authority files used for the identification of chemical substances cited in National Library of Medicine (NLM) databases, including the TOXNET system. The database contains over 350,000 chemical records, of which over 80,000 include chemical structures and allows users to draw a chemical structure to search for similar substances using PubChem Substructure fingerprints (NLM, 2009; Liwanag et al., 2000). NLM retired ChemIDplus in December 2022.

<sup>7</sup>The U.S. EPA’s CompTox Chemicals Dashboard provides publicly accessible chemistry, toxicity, and exposure information for over one million chemicals (Williams et al., 2017). Using EPAM’s Bingo fingerprints, the “Similar Compounds” tab provides a list of chemicals that are similar in structure to the selected chemical, based on the Tanimoto similarity search metric with a minimum similarity factor threshold of 0.8 (EPAM, 2024).

<sup>8</sup>The OECD QSAR Toolbox is a software application intended to be used by government, industry and other stakeholders to fill gaps in data needed for assessing the hazards of chemicals. The application allows users to search for analogues based on structure similarity criteria and input similarity thresholds (OECD, 2017). It also contains metabolism simulators which are simplified versions of the simulators in CATALOGIC and TIMES and consist of hierarchically ordered molecular transformations (Yordanova et al., 2019).

<sup>9</sup>The CompTox Chemicals Dashboard “Related Substances” tab provides a chemical list of all chemicals related to the queried chemical through mapped relationships underlying the database. Relationships include searched chemical (self-relationship), salt form, monomer, polymer, predecessor component, component, Markush parent, Markush child, transformation parent, and transformation product (Williams et al., 2021).

<sup>10</sup>Operationalized within the CompTox Chemicals Dashboard, GenRA is an algorithmic approach that makes read-across predictions on the basis of a similarity weighted activity of source analogues (nearest neighbors). GenRA gives users the ability to identify candidate analogues based on structural and bioactivity information (U.S. EPA, 2022c).

analogues are clustered using the Chemical Assessment Clustering Engine (ChemACE)<sup>11</sup> ([U.S. EPA, 2011b](#)) based on chemical fragments to support expert-driven refinement of the candidate pool. The ChemACE output is reviewed by an experienced chemist, who narrows the list of structural analogues based on expert judgment of multiple lines of evidence including known or expected structure-activity relationships, reactivity, and known or expected metabolic pathways. Initially, candidate analogues are screened for structural and chemical similarity to confirm that the analogues have the same reactive functional groups and similar overall size and structural features as the target chemical. Chemicals lacking key functionality or bearing additional functionality relative to the target are less desirable as analogues and are not selected as structural analogues. The selection may be expanded to include chemicals expected to be part of a metabolic series (either as metabolic precursors or as metabolites) of the target chemical. Chemicals that produce metabolites in common with the target may also be selected if the metabolite is known or suspected to be part of the mechanism of action. All candidate analogues are then screened for structural features that can influence their activity relative to the target. Examples of such features include steric influences of bulky substituent groups, branching, rigidity, presence of blocking groups on a functional group, and differing substitution patterns on aromatic rings. Finally, key physical and chemical properties of the candidate analogues are compared with the target to confirm that they can be expected to have similar bioavailability, similar transport, and similar abiotic transformation properties.

Toxicokinetic studies tagged as potentially relevant supplemental material during screening are used to identify metabolic analogues (metabolites and metabolic precursors). Metabolites are also identified from two OECD QSAR Toolbox metabolism simulators (in vivo rat metabolism simulator and rat liver S9 metabolism simulator). Targeted PubMed searches are conducted to identify metabolic precursors and other compounds that share any of the observed or predicted metabolites identified for the target chemical.

In vivo toxicity data for the target chemical (if available) are evaluated to determine whether characteristic effects associated with a particular mechanism of toxicity are observed (e.g., cholinesterase inhibition, inhibition of oxidative phosphorylation). In addition, in vitro mechanistic data tagged as potentially relevant supplemental material during screening or obtained from tools including GenRA, ToxCast/Tox21<sup>12</sup>, and Comparative Toxicogenomics Database (CTD)<sup>13</sup> ([CTD, 2022](#)) are also evaluated for this purpose. ToxCast/Tox21 data available from the CompTox Chemicals Dashboard are collected for the target chemical to determine bioactivity in in vitro assays that may indicate potential mechanism(s) of action. The GenRA tool is used to search for analogues using Morgan, Torsion and ToxPrints fingerprint

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<sup>11</sup>ChemACE clusters chemicals into groups based on structural features and a reasonable presumption that toxicity may be influenced by such structural characteristics (e.g., structural alerts, toxicophores). ChemACE identifies structural diversity in a large chemical inventory and highlights analogous clusters for potential read across. In the expanded analogue approach, clustering with ChemACE supports expert refinement of the candidate analogue pool. The ChemACE methodology is based on logic implemented in the Analog Identification Methodology (AIM) tool (<http://aim.epa.gov>) that identifies analogues based on the presence of common fragments using a tiered approach ([U.S. EPA, 2011a](#)).

<sup>12</sup>ToxCast and Tox21 are publicly available databases containing high-throughput assay endpoints covering a range of high-level cell responses ([Thomas et al., 2018](#); [U.S. EPA, 2018b](#)).

<sup>13</sup>The CTD is a publicly available database that provides manually curated information about chemical–gene/protein interactions, chemical–disease and gene–disease relationships. The CTD allows users to identify chemicals that induce gene interactions similar to those induced by the target chemical ([Davis et al., 2021](#)).

similarities and activity in ToxCast/Tox21 in vitro assays or ToxRef data (10 analogues collected from each neighbors data set). Using the ToxCast/Tox21 bioactivity data, nearest neighbors identified may be considered potential candidate analogues. The CTD is searched to identify compounds with gene interactions similar to those induced by the target chemical; compounds with gene interactions similar to the target chemical (similarity index >0.5) may be considered potential candidate analogues.

Candidate analogues identified on the basis of the structural, metabolic, and toxicodynamic similarity contexts are interrogated through the CompTox Chemicals Dashboard, where QSAR-ready simplified molecular-input line-entry system (SMILES) are collected and toxicity value availability is determined (e.g., from the Agency for Toxic Substances and Disease Registry [ATSDR], California Environmental Protection Agency [CalEPA] Office of Environmental Health Hazard Assessment [OEHHA], the U.S. EPA's Integrated Risk Information System [IRIS], PPRTVs). Analogues that have subchronic or chronic toxicity data or toxicity values available from other public health agencies are flagged for potential consideration as supportive evidence.

### **Analogue Search Results for *p*-Isopropyltoluene (Inhalation Exposure)**

As mentioned above, candidate analogues for *p*-isopropyltoluene for inhalation exposure were identified based on structural, metabolic, and toxicity/mechanisms/MOA relationships. For candidates identified through these approaches, the U.S. EPA (IRIS and PPRTV), ATSDR, and CalEPA sources were searched for subchronic, intermediate, and chronic inhalation toxicity values. Details are provided below.

#### ***Identification of Structural Analogues with Established Toxicity Values***

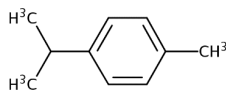
*p*-Isopropyltoluene is not a member of an existing OECD or New Chemical category. Candidate structural analogues for *p*-isopropyltoluene were identified using similarity searches in the OECD Toolbox ([OECD, 2022](#)), the U.S. EPA CompTox Chemicals Dashboard ([U.S. EPA, 2022a](#)), and ChemIDplus tools ([NLM, 2022a](#)). A total of 547 unique structural analogues were identified for *p*-isopropyltoluene in the Dashboard, OECD QSAR Toolbox, and ChemIDplus (80% similarity threshold).

The list of potential analogues was reviewed by a chemist with expertise in read-across. Based on the structural features expected to influence toxicokinetics and/or toxicity, the criteria for including candidate analogues were as follows:

1. One aromatic ring with two or fewer substituents.
2. Preferred substituents on the ring are one methyl group and one isopropyl group; however, *sec*-butyl groups are also acceptable since they have active benzylic positions analogous to isopropyl groups.
  - a. The carbon atoms at the benzylic positions are either primary (methyl) or tertiary (isopropyl or *sec*-butyl) because radicals can form at these positions. Analogues that can form similar radicals at a benzylic position were included, since radical formation may be part of the biological activity of *p*-isopropyltoluene.

- b. The benzylic positions are sites for metabolic transformations, and the substitution patterns at the benzylic position can influence the metabolites formed.
3. In order to select analogues with similar bioavailability, preferred candidate chemicals will have a log  $K_{ow}$  (octanol-water partition coefficient) within 1 log unit of the target chemical.
4. Toluene was excluded due to expected differences in its metabolic pathways relative to *p*-isopropyltoluene.
  - a. *p*-Isopropyltoluene is primarily metabolized via side-chain oxidation pathways in laboratory animals. Ring-oxidation products are not formed in large quantities ([Boyle et al., 1999](#); [Matsumoto et al., 1992](#); [Walde et al., 1983](#); [Ishida et al., 1981](#); [Bakke and Scheline, 1970](#)).
  - b. Toluene is metabolized via ring oxidation pathways in addition to oxidation of the methyl group. Its metabolites include more epoxides and phenols than have been reported for *p*-isopropyltoluene ([ATSDR, 2017](#)).
5. Ethylbenzene and ethyl-substituted benzenes were excluded due to expected differences in their metabolic pathways relative to *p*-isopropyltoluene.
  - a. *p*-Isopropyltoluene is primarily metabolized via side-chain oxidation pathways. Ring-oxidation products are not formed in large quantities ([Boyle et al., 1999](#); [Matsumoto et al., 1992](#); [Walde et al., 1983](#); [Ishida et al., 1981](#); [Bakke and Scheline, 1970](#)).
  - b. Ethylbenzene is metabolized via ring oxidation pathways in addition to oxidation of the ethyl group. Its metabolites include more epoxides and phenols than have been reported for *p*-isopropyltoluene ([ATSDR, 2010](#)).
  - c. Oxidation of the ethyl group occurs at the benzylic position first, yielding acetophenone ([ATSDR, 2010](#)). This transformation is not possible for *p*-isopropyltoluene.
6. Xylene isomers were not reported in the similarity tool outputs (OECD QSAR Toolbox, Dashboard, or ChemIDplus) but were included based on shared structural features, including a single aromatic ring with up to two methyl or isopropyl substituents.
  - a. Metabolism of xylenes occurs primarily through oxidation of the methyl substituents ([ATSDR, 2007](#)), which is similar to *p*-isopropyltoluene.

Using these criteria, a total of 10 candidate structural analogues for *p*-isopropyltoluene were identified, as shown in Table A-5. Two of the identified structural analogues, isopropylbenzene and xylenes (mixed isomers), had available inhalation toxicity values from the searched databases.

**Table A-5. Candidate Structural Analogues Identified for *p*-Isopropyltoluene Based on Tools and Expert Judgment**

Tool (method)	Analogue (CASRNs) Selected for Toxicity Value Searches	Structure
Dashboard (Tanimoto), OECD Toolbox (method not described) <sup>a</sup>	<i>m</i> -Isopropyltoluene (CASRN 535-77-3)	
Dashboard (Tanimoto) <sup>a</sup>	<i>o</i> -Isopropyltoluene (CASRN 527-84-4)	
	Benzene, 1,2-bis(1-methylethyl)- (CASRN 577-55-9)	
	1-(Butan-2-yl)-3-methylbenzene (CASRN 1772-10-7)	
	1-(Butan-2-yl)-4-methylbenzene (CASRN 1595-16-0)	
	<i>sec</i> -Butylbenzene (CASRN 135-98-8)	
	<b>Isopropylbenzene (cumene) (CASRN 98-82-8)</b>	
Expert judgment <sup>b</sup>	<b>Xylene, mixed isomers (CASRN 1330-20-7)</b>	

<sup>a</sup>80% similarity threshold was applied.<sup>b</sup>See structural analogue inclusion criteria number 6.**Bold** shows compounds with inhalation toxicity values (see Table A-9).

### ***Identification of Toxicokinetic Precursors or Metabolites with Established Toxicity Values***

*p*-Isopropyltoluene metabolism has been studied in rats, rabbits, guinea pigs, and marsupials [possum and greater glider] ([Boyle et al., 1999](#); [Matsumoto et al., 1992](#); [Walde et al., 1983](#); [Ishida et al., 1981](#); [Bakke and Scheline, 1970](#)). These studies demonstrated that *p*-isopropyltoluene undergoes extensive oxidation of the methyl substituent and isopropyl side-chain to yield polar oxygenated metabolites (see Section 2.3.4 for more details). The primary metabolites include monohydric alcohols, diols, mono- and dicarboxylic acids, and hydroxy acids. These metabolites are either excreted unchanged in the urine or undergo conjugation with glucuronic acid and/or glycine, followed by excretion in the urine. Ring-hydroxylation was not observed in *in vivo* animal studies ([Boyle et al., 1999](#); [Matsumoto et al., 1992](#); [Walde et al., 1983](#); [Ishida et al., 1981](#); [Bakke and Scheline, 1970](#)), with the single exception of trace amounts of 5-isopropyl-2-methylphenol (carvacrol) found in the urine of guinea pigs ([Walde et al., 1983](#)). An *in vitro* study using human recombinant cytochrome P450 (CYP) enzymes identified 2-isopropyl-5-methylphenol (thymol) as a major metabolite ([Meesters et al., 2009](#)). Phenolic metabolites were not observed in an *in vitro* study using liver microsomes obtained from rats or marsupials (possum and koala) ([Pass et al., 2002](#)). [Southwell et al. \(1980\)](#) reported *p*-cresol as a metabolite of *p*-isopropyltoluene in bushtail possums; however, this is a poorly reported study with significant limitations. Dealkylation of the isopropyl group to form *p*-cresol is unlikely, and this metabolite is not reported in any other study. In addition, endogenous *p*-cresol is produced via digestion of tyrosine (from food proteins) in the intestine. Free *p*-cresol formed in this way is absorbed from the intestine and eliminated in the urine as conjugates ([IPCS, 1995](#)). Data were not provided for control animals; therefore, the source of urinary *p*-cresol could not be conclusively attributed to *p*-isopropyltoluene administration. *p*-Cresol was not included as a candidate metabolic analogue of *p*-isopropyltoluene.

Predicted metabolites were collected from the OECD QSAR Toolbox ([OECD, 2022](#)). Predicted metabolites of *p*-isopropyltoluene collected from the OECD QSAR Toolbox also consist of monohydric alcohols, diols, mono- and dicarboxylic acids, and hydroxy acid metabolites. All of the predicted metabolites were also identified as observed metabolites except for *p*-isopropylbenzaldehyde (CASRN 122-03-2); 2-*p*-tolylpropionaldehyde (CASRN 99-72-9); 4-(1-hydroxy-1-methyl-ethyl)benzaldehyde (CASRN 81036-81-9); 2-[4-(hydroxymethyl)phenyl]propanal, 4-(1-hydroxy-2-propanyl)benzaldehyde (CASRN 1512868-96-0); and 2-[4-(hydroxymethyl)phenyl]-1,2-propanediol (CASRN 1822818-61-0).

PubMed searches (searching “*p*-isopropyltoluene” or “99-87-6” and “metabolite”) were conducted to identify metabolic precursors to *p*-isopropyltoluene. No metabolic precursors were identified. PubMed was also searched to identify other compounds that are metabolized to any of the observed or predicted metabolites of *p*-isopropyltoluene (searching the metabolite name or [CASRN if available] and “metabolite”). No compounds that share at least one metabolite with *p*-isopropyltoluene were identified in these searches.

Table A-6 summarizes the 22 candidate metabolic analogues for *p*-isopropyltoluene (17 observed metabolites and 5 additional predicted metabolites). Searches for relevant toxicity

values for the observed or predicted candidate metabolic analogues of *p*-isopropyltoluene did not identify candidate analogues with inhalation toxicity values.

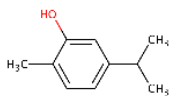
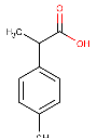
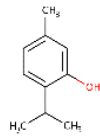
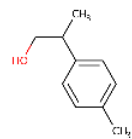
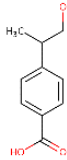
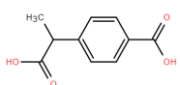
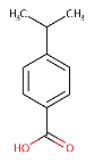
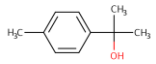
<b>Table A-6. Candidate Metabolic Analogues of <i>p</i>-Isopropyltoluene</b>		
<b>Relationship to <i>p</i>-Isopropyltoluene</b>	<b>Compound (CASRN)</b>	<b>Structure</b>
Metabolic precursor	None identified	Not applicable
Metabolite	5-Isopropyl-2-methylphenol (carvacrol) (CASRN 499-75-2) <sup>a,b</sup>	
	Hydroxycarvacrol (location of second hydroxyl group undefined) <sup>a,b,c</sup>	Not provided
	2-( <i>p</i> -Tolyl)propanoic acid (CASRN 938-94-3) <sup>a,b</sup>	
	2-Isopropyl-5-methylphenol (thymol) (CASRN 89-83-8) <sup>a,b</sup>	
	2-( <i>p</i> -Tolyl)-1-propanol (CASRN 4371-50-0) <sup>a,b</sup>	
	2- <i>p</i> -Carboxyphenyl-1-propanol (CASRN 88416-61-9) <sup>a,b</sup>	
	2- <i>p</i> -Carboxyphenylpropionic acid (CASRN 67381-50-4) <sup>a,b</sup>	
	<i>p</i> -Isopropylbenzoic acid (cumic acid) (CASRN 536-66-3) <sup>a,b</sup>	
	2- <i>p</i> -tolylpropan-2-ol (CASRN 1197-01-9) <sup>a,b</sup>	

Table A-6. Candidate Metabolic Analogues of *p*-Isopropyltoluene

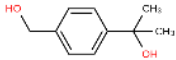
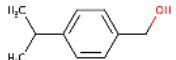
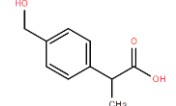
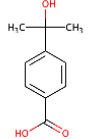
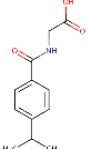
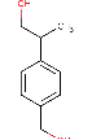
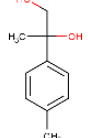
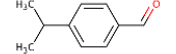
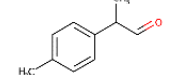
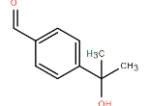
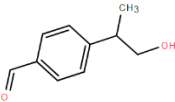
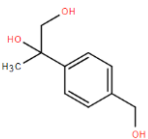
Relationship to <i>p</i> -Isopropyltoluene	Compound (CASRN)	Structure
	2- <i>p</i> -(Hydroxymethyl)phenyl-2-propanol (CASRN 88416-58-4) <sup>a,b</sup>	
	<i>p</i> -Isopropylbenzyl alcohol (CASRN 536-60-7) <sup>a,b</sup>	
	2- <i>p</i> -(Hydroxymethyl)phenylpropanoic acid (CASRN 88416-60-8; 1630333-50-4, 1630342-91-4) <sup>a,b</sup>	
	2-( <i>p</i> -Tolyl)-2-propanol (CASRN 3609-50-5) <sup>a,b</sup>	
	N-(4-Isopropylbenzoyl)glycine (CASRN 88416-62-0) <sup>a,b</sup>	
	Glucuronides of 2-( <i>p</i> -tolyl)-1-propanol; 4-(1-carboxyethyl)benzoic acid; <i>p</i> -isopropylbenzoic acid, 2- <i>p</i> -carboxyphenylpropionic acid; and 2-( <i>p</i> -tolyl)-2-propanol <sup>a,b,c</sup>	Not Provided
	2- <i>p</i> -(Hydroxymethyl)phenyl-2-propanol (CASRN 88416-59-5) <sup>a,b</sup>	
	2-( <i>p</i> -Tolyl)-1,2-propanediol (CASRN 88416-64-2) <sup>a,b</sup>	
	<i>p</i> -Isopropylbenzaldehyde (CASRN 122-03-2) <sup>b</sup>	
	2- <i>p</i> -Tolylpropionaldehyde (CASRN 99-72-9) <sup>b</sup>	
	4-(1-Hydroxy-1-methyl-ethyl)benzaldehyde (CASRN 81036-81-9) <sup>b</sup>	

Table A-6. Candidate Metabolic Analogues of <i>p</i> -Isopropyltoluene		
Relationship to <i>p</i> -Isopropyltoluene	Compound (CASRN)	Structure
	4-(1-hydroxy-2-propanyl)benzaldehyde (CASRN 1512868-96-0) <sup>b</sup>	
	2-[4-(Hydroxymethyl)phenyl]-1,2-propanediol (CASRN 1822818-61-0) <sup>b</sup>	
Share common metabolite(s)	None identified	Not applicable

<sup>a</sup>Observed metabolites reported in the scientific literature.

<sup>b</sup>Predicted metabolites from OECD QSAR Toolbox metabolism simulators (OECD, 2022).

<sup>c</sup>CASRN not available for this metabolite; consequently, the chemical structure is not provided.

OECD = Organisation for Economic Co-operation and Development; QSAR = quantitative structure-activity relationship.

### ***Identification of Analogues on the Basis of Toxicity/Mechanistic/MOA Information and Established Toxicity Values***

The mechanistic and supplemental data for *p*-isopropyltoluene (summarized in Section 2.3), described in the main document above, do not suggest any characteristic effects associated with a particular MOA (e.g., cholinesterase inhibition, inhibition of oxidative phosphorylation) that could be used to identify candidate analogues.

*p*-Isopropyltoluene was only active in 9 out of 845 ToxCast assays reported in the Dashboard (*invitro version 3.3*) (U.S. EPA, 2020a). There were no PubChem assays in which *p*-isopropyltoluene was active (0 out of 479 assays) (U.S. EPA, 2022a, 2020b). The GenRA option within the Dashboard enables a search for analogues based on similarities in activity in ToxCast in vitro assays. Using the ToxCast bioactivity data, none of the nearest neighbors identified by GenRA had a similarity index  $\geq 0.5$ . No candidate analogues were identified from bioactivity data on the basis of toxicodynamic similarity (U.S. EPA, 2022b).

The CTD (2022) identified several compounds with gene interactions similar to interactions induced by *p*-isopropyltoluene. In the CTD, similarity is measured by the Jaccard index, calculated as the size of the intersection of interacting genes for chemical A and chemical B divided by the size of the union of those genes (range 0 [no similarity] to 1 [complete similarity]). Among the compounds with gene interactions similar to *p*-isopropyltoluene, similarity indices ranged from 0.4 to 0.5. There were several compounds with a similarity index of 0.5 (2-(4'-chlorophenyl)benzothiazole, 2-mercaptomethylbenzimidazole, 2-methylanthracene, 4'-chloroflavone, 4'-iodoflavone, acetylenugenol, AG 494, dibenzo(*aj*)anthracene, M50354, and mineral waters). Although the similarity indices for these compounds were 0.5, the similarities were based on only two gene interactions, so these compounds were not considered candidate

analogues. No candidate mechanistic analogues for *p*-isopropyltoluene were identified using the methods outlined above.

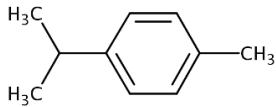
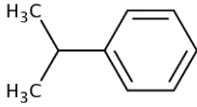
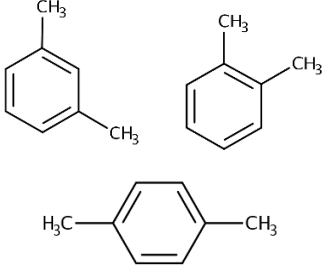
### ***Candidate Analogues Moving Forward for Evaluation***

Searches for metabolic, structural, and toxicity/mechanistic analogues for *p*-isopropyltoluene yielded a total of 32 unique candidate analogues: 10 structural analogues and 22 metabolites. Of the candidates, two structural analogues have inhalation toxicity values (isopropylbenzene and xylene, mixed isomers); these analogues were further evaluated on basis of structural, physicochemical properties, toxicokinetic, and toxicodynamic similarity comparisons.

### **Structural Analogues**

Table A-7 summarizes available structural and physicochemical properties data for *p*-isopropyltoluene and the structurally similar compounds (isopropylbenzene and xylene, mixed isomers) identified as candidate analogues. The target compound and candidate analogues share a similar general structure that consists of a single benzene ring containing one or two methyl and/or isopropyl substituents. Specifically, *p*-isopropyltoluene contains methyl and isopropyl groups in *para*- positions on the benzene ring. Isopropylbenzene contains a single isopropyl substituent, while xylene (mixed isomers) contains two methyl substituents in the *ortho*-, *meta*-, and/or *para*- positions. All compounds are liquids, with melting points <25°C. Measured vapor pressures indicate that these chemicals will exist mostly in the vapor (gas) phase in the atmosphere. *p*-Isopropyltoluene and the candidate analogues are expected to volatilize from water to air and soil to air, based on their Henry's law constants and vapor pressures, respectively. *p*-Isopropyltoluene, isopropylbenzene, and xylene are slightly to moderately soluble in water and have similar measured log  $K_{ow}$  values. The target compound and candidate analogues are expected to be bioavailable by the oral and inhalation routes (based on vapor pressure, water solubility, and log  $K_{ow}$  values). Based on the available data, both candidate analogues appear to be suitable analogues for *p*-isopropyltoluene on the basis of structural and physicochemical properties.

**Table A-7. Physicochemical Properties of *p*-Isopropyltoluene (CASRN 99-87-6) and its Candidate Structural Analogues<sup>a</sup>**

Property	Target Chemical	Candidate Analogues	
	<i>p</i> -Isopropyltoluene <sup>a</sup>	Isopropylbenzene <sup>b</sup>	Xylene (mixed isomers)
Structure			
CASRN	99-87-6	98-82-8	Mixture: 1330-20-7 <sup>c</sup> <i>m</i> -Xylene: 108-38-3 <sup>d</sup> <i>o</i> -Xylene: 95-47-6 <sup>e</sup> <i>p</i> -Xylene: 106-42-3 <sup>f</sup>
Molecular weight (g/mol)	134.222	120.195	106.168
Melting point (°C)	-68.2	-96.0	Mixture: no data <i>m</i> -Xylene: -47.5 <i>o</i> -Xylene: -28.3 <i>p</i> -Xylene: 12.8
Boiling point (°C)	177	152	Mixture: 137-140 <sup>g</sup> <i>m</i> -Xylene: 139 <i>o</i> -Xylene: 143 <i>p</i> -Xylene: 138
Vapor pressure (mm Hg at 25°C)	0.772	4.50	Mixture: 6-16 <sup>g</sup> <i>m</i> -Xylene: 8.29 <i>o</i> -Xylene: 6.61 <i>p</i> -Xylene: 8.84
Henry's law constant (atm·m <sup>3</sup> /mole at 25°C)	$7.94 \times 10^{-3}$ (predicted)	$1.15 \times 10^{-2}$	Mixture: no data <i>m</i> -Xylene: $7.18 \times 10^{-3}$ <i>o</i> -Xylene: $5.18 \times 10^{-3}$ <i>p</i> -Xylene: $6.90 \times 10^{-3}$
Solubility in water (mg/L at 25°C)	23.2 (reported as $1.73 \times 10^{-4}$ mol/L)	63.0 (reported as $5.24 \times 10^{-4}$ mol/L)	Mixture: 160 (reported as $1.51 \times 10^{-3}$ mol/L) <i>m</i> -Xylene: 160 (reported as $1.51 \times 10^{-3}$ mol/L) <i>o</i> -Xylene: 175 (reported as $1.65 \times 10^{-3}$ mol/L) <i>p</i> -Xylene: 171 (reported as $1.61 \times 10^{-3}$ mol/L)

<b>Table A-7. Physicochemical Properties of <i>p</i>-Isopropyltoluene (CASRN 99-87-6) and its Candidate Structural Analogues<sup>a</sup></b>			
<b>Property</b>	<b>Target Chemical</b>	<b>Candidate Analogues</b>	
	<i>p</i> -Isopropyltoluene <sup>a</sup>	Isopropylbenzene <sup>b</sup>	Xylene (mixed isomers)
Octanol-water partition coefficient (log $K_{ow}$ )	4.10	3.66	Mixture: 3.12–3.20 <sup>§</sup> <i>m</i> -Xylene: 3.20 <i>o</i> -Xylene: 3.12 <i>p</i> -Xylene: 3.15

<sup>a</sup>Unless otherwise noted, average values for *p*-isopropyltoluene were extracted from the U.S. EPA CompTox Chemicals Dashboard (<https://comptox.epa.gov/dashboard/chemical/details/DTXSID3026645>. Accessed May 21, 2024); [U.S. EPA \(2024a\)](#). Values are experimental unless otherwise specified.

<sup>b</sup>Unless otherwise noted, average values for isopropylbenzene were extracted from the U.S. EPA CompTox Chemicals Dashboard (<https://comptox.epa.gov/dashboard/chemical/details/DTXSID1021827>. Accessed May 29, 2024); [U.S. EPA \(2024a\)](#). Values are experimental unless otherwise specified.

<sup>c</sup>Unless otherwise noted, average values for mixed xylenes were extracted from the U.S. EPA CompTox Chemicals Dashboard (<https://comptox.epa.gov/dashboard/chemical/details/DTXSID2021446>. Accessed May 29, 2024); [U.S. EPA \(2024a\)](#). Values are experimental unless otherwise specified.

<sup>d</sup>Unless otherwise noted, average values for *m*-xylene were extracted from the U.S. EPA CompTox Chemicals Dashboard (<https://comptox.epa.gov/dashboard/chemical/properties/DTXSID6026298>. Accessed May 29, 2024); [U.S. EPA \(2024a\)](#). Values are experimental unless otherwise specified.

<sup>e</sup>Unless otherwise noted, average values for *o*-xylene were extracted from the U.S. EPA CompTox Chemicals Dashboard (<https://comptox.epa.gov/dashboard/chemical/properties/DTXSID3021807>. Accessed May 29, 2024); [U.S. EPA \(2024a\)](#). Values are experimental unless otherwise specified.

<sup>f</sup>Unless otherwise noted, average values for *p*-xylene were extracted from the U.S. EPA CompTox Chemicals Dashboard (<https://comptox.epa.gov/dashboard/chemical/properties/DTXSID2021868>. Accessed May 29, 2024); [U.S. EPA \(2024a\)](#). Values are experimental unless otherwise specified.

<sup>§</sup>[U.S. EPA \(2003\)](#). Values are experimental unless otherwise specified.

Relevant structural alerts and toxicity predictions for noncancer health effects were identified using computational tools from the [OECD \(2022\)](#) QSAR Toolbox profilers, ToxAlerts [OCHEM \(2022\)](#) ToxAlerts, and [IDEAconsult \(2018\)](#) Toxtree. The model results for *p*-isopropyltoluene and its analogue compounds (isopropylbenzene and xylene, mixed isomers) are shown in Figure A-1. Concerns for protein binding, developmental/reproductive toxicity, and metabolism/reactivity were indicated for *p*-isopropyltoluene and its structural analogues.

Structural Category	Compounds			
	Target Chemical	Candidate Analogues		Source
	99-87-6 <i>p</i> -Isopropyltoluene	98-82-8 Isopropylbenzene	1330-20-7 Xylene (mixed isomers)	
<b>Protein Binding</b>				
Protein binding (based on a Michael acceptor alert)				Toxtree
Protein binding (based on SN2-nucleophilic aliphatic substitution alert)				Toxtree
<b>Hepatotoxicity and Renal Toxicity</b>				
Hepatotoxicity (based on mefenamic acid and acetaminophen alerts); HESS model				OECD QSAR Toolbox
Renal toxicity (based on styrene and toluene alerts); HESS model				OECD QSAR Toolbox
Renal toxicity (based on acetaminophen alert); HESS model				OECD QSAR Toolbox
Renal toxicity (based on propranolol alert); HESS model				OECD QSAR Toolbox
<b>Developmental/Reproductive Toxicity</b>				
Known precedent of reproductive and developmental toxic potential (based on toluene and small alkyl benzene or toluene derivatives); DART scheme				OECD QSAR Toolbox
<b>Metabolism/Reactivity</b>				
Cytochrome P450-mediated drug metabolism predicted (based on sp3 and sp2 hybridized carbon atoms)				ToxAlerts

Model results or structural alerts indicating concern for noncancer toxicity/endpoint of interest.

Model results or structural alert indicating no concern for noncancer toxicity/endpoint of interest.

<sup>a</sup>Models with results are presented in the heat map (models without results indicate that the queried chemical fell outside of the applicability domain and are omitted).

DART = developmental and reproductive toxicity; HESS = Hazard Evaluation Support System;

OECD = Organisation for Economic Co-operation and Development; QSAR = quantitative structure-activity relationship

### Figure A-1. Structural Alerts for *p*-Isopropyltoluene and its Candidate Analogues

Toxtree indicated potential for protein binding based on being Michael acceptors for *p*-isopropyltoluene and the candidate analogues. A potential for protein binding was also indicated for *p*-isopropyltoluene and isopropylbenzene based on SN2-nucleophilic aliphatic substitution; this was not indicated for xylene (mixed isomers).

The OECD QSAR Toolbox Hazard Evaluation Support System (HESS) model showed a concern for hepatotoxicity for both analogues based on structural similarity to mefenamic acid (allergic, acute, hepatocyte damage) and acetaminophen (oxidative stress, hepatocellular injury); the HESS model did not show a hepatotoxicity concern for the target chemical, *p*-isopropyltoluene.

The OECD QSAR Toolbox HESS model showed a concern for renal toxicity for both analogues based on structural similarity to styrene (epithelial necrosis of renal tubules) and toluene (renal tubular acidosis, proteinuria). The HESS model also showed a concern for renal toxicity for xylene based on structural similarity to acetaminophen (proximal tubular toxicity, interstitial nephritis) and for isopropylbenzene based on structural similarity to propranolol (nephrotoxicity not specified). No renal toxicity concerns were predicted for the target chemical, *p*-isopropyltoluene.

The OECD QSAR Toolbox developmental and reproductive toxicity (DART) scheme indicated a potential for developmental and/or reproductive toxicity for *p*-isopropyltoluene and both analogues based on the benzene or toluene structure with an alkyl chain substituent of fewer than five carbon atoms. The alert for reproductive and/or developmental toxicity for toluene and small alkyl benzene or toluene derivatives is based on the training set of chemicals that includes *o*-, *m*-, and *p*-xylene, butyltoluene, and 4-*tert*-butyltoluene.

The ToxAlerts tool showed potential for CYP-mediated drug metabolism for *p*-isopropyltoluene and both analogues based on the presence of sp<sup>3</sup> and sp<sup>2</sup> hybridized carbon atoms.

In summary, *p*-isopropyltoluene and its candidate analogues showed structural alert data for protein binding, reproductive and developmental toxicity, and metabolism by CYP. Isopropylbenzene and xylene also showed positive alerts for liver and kidney toxicity. While these alerts were negative for *p*-isopropyltoluene, available toxicity data for *p*-isopropyltoluene showed liver and kidney effects in experimental animals treated by oral exposure ([Symrise, 2018](#)) (see Section 2.2.1).

### **Metabolic Analogues**

Table A-8 summarizes available toxicokinetic data for *p*-isopropyltoluene and the structurally similar compounds identified as candidate analogues (isopropylbenzene and xylene, mixed isomers).

Table A-8. Comparison of ADME Data for *p*-Isopropyltoluene (CASRN 99-87-6) and its Candidate Analogues

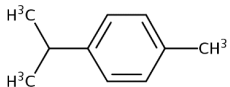
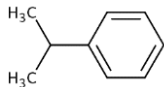
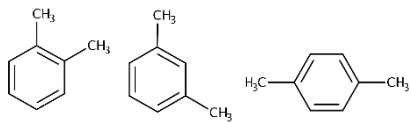
Type of Data	<i>p</i> -Isopropyltoluene	Isopropylbenzene	Xylene (mixed isomers)
Structure			
CASRN	99-87-6	98-82-8	1330-20-7
<b>Absorption</b>			
Rate and extent of absorption	<p><b>Laboratory animals (all routes):</b></p> <ul style="list-style-type: none"> <li>Excretion data suggest absorption in rats, rabbits, guinea pigs, and marsupials by oral route (<a href="#">Boyle et al., 1999</a>; <a href="#">Matsumoto et al., 1992</a>; <a href="#">Walde et al., 1983</a>; <a href="#">Ishida et al., 1981</a>); in rats and guinea pigs by inhalation route (<a href="#">Walde et al., 1983</a>); and in mice by dermal route (<a href="#">Wepierre et al., 1968</a>).</li> <li>Urinary excretion data in rats and guinea pigs suggest that absorption is rapid and extensive by the oral and inhalation routes (60–80% of administered or inhaled dose excreted within 48 h) (<a href="#">Walde et al., 1983</a>).</li> </ul>	<p><b>Humans (inhalation):</b></p> <ul style="list-style-type: none"> <li>Absorption was demonstrated in volunteer studies; respiratory tract absorption ranged from 45 to 64% [Senczuk and Litewka (1976) as cited in <a href="#">WHO (1999)</a>; and <a href="#">U.S. EPA (1997)</a>].</li> </ul> <p><b>Laboratory animals (all routes):</b></p> <ul style="list-style-type: none"> <li>Rapid absorption by inhalation; blood concentrations detectable within 5 min [Research Triangle Institute (1989) as cited in <a href="#">WHO (1999)</a>; and <a href="#">U.S. EPA (1997)</a>].</li> <li>Readily absorbed following gavage administration, with maximum blood concentrations at 4 h (earliest time point measured) for the lower dose (33 mg/kg-d) and 8–16 h for the higher dose (1,350 mg/kg-d) [Research Triangle Institute (1989) as cited in <a href="#">WHO (1999)</a>; and <a href="#">U.S. EPA (1997)</a>].</li> <li>Dermal absorption was demonstrated in rats and rabbits [Monsanto Co. (1984) as cited in <a href="#">WHO (1999)</a>].</li> </ul>	<p><b>Humans (inhalation):</b></p> <ul style="list-style-type: none"> <li>Absorption was demonstrated in volunteer studies and was similar for the <i>m</i>-, <i>o</i>-, and <i>p</i>- isomers [Wallen et al. (1985); Riihimaki and Savolainen (1980); David et al. (1979); Astrad et al. (1978); Riihimaki and Pfaffli (1978); Sedivec and Flek (1976a); Ogata et al. (1970) as cited in <a href="#">ATSDR (2007)</a>; and <a href="#">U.S. EPA (2003)</a>].</li> <li>Respiratory tract absorption ranged from 50 to 73%.</li> <li>Blood-air partition coefficients for the three isomers ranged from 26.4 to 39, suggesting that xylene (<i>m</i>-, <i>o</i>-, and <i>p</i>- isomers) is readily transferred to blood [Thrall et al. (2002); Pierce et al. (1996); Sato and Nakajima (1979) as cited in <a href="#">ATSDR (2007)</a>].</li> <li>Dermal absorption was demonstrated in humans (<i>m</i>-xylene); however, the extent of absorption is lower than that resulting from inhalation [Riihimaki (1979b); Riihimaki and Pfaffli (1978); Engstrom et al. (1977) as cited in <a href="#">ATSDR (2007)</a>].</li> </ul> <p><b>Laboratory animals (all routes):</b></p> <ul style="list-style-type: none"> <li>Oral absorption is extensive: 87–92% absorption of xylene (<i>m</i>-, <i>o</i>-, and <i>p</i>- isomers)</li> </ul>

Table A-8. Comparison of ADME Data for *p*-Isopropyltoluene (CASRN 99-87-6) and its Candidate Analogues

Type of Data	<i>p</i> -Isopropyltoluene	Isopropylbenzene	Xylene (mixed isomers)
			<p>in rats via gavage [Bray et al. (1949) as cited in <a href="#">ATSDR (2007)</a>].</p> <ul style="list-style-type: none"> <li>• Oral absorption is rapid. Blood levels of <i>m</i>-xylene peaked within 20 min after gavage and the half-life absorption was faster in female rats (<math>t_{1/2} = 0.31</math> h) compared to male rats (<math>t_{1/2} = 0.64</math> h) [Turkall et al. (1992) as cited in <a href="#">ATSDR (2007)</a>; and <a href="#">U.S. EPA (2003)</a>].</li> <li>• Absorption via inhalation has not been quantified but it can be inferred by recovery of urine metabolites after inhalation of xylene [Elovaara et al. (1987); Elovaara (1982); Carlsson (1981); David et al. (1979); Patel et al. (1978) as cited in <a href="#">ATSDR (2007)</a>].</li> <li>• Blood-air partition coefficients in rats for the three isomers ranged from 37 to 46 [Thrall et al. (2002); Kumarathasan et al. (1998); Kaneko et al. (1991a); Gargas et al. (1989) as cited in <a href="#">ATSDR (2007)</a>].</li> <li>• Dermal absorption of <i>m</i>-xylene was demonstrated in rats [Morgan et al. (1991); McDougal et al. (1990); Skowronski et al. (1990) as cited in <a href="#">ATSDR (2007)</a>].</li> </ul>
<b>Distribution</b>			
Extent of distribution	<p><b>Laboratory animals (all routes):</b></p> <ul style="list-style-type: none"> <li>• No data are available on blood or tissue concentrations following exposure by any route.</li> <li>• Based on a log <math>K_{ow}</math> value &gt;4, <i>p</i>-isopropyltoluene is hydrophobic and is likely to partition to fat compartments.</li> </ul>	<p><b>Laboratory animals (all routes):</b></p> <ul style="list-style-type: none"> <li>• Isopropylbenzene is widely distributed throughout the body; found in endocrine organs (not specified), the central nervous system (not further specified), bone marrow, spleen, and liver [Fabre et al. (1955) as cited in <a href="#">WHO (1999)</a>].</li> <li>• Elevated tissue/blood ratios were detected in adipose tissue, liver, and kidney in rats via oral,</li> </ul>	<p><b>Humans (inhalation):</b></p> <ul style="list-style-type: none"> <li>• Accumulation of xylene isomers in human adipose tissue ranged from 4 to 10% of the absorbed dose [Astrand (1982); Riihimaki et al. (1979b); Engstrom and Bjurstrom (1978) as cited in <a href="#">ATSDR (2007)</a>; and <a href="#">U.S. EPA (2003)</a>].</li> </ul>

Table A-8. Comparison of ADME Data for *p*-Isopropyltoluene (CASRN 99-87-6) and its Candidate Analogues

Type of Data	<i>p</i> -Isopropyltoluene	Isopropylbenzene	Xylene (mixed isomers)
		<p>inhalation, and intravenous exposure routes [Research Triangle Institute (1989) as cited in <a href="#">WHO (1999)</a>; and <a href="#">U.S. EPA (1997)</a>].</p> <ul style="list-style-type: none"> <li>• Following inhalation exposure in rats, the <math>t_{1/2}</math> for elimination from blood was 3.9–6.6 h [Research Triangle Institute (1989) as cited in <a href="#">WHO (1999)</a>; and <a href="#">U.S. EPA (1997)</a>].</li> <li>• Following gavage exposure in rats, the <math>t_{1/2}</math> for elimination from blood was 9–16 h [Research Triangle Institute (1989) as cited in <a href="#">WHO (1999)</a>; and <a href="#">U.S. EPA (1997)</a>].</li> </ul>	<ul style="list-style-type: none"> <li>• Fat-air partition coefficients for xylene (<i>m</i>-, <i>o</i>-, and <i>p</i>- isomers) ranged from 1,919 to 2,460 [Pierce et al. (1996) as cited in <a href="#">ATSDR (2007)</a>].</li> <li>• The milk-air partition coefficient (<i>m</i>-, <i>o</i>-, and <i>p</i>-xylenes) was 134 [Fisher et al. (1997) as cited in <a href="#">ATSDR (2007)</a>].</li> <li>• Elimination from the blood was biphasic, with <math>t_{1/2}</math> values of 0.5–1 and 20–30 h [Riihimäki and Savolainen (1980) as cited in <a href="#">U.S. EPA (2003)</a>].</li> </ul> <p><b>Laboratory animals (oral and inhalation):</b></p> <ul style="list-style-type: none"> <li>• Inhalation studies in rats and mice showed wide distribution of <i>m</i>- or <i>p</i>-xylenes with accumulation occurring primarily in adipose tissue [Ito et al. (2002); Ghantous and Danielsson (1986); Bergman (1983); Carlsson (1981) as cited in <a href="#">ATSDR (2007)</a>; and <a href="#">U.S. EPA (2003)</a>].</li> <li>• Accumulation in fat tissues has also been demonstrated in oral rat studies with <i>m</i>-xylene [Turkall et al. (1992) as cited in <a href="#">ATSDR (2007)</a>].</li> <li>• Xylenes (<i>p</i>- and <i>o</i>- isomers) readily cross the placenta and have been detected in amniotic fluid and fetal tissue [Ghantous and Danielsson 1986; Ungvary et al. 1980b as cited in <a href="#">ATSDR (2007)</a>].</li> <li>• Oil-blood partition coefficients for the three isomers ranged from 98 to 146, suggesting transfer to lipid-rich tissues [Sato and Nakajima (1979) as cited in <a href="#">U.S. EPA (2003)</a>].</li> <li>• Fat-air partition coefficient for xylenes (<i>m</i>-, <i>o</i>-, and <i>p</i>- isomers) ranged from 1,748 to</li> </ul>

Table A-8. Comparison of ADME Data for *p*-Isopropyltoluene (CASRN 99-87-6) and its Candidate Analogues

Type of Data	<i>p</i> -Isopropyltoluene	Isopropylbenzene	Xylene (mixed isomers)
			2,930 [Kumarathasan et al. (1998); Pierce et al. (1996); Kaneko et al. (1991a); Gargas et al. (1989) as cited in <a href="#">ATSDR (2007)</a> ]. <ul style="list-style-type: none"> <li>Tissue-blood partition coefficients were 1.5–3.7 for brain, muscle and kidney, 3.2–5.7 for liver, and 37–67 for adipose tissue [Kumarathasan et al. (1998) as cited in <a href="#">U.S. EPA (2003)</a>].</li> </ul>
<b>Metabolism</b>			
Rate; primary metabolites	<p><b>Humans (in vitro):</b></p> <ul style="list-style-type: none"> <li>Human recombinant CYP enzymes identified one phenolic metabolite (2-isopropyl-5-methylphenol) in addition to metabolites of side-chain oxidation (<i>p</i>-isopropyl benzylalcohol, 2-<i>p</i>-tolylpropan-2-ol, and <i>p</i>-isopropylbenzyl aldehyde) (<a href="#">Meesters et al., 2009</a>).</li> </ul> <p><b>Laboratory animals (all routes):</b></p> <ul style="list-style-type: none"> <li>Extensive oxidation of the methyl substituent and isopropyl side chain in rats, rabbits, guinea pigs, and marsupials (<a href="#">Boyle et al., 1999</a>; <a href="#">Matsumoto et al., 1992</a>; <a href="#">Walde et al., 1983</a>; <a href="#">Ishida et al., 1981</a>; <a href="#">Bakke and Scheline, 1970</a>). <ul style="list-style-type: none"> <li>Primary metabolites include monohydric alcohols, diols, mono- and dicarboxylic acids, and hydroxyacids.</li> <li>Oxidative metabolites were conjugated with glucuronic acid and/or glycine.</li> <li>Ring-hydroxylation was not observed in in vivo studies in rats, rabbits, or marsupials.</li> </ul> </li> </ul>	<p><b>Humans (inhalation):</b></p> <ul style="list-style-type: none"> <li>2-Phenyl-2-propanol was measured in urine (isopropyl side-chain oxidation) [Senczuk and Litewka (1976) as cited in <a href="#">WHO (1999)</a>; and <a href="#">U.S. EPA (1997)</a>].</li> </ul> <p><b>Laboratory animals (all routes):</b></p> <ul style="list-style-type: none"> <li>Oxidized via CYP in liver and lung, with the primary metabolite identified as 2-phenyl-2-propanol [Sato and Nakajima (1987) as cited in <a href="#">WHO (1999)</a>; and <a href="#">U.S. EPA (1997)</a>].</li> <li>2-Phenyl-1,2-propanediol and an unknown metabolite were also detected in rats and rabbits; dicarboxylic acid formation was suggested, although not confirmed [MAK (1996); Ishida and Matsumoto (1992); Research Triangle Institute (1989) as cited in <a href="#">WHO (1999)</a>]. <ul style="list-style-type: none"> <li>No phenolic metabolites were detected.</li> <li>Oxidative metabolites were conjugated with glucuronic acid and sulfate esters.</li> </ul> </li> </ul>	<p><b>Humans (inhalation):</b></p> <ul style="list-style-type: none"> <li>The primary metabolic pathway of xylenes (<i>m</i>-, <i>o</i>-, and <i>p</i>- isomers) involves methyl group oxidation. Methylbenzyl alcohols are converted to methylbenzoic acids, followed by glycine conjugation to form methylhippuric acids [Norstrom et al. (1989); Ogata et al. (1979); Riihimaki et al. (1979a); Astrand et al. (1978); Senczuk and Orłowski (1978); Sedivec and Flek (1976b); Ogata et al. (1970) as cited in <a href="#">ATSDR (2007)</a>; and <a href="#">U.S. EPA (2003)</a>]. <ul style="list-style-type: none"> <li>Metabolism to phenols accounts for &lt;2% of total metabolites formed.</li> </ul> </li> </ul> <p><b>Laboratory animals (all routes)</b></p> <ul style="list-style-type: none"> <li>Similar metabolism as in humans, with methylhippuric acid as the primary metabolite [van Doorn et al. (1980); Ogata et al. (1979); Sugihara and Ogata (1978); Bakke and Scheline (1970); Bray et al. (1949) as cited in <a href="#">ATSDR (2007)</a>; and <a href="#">U.S. EPA (2003)</a>]. <ul style="list-style-type: none"> <li>In a minor pathway, methylbenzoic acids are conjugated with glucuronide or sulfate.</li> </ul> </li> </ul>

Table A-8. Comparison of ADME Data for *p*-Isopropyltoluene (CASRN 99-87-6) and its Candidate Analogues

Type of Data	<i>p</i> -Isopropyltoluene	Isopropylbenzene	Xylene (mixed isomers)
	<ul style="list-style-type: none"> <li>Trace amounts of 5-isopropyl-2-methylphenol (carvacrol) were found in the urine of guinea pigs (<a href="#">Walde et al., 1983</a>).</li> </ul> <p><b>Laboratory animals (in vitro):</b></p> <ul style="list-style-type: none"> <li>Eight metabolites were detected from microsomes obtained from Wistar rats, brushtail possums, and koalas; same sites of oxidation as observed in in vivo studies in the same species (<a href="#">Pass et al., 2002</a>).</li> </ul>		<ul style="list-style-type: none"> <li>Ring oxidation to form phenols is negligible (&lt;1%).</li> </ul>
<b>Elimination</b>			
Elimination half-time; route of excretion	<p><b>Laboratory animals (oral, inhalation):</b></p> <ul style="list-style-type: none"> <li>Metabolites are either excreted unchanged or as glucuronide or glycine conjugates in the urine of rats, rabbits, guinea pigs, and marsupials (<a href="#">Boyle et al., 1999</a>; <a href="#">Matsumoto et al., 1992</a>; <a href="#">Walde et al., 1983</a>; <a href="#">Ishida et al., 1981</a>; <a href="#">Bakke and Scheline, 1970</a>). <ul style="list-style-type: none"> <li>No metabolites were identified in the feces.</li> </ul> </li> <li>In rats and guinea pigs, 60–80% of the administered dose was excreted as metabolites in the urine within 48 h of oral or inhalation dosing (<a href="#">Walde et al., 1983</a>).</li> </ul>	<p><b>Humans (inhalation):</b></p> <ul style="list-style-type: none"> <li>2-Phenyl-2-propanol excretion was maximal at 6–8 h after exposure and near complete at 40 h after exposure [<a href="#">Senczuk and Litewka (1976)</a> as cited in (<a href="#">WHO, 1999</a>; and <a href="#">U.S. EPA, 1997</a>)]. <ul style="list-style-type: none"> <li>Urinary <math>t_{1/2}</math> values show a rapid early phase (<math>t_{1/2} = 2</math> h) and a slower late phase (<math>t_{1/2} = 40</math> h).</li> </ul> </li> </ul> <p><b>Laboratory animals (all routes):</b></p> <ul style="list-style-type: none"> <li>Urine is the primary excretion route in rats after oral, inhalation, and intravenous exposure (<math>\geq 70\%</math> of administered dose was excreted in urine) [<a href="#">Research Triangle Institute (1989)</a> as cited in (<a href="#">WHO, 1999</a>; and <a href="#">U.S. EPA, 1997</a>)]. <ul style="list-style-type: none"> <li>Total body clearance in rats was rapid, with &lt;1% of the absorbed fraction remaining after 72 h.</li> <li>Metabolites are either excreted unchanged or as glucuronide or sulfate conjugates in urine.</li> </ul> </li> </ul>	<p><b>Humans (inhalation):</b></p> <ul style="list-style-type: none"> <li>95% of absorbed xylene (mixed isomers) is excreted in urine; 5% is excreted unchanged in exhaled air [<a href="#">Pellizzari et al. (1992)</a>; <a href="#">Ogata et al. (1979)</a>; <a href="#">Riihimäki et al. (1979b)</a>; <a href="#">Astrand et al. (1978)</a>; <a href="#">Senczuk and Orłowski (1978)</a>; <a href="#">Sedivec and Flek (1976b)</a> as cited in <a href="#">ATSDR (2007)</a>; and <a href="#">U.S. EPA (2003)</a>]. <ul style="list-style-type: none"> <li>Excretion is rapid with metabolites detected within 2 h of exposure; 50–60% excreted by 18 h after exposure.</li> </ul> </li> <li>Urinary <math>t_{1/2}</math> values show a rapid early phase (<math>t_{1/2} = 1</math> h) and a slower late phase (<math>t_{1/2} = 20</math> h) [<a href="#">Riihimäki and Savolainen (1980)</a> as cited in as cited in <a href="#">U.S. EPA (2003)</a>].</li> </ul> <p><b>Laboratory animals (oral, inhalation):</b></p> <ul style="list-style-type: none"> <li>Excreted primarily in the urine (~74–96% of administered dose) over 48 h after oral dosing with the remainder excreted unchanged in expired air [<a href="#">Turkall et al. (1992)</a> as cited in <a href="#">ATSDR (2007)</a>].</li> </ul>

Table A-8. Comparison of ADME Data for *p*-Isopropyltoluene (CASRN 99-87-6) and its Candidate Analogues

Type of Data	<i>p</i> -Isopropyltoluene	Isopropylbenzene	Xylene (mixed isomers)
			<ul style="list-style-type: none"> <li>- Cumulative amounts of methylhippuric acid (primary excretion product) in urine increased through 12 h and then reached a plateau.</li> <li>- Elimination in urine after oral dosing is rapid, with 52–59% of the administered dose excreted within the first 12 h.</li> <li>• Following dermal administration, elimination within 48 h occurred in expired air (~60%) and urine (~40%) [Skowronski et al. (1990) as cited in <a href="#">ATSDR (2007)</a>].</li> </ul>
<b>References:</b>	<a href="#">Meesters et al. (2009)</a> ; <a href="#">Pass et al. (2002)</a> ; <a href="#">Boyle et al. (1999)</a> ; <a href="#">Matsumoto et al. (1992)</a> ; <a href="#">Walde et al. (1983)</a> ; <a href="#">Ishida et al. (1981)</a> ; <a href="#">Bakke and Scheline (1970)</a>	<a href="#">WHO (1999)</a> ; <a href="#">U.S. EPA (1997)</a>	<a href="#">ATSDR (2007)</a> ; <a href="#">U.S. EPA (2003)</a> ; <a href="#">David et al. (1979)</a>

ADME = absorption, distribution, metabolism, and excretion; CYP = cytochrome P450;  $K_{ow}$  = octanol-water partition coefficient;  $t_{1/2}$  = half-life.

Animal studies demonstrate absorption of *p*-isopropyltoluene via oral, inhalation, and dermal routes (see Table A-8). Absorption of *p*-isopropyltoluene in rats and guinea pigs was rapid and extensive (60–80% of administered or inhaled dose within 48 hours) ([Walde et al., 1983](#)) following oral and inhalation exposure. Absorption data in humans and animals were similar for the candidate analogues, showing that isopropylbenzene and xylene (*m*-, *o*-, and *p*- isomers) are well absorbed by multiple routes (oral, inhalation, and dermal routes). For example, respiratory tract absorption ranges were 45–64 and 50–73% for isopropylene and xylene, respectively, in volunteer studies (see Table A-8).

No in vivo human or animal studies reporting the distribution of *p*-isopropyltoluene were identified; however, based on a log  $K_{ow}$  value >4, it is expected to accumulate in fatty tissues. For the candidate analogues, initial distribution is rapid and widespread throughout the body (see Table A-8). Tissue-blood ratios were elevated in liver, kidney, and adipose tissue in rats after oral, inhalation, and intravenous exposure to isopropylbenzene. For xylene, accumulation occurs primarily in fat tissue in both humans and rats, and it has also been detected in amniotic fluid and fetal tissues.

The primary metabolic pathway for *p*-isopropyltoluene in laboratory animals involves extensive oxidation of the methyl substituent and isopropyl side chain (see Table A-8 and Figure 2 in Section 2.3.4 for more details). Metabolites include monohydric alcohols, diols, mono- and dicarboxylic acids, and hydroxy acids. Ring-hydroxylation was not observed in in vivo studies of rats, rabbits, or marsupials. Trace amounts of one phenolic metabolite (5-isopropyl-2-methylphenol) of *p*-isopropyltoluene were reported in guinea pigs. Oxidative metabolites were conjugated with glucuronic acid and/or glycine. Similar to the target compound, the candidate analogues are primarily metabolized by side-chain oxidation pathways in animals (see Table A-8). The primary metabolite for isopropylbenzene was identified as 2-phenyl-2-propanol. No phenolic metabolites arising from ring oxidation were seen. Oxidative metabolites were conjugated with glucuronic acid and sulfate esters. Xylene undergoes methyl group oxidation. Methylbenzyl alcohols are converted to methylbenzoic acids, followed by glycine conjugation to form methylhippuric acids. In a minor pathway, methylbenzoic acids are conjugated with glucuronide or sulfate. Ring oxidation to form phenols is negligible (<1%). Metabolism data in humans for *p*-isopropyltoluene is limited. A phenolic product (2-isopropyl-5-methylphenol) was identified as a metabolite of *p*-isopropyltoluene in in vitro human recombinant CYP assays (see Table A-8); however, the evidence is insufficient to determine whether ring hydroxylation constitutes an important metabolic pathway in humans. For the analogues, isopropylbenzene and xylene, the available evidence in humans suggests that ring hydroxylation is not a major pathway (see Table A-8).

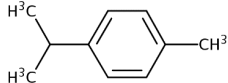
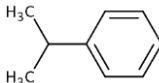
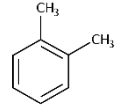
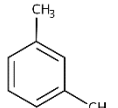
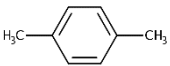
*p*-Isopropyltoluene metabolites are excreted unchanged or as glucuronide or glycine conjugates in the urine of experimental animals (60–80% of the administered dose in rats and guinea pigs within 48 hours; see Table A-8). No metabolites were identified in the feces. Urine is also the primary excretion route for isopropylbenzene. Oxidative metabolites are excreted unchanged or as glucuronide or sulfate conjugates in urine ( $\geq 70\%$  of administered oral, inhalation, and intravenous dose within 72 hours; see Table A-8). Xylene are excreted primarily as methylhippuric acid in the urine (~74–96% of administered oral dose within 48 hours), with the remainder excreted unchanged in expired air (see Table A-8).

In summary, toxicokinetic data suggest that the target compound and candidate analogues are well absorbed via multiple routes (including inhalation exposure). No distribution data are available for *p*-isopropyltoluene; however, the log  $K_{ow}$  value indicates hydrophobicity and suggests that *p*-isopropyltoluene will partition to fat compartments. Both candidate analogues were shown to be distributed widely throughout the body and to accumulate in adipose tissue. Metabolic pathways are similar for the target compound and both candidate analogues in laboratory animals, involving oxidation of side-chain substituents (i.e., methyl and/or isopropyl substituents). Ring oxidation to form phenolic metabolites was negligible for all three compounds. Oxidative metabolites were conjugated with glycine, glucuronic acid, and/or sulfate and excreted in the urine. Fecal excretion was not reported for the target compound or the candidate analogues. A small fraction of unchanged xylene was excreted in expired air following inhalation. Based on the available toxicokinetic data, both candidate analogues appear to be suitable analogues for *p*-isopropyltoluene.

### **Toxicodynamic Analogues**

As mentioned in Section 2.2, no adequate subchronic or chronic inhalation toxicity studies are available for the target chemical, *p*-isopropyltoluene. Inhalation toxicity values for the candidate analogues are presented in Table A-9. The critical effects for the two candidate analogue compounds include respiratory irritation (POD human equivalent concentration [HEC] of 61 mg/m<sup>3</sup>) and neurological effects (impaired motor coordination, decreased pain sensitivity, and floating sensation; POD (HEC) range of 39–217 mg/m<sup>3</sup>) for xylene (mixed isomers) and increased kidney and adrenal weights (POD (HEC) of 435 mg/m<sup>3</sup>) for isopropylbenzene. A discussion of available toxicity data for the target compound and analogues for these (and other) relevant endpoints is provided following Table A-9.

**Table A-9. Comparison of Available Inhalation Toxicity Values for *p*-Isopropyltoluene (CASRN 99-87-6) and its Candidate Analogues**

Chemical	<i>p</i> -Isopropyltoluene	Isopropylbenzene	Xylene (Mixed Isomers)		
Structure					
CASRN	99-87-6	98-82-8	1330-20-7		
<b>Subchronic inhalation toxicity values</b>					
Source			<a href="#">U.S. EPA (2009)</a>	<a href="#">ATSDR (2007)</a>	
POD	ND	ND	39 mg/m <sup>3</sup> (9.0 ppm) <sup>a</sup>	50 ppm (217 mg/m <sup>3</sup> )	
POD type	ND	ND	NOAEL <sub>HEC</sub>	LOAEL <sub>HEC</sub>	
Subchronic UF <sub>C</sub>	ND	ND	100 (UF <sub>A</sub> , UF <sub>D</sub> , UF <sub>H</sub> )	90 (UF <sub>A</sub> , UF <sub>H</sub> , UF <sub>L</sub> )	
Subchronic p-RfC (mg/m <sup>3</sup> )	ND	ND	0.4 mg/m <sup>3</sup>	0.6 ppm (2.6 mg/m <sup>3</sup> )	
Critical effects	ND	ND	Neurological effects (impaired motor coordination)	Decreased mean latency of the paw-lick response	
Species	ND	ND	Rat		
Duration	ND	ND	3 mo (6 h/d, 5 d/wk)		
Route (method)	ND	ND	Inhalation		
Source	ND	ND	Korsak et al. (1994) as cited in <a href="#">U.S. EPA (2009)</a> ; and <a href="#">ATSDR (2007)</a>		

**Table A-9. Comparison of Available Inhalation Toxicity Values for *p*-Isopropyltoluene (CASRN 99-87-6) and its Candidate Analogues**

Chemical	<i>p</i> -Isopropyltoluene	Isopropylbenzene	Xylene (Mixed Isomers)	
<b>Chronic inhalation toxicity values</b>				
POD	ND	435 mg/m <sup>3</sup> (88.5 ppm) <sup>b</sup>	39 mg/m <sup>3</sup> (9.0 ppm) <sup>a</sup>	14 ppm (61 mg/m <sup>3</sup> )
POD type	ND	NOAEL <sub>HEC</sub>	NOAEL <sub>HEC</sub>	LOAEL
Chronic UF <sub>c</sub>	ND	1,000 (UF <sub>A</sub> , UF <sub>D</sub> , UF <sub>H</sub> , UF <sub>S</sub> )	300 (UF <sub>A</sub> , UF <sub>D</sub> , UF <sub>H</sub> , UF <sub>S</sub> )	300 (UF <sub>H</sub> , UF <sub>D</sub> , UF <sub>L</sub> )
Chronic p-RfC/MRL	ND	0.4 mg/m <sup>3</sup>	0.1 mg/m <sup>3</sup>	0.05 ppm (0.2 mg/m <sup>3</sup> )
Critical effects	ND	Increased kidney weights and adrenal weights	Neurological effects (impaired motor coordination)	Respiratory and neurological effects (nose and throat irritation; floating sensation)
Species	ND	Rat	Rat	Human
Duration	ND	13 wk	3 mo (6 h/d, 5 d/wk)	7 yr
Route (method)	ND	Inhalation	Inhalation	Inhalation (occupational)
Source	ND	Cushman et al. (1995) as cited in <a href="#">U.S. EPA (1997)</a>	Korsak et al. (1994) as cited in <a href="#">U.S. EPA (2003)</a>	Uchida et al. (1993) as cited in <a href="#">ATSDR (2007)</a>
<b>Acute inhalation lethality data</b>				
Inhalation LC <sub>50</sub> (mg/m <sup>3</sup> )	19,500–24,000 (mouse, 2–4 h)	10,000–15,300 (mouse, 2–7 h); 35,000–39,000 (rat, 4 h)	17,000–23,000 (mouse, 6 h) 21,000–29,000 (rat, 4 h)	
Toxicity at LC <sub>50</sub>	ND	Effects on liver, kidney (changes in tubules and glomeruli), ureter, bladder, and spleen	ND	
Source	<a href="#">NLM (2022b)</a>	<a href="#">NLM (2022c)</a>	<a href="#">ATSDR (2007)</a>	

<sup>a</sup>POD has been adjusted for duration to continuous exposure. Unadjusted values reported as 50 ppm (217 mg/m<sup>3</sup>) according to [U.S. EPA \(2003\)](#).

<sup>b</sup>POD has been adjusted for duration to continuous exposure. Unadjusted values reported as 496 ppm (2,438 mg/m<sup>3</sup>) according to [U.S. EPA \(1997\)](#).

HEC = human equivalent concentration; LC<sub>50</sub> = median lethal concentration; LOAEL = lowest-observed-adverse-effect level; MRL = minimal risk level; ND = no data; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; UF<sub>A</sub> = interspecies uncertainty factor; UF<sub>C</sub> = composite uncertainty factor; UF<sub>D</sub> = database uncertainty factor; UF<sub>H</sub> = intraspecies uncertainty factor; UF<sub>L</sub> = LOAEL-to-NOAEL uncertainty factor; UF<sub>S</sub> = subchronic-to-chronic uncertainty factor.

Figure A-2 compares hepatic, renal, and adrenal effects for the candidate analogues (no data available for *p*-isopropyltoluene) from repeated-dose inhalation toxicity studies in rats. Liver effects (hepatocyte hypertrophy and/or increased liver weights) occurred at similar concentrations for isopropylbenzene (214.6 ppm or 1,055 mg/m<sup>3</sup>) and xylene (164 ppm or 710 mg/m<sup>3</sup>). Kidney and adrenal effects (increased kidney and adrenal weights) were observed for isopropylbenzene only ( $\geq 108$  ppm or 530 mg/m<sup>3</sup> for kidney weight and 214.6 ppm or 1,055 mg/m<sup>3</sup> for adrenal weight). Liver effects (increased liver weights, serum ALP levels, and hepatocyte hypertrophy in male and female rats) were reported for *p*-isopropyltoluene after subchronic oral exposure at  $\geq 50$  mg/kg-day (see Figure A-3) and were used for the derivation of screening subchronic and chronic p-RfDs (see ORAL NONCANCER TOXICITY VALUES above). Increased liver weights and ALT levels in rats were also reported for xylene at  $\geq 571$  mg/kg-day following oral exposure, while no effects on liver histopathology were reported after isopropylbenzene oral exposure up to 551 mg/kg-day (see Figure A-3). Possible renal effects occurred in male rats exposed to *p*-isopropyltoluene (hyaline droplet accumulation, tubular epithelial vacuolation and basophilia, and increased BUN at 200 mg/kg-day) following oral dosing (see Figure A-4). Renal effects in female rats were found after oral exposure to isopropylbenzene at  $\geq 331$  mg/kg-day (increased kidney weight) and xylene at  $\geq 750$  mg/kg-day (increased kidney weight and mild nephropathy) (see Figure A-4).

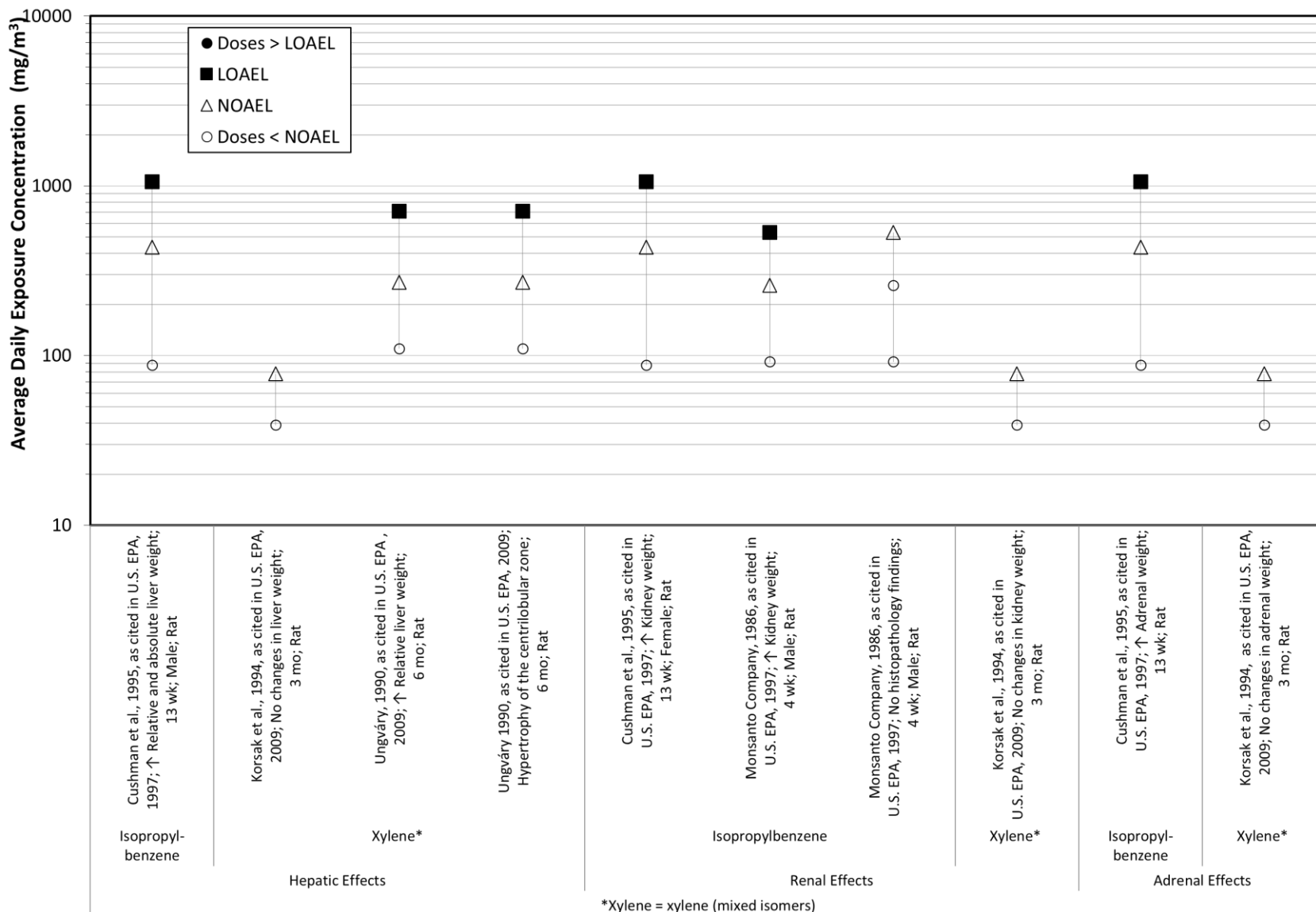
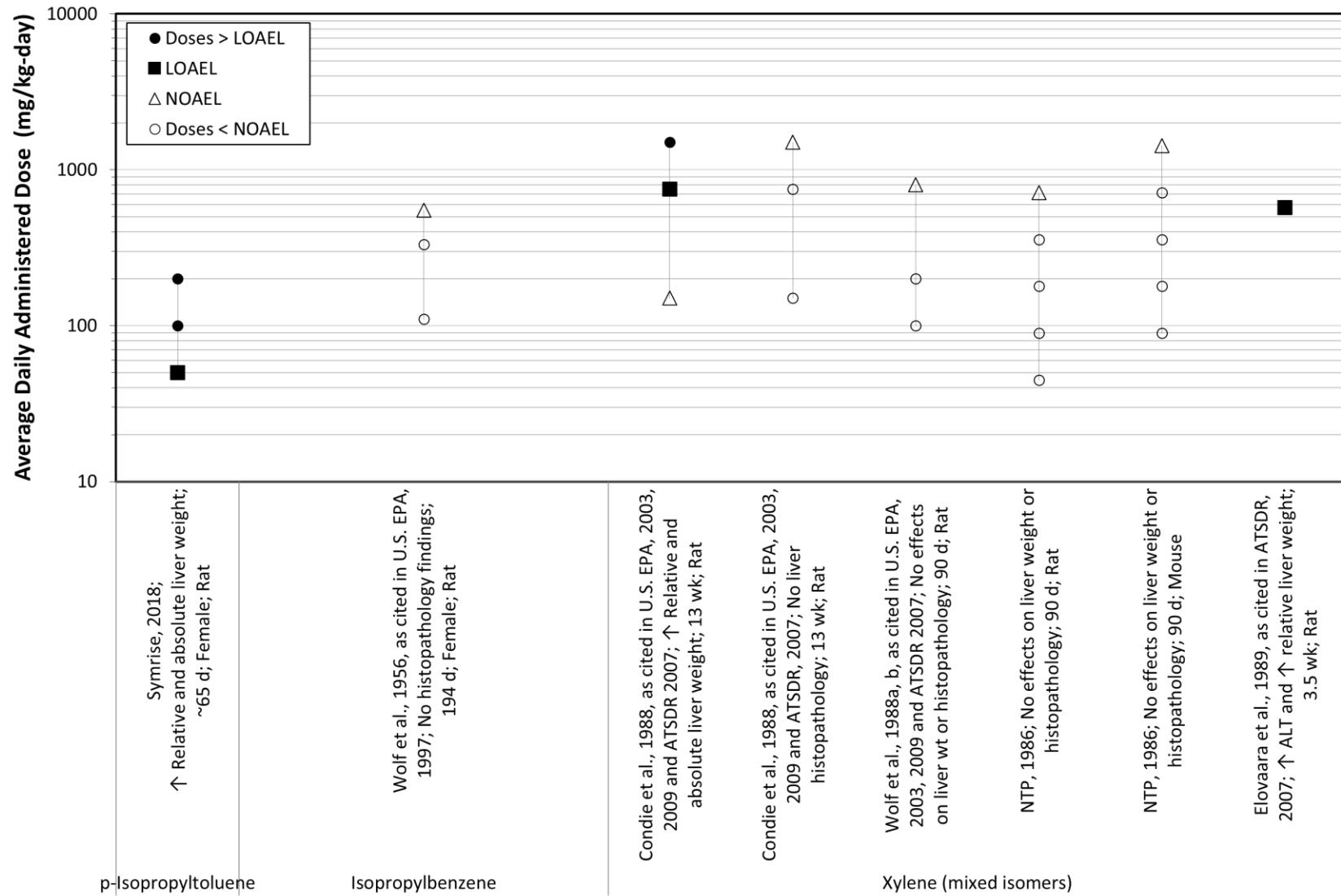


Figure A-2. Hepatic, Renal, and Adrenal Effects Following Inhalation Exposure to Candidate *p*-Isopropyltoluene Analogues



**Figure A-3. Hepatic Effects Following Oral Exposure to *p*-Isopropyltoluene and its Candidate Analogues**

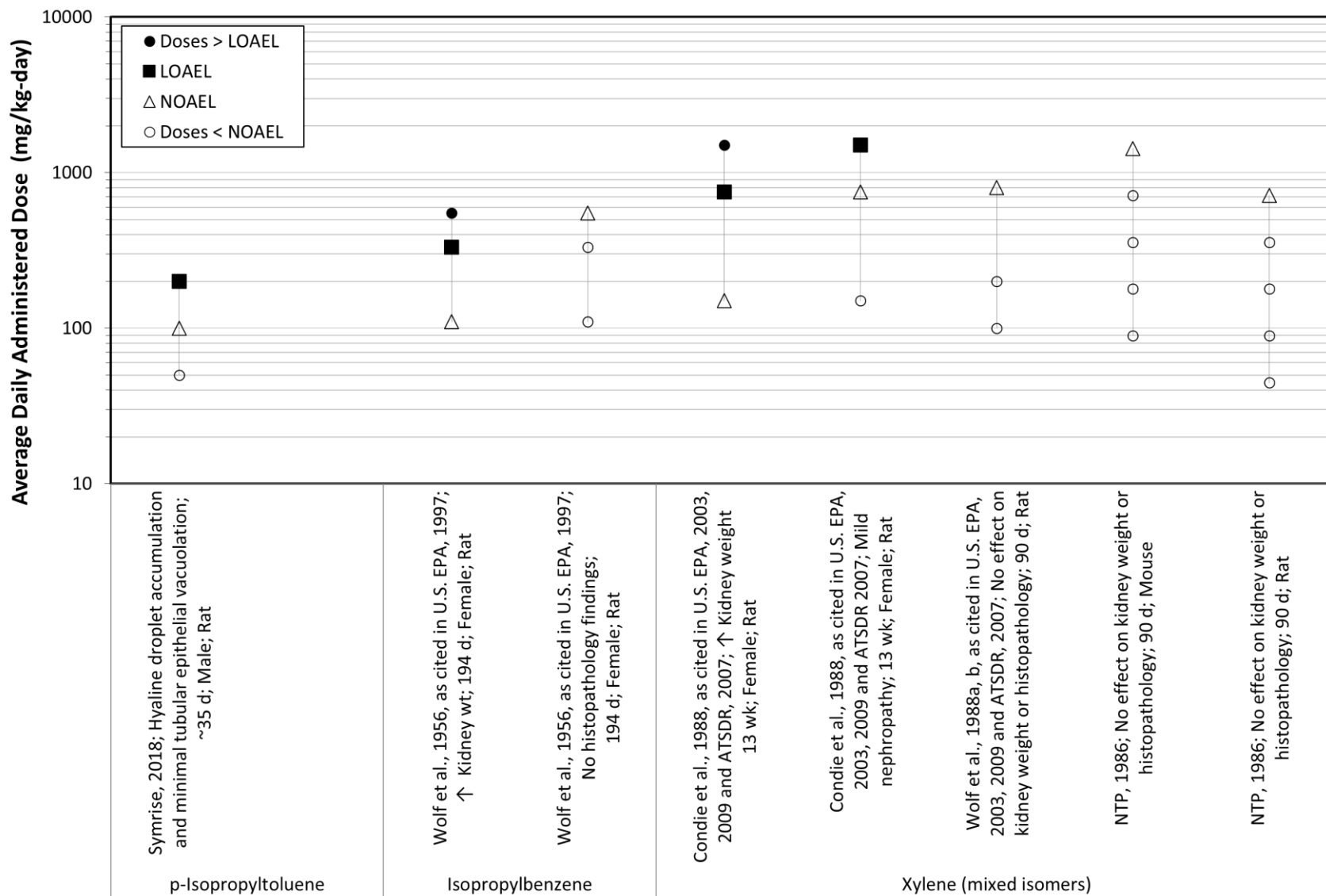


Figure A-4. Renal Effects Following Oral Exposure to *p*-Isopropyltoluene and its Candidate Analogues

Neurological effects were observed following inhalation exposure to the candidate analogue, xylene (see Figure A-5). Altered rotarod performance, latency in paw-lick response, motor activity, passive avoidance test, and auditory effects were noted in rats exposed to xylene at  $\geq 18$  ppm ( $78 \text{ mg/m}^3$ ) across several repeated-dose studies. In the case of isopropylbenzene, no reproducible effects in FOB tests, motor activity tests, or neurohistopathology were observed in a 13-week inhalation rat study up to 214.6 ppm ( $1,055 \text{ mg/m}^3$ ) (see Figure A-5). No subchronic or chronic inhalation data are available for the target compound. There is limited evidence of neurological effects following repeated-dose oral exposure to *p*-isopropyltoluene and xylene (see Figure A-6), although the measured endpoints reported for these compounds were different (reduced grip strength in male rats exposed to 200 mg/kg-day of *p*-isopropyltoluene and aggression and hyperactivity in rodents exposed to  $\geq 714$  mg/kg-day of xylene). Oral neurotoxicity data were not available for isopropylbenzene. Neurological effects were reported after acute/short-term exposure to the target chemical via multiple exposure routes (reduced mobility in mice orally exposed to 1,650 mg/kg-day for 24–28 days; analgesic effects in mice after an oral dose of 40 mg/kg; transient clonic convulsions in rats and guinea pigs after a single inhalation exposure at  $9,700 \text{ mg/m}^3$ ; reduced spontaneous activity, analgesia, reduced urination and defecation, and antinociceptive effects in mice exposed to 25–200 mg/kg via acute i.p. injection) (see Section 2.3.2 for more details). This is consistent with evidence for the candidate analogues and other solvents that produce acute neurological effects in humans and/or animals indicative of central nervous system depressant activity mostly at high exposure levels ( $>500$  ppm or  $2,460 \text{ mg/m}^3$  for isopropylbenzene and  $>100$  ppm or  $434 \text{ mg/m}^3$  for xylene after inhalation exposure) ([U.S. EPA, 2003, 1997](#)).

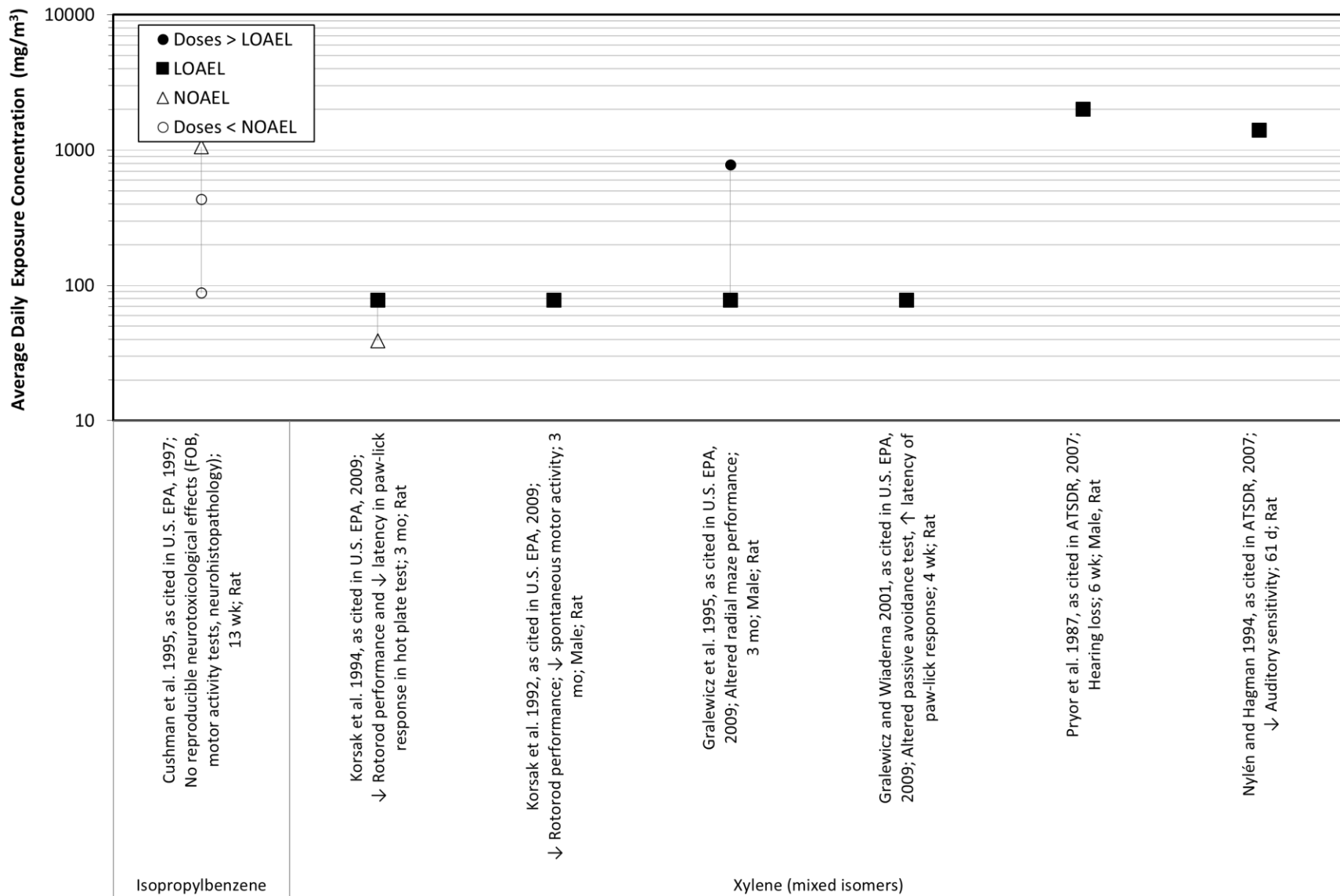


Figure A-5. Neurological Effects Following Inhalation Exposure to *p*-Isopropyltoluene Candidate Analogues

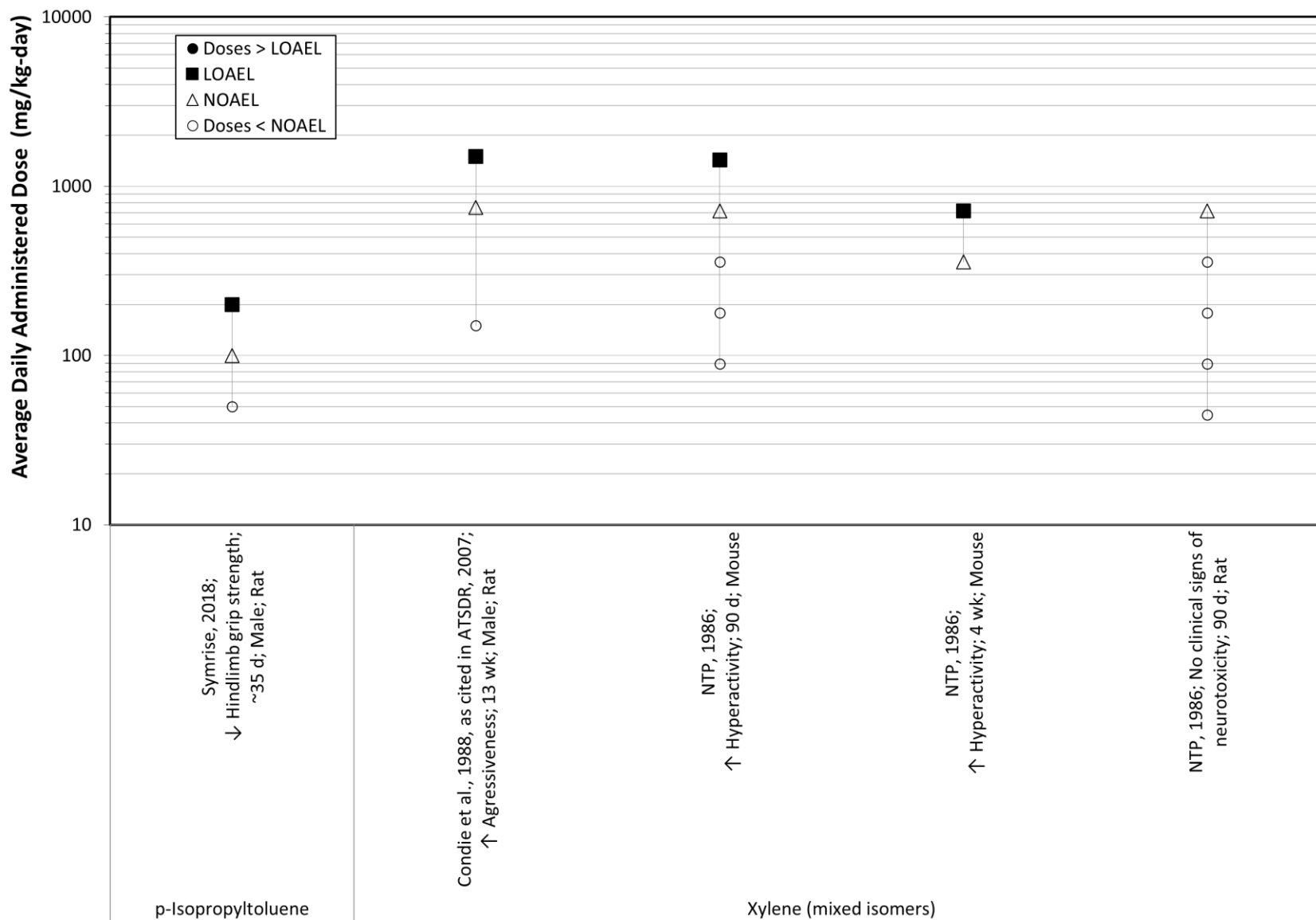
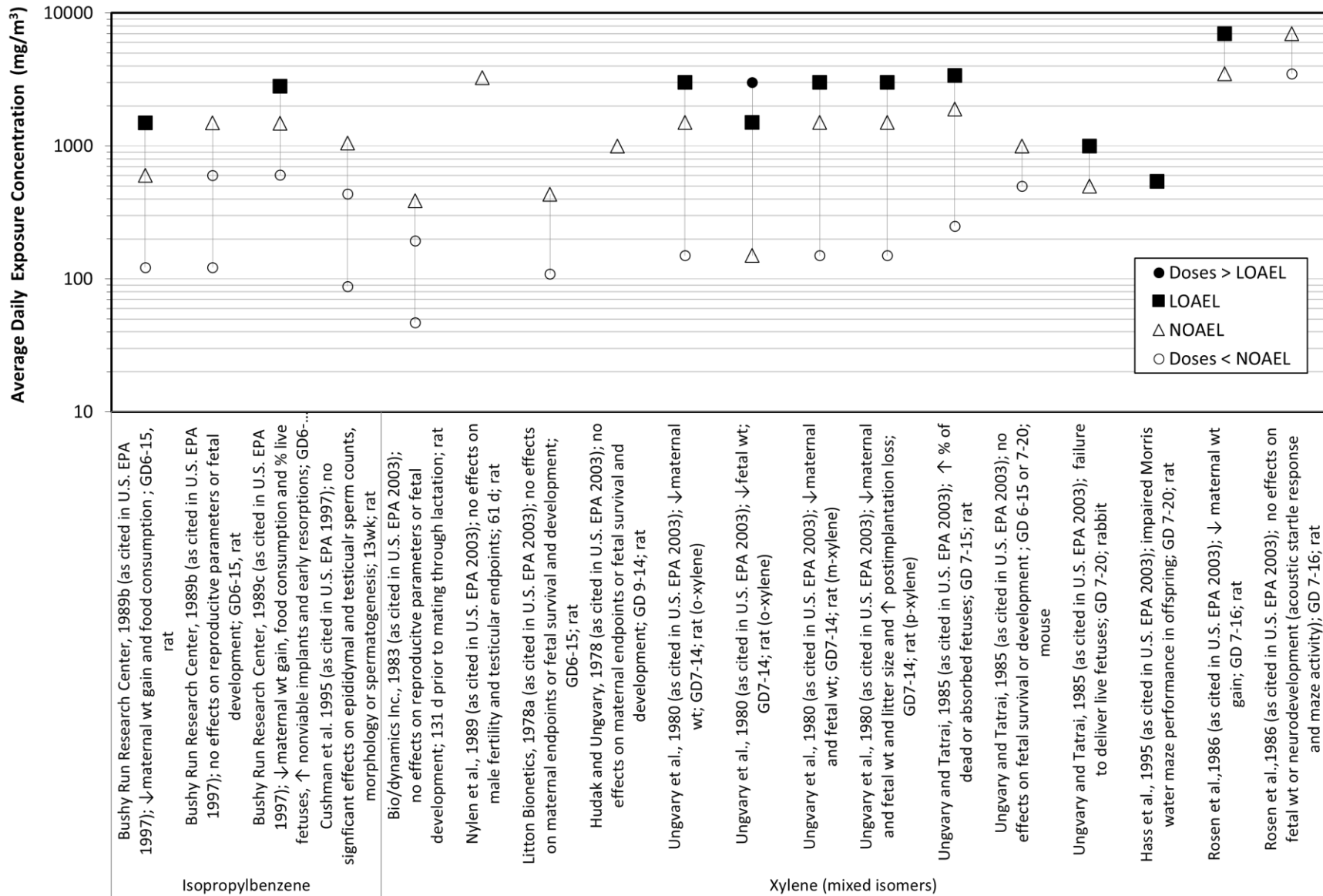
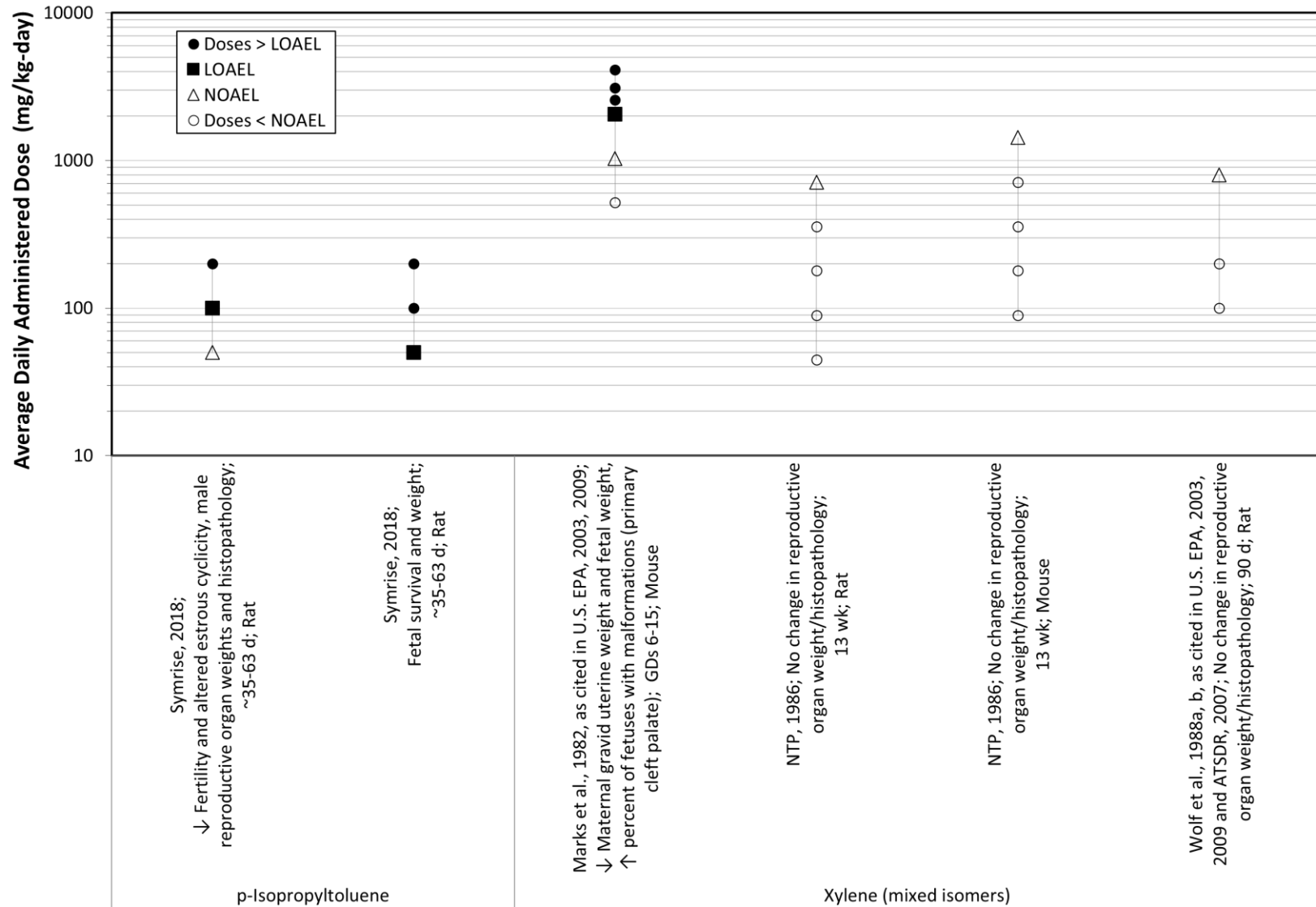


Figure A-6. Neurological Effects Following Oral Exposure to *p*-Isopropyltoluene and its Candidate Analogue

Developmental and reproductive toxicity have not been examined following inhalation exposure to *p*-isopropyltoluene. For isopropylbenzene, limited evidence of developmental toxicity (increased nonviable implants and early resorptions and decreased percentage of live fetuses; effects were not statistically significant but showed a coherent pattern) in the presence of decreased maternal body weight gain and food consumption was found at 574.3 ppm (2,823 mg/m<sup>3</sup>) in an inhalation rabbit study with gestational exposure (gestation days [GDs] 6–18) (see Figure A-7). For xylene, reversible neurodevelopmental effects (impaired Morris water maze performance in offspring) were reported in rats exposed in utero on GDs 7–20 at 125 ppm (543 mg/m<sup>3</sup>), while effects on offspring survival and development (decreased fetal body weight) occurred at higher concentrations ( $\geq 345.5$  ppm or  $\geq 1,500$  mg/m<sup>3</sup>) in animals exposed during gestation (see Figure A-7); maternal toxicity (decreased maternal weight and failure to deliver live fetuses) was observed at  $\geq 230$  ppm (or  $\geq 1,000$  mg/m<sup>3</sup>) in the gestational exposure studies (see Figure A-7). No effects on reproductive parameters were detected in a one-generation rat study at 89.4 ppm (388 mg/m<sup>3</sup>) or a subchronic study examining male fertility and testicular toxicity in rats at 749.9 ppm (3,256 mg/m<sup>3</sup>) after inhalation exposure to xylene (see Figure A-7). Effects on the reproductive system (decreased fertility, altered estrous cyclicity, and male reproductive organ weights and histopathology at  $\geq 100$  mg/kg-day) and developing offspring (decreases in survival and body weights at  $\geq 50$  mg/kg-day) were observed for *p*-isopropyltoluene after subchronic oral exposure in rats (see Figure A-8). No data on potential reproductive/developmental effects are available for isopropylbenzene via the oral route. Data on xylene include a gestational gavage study in mice that reported effects on fetal development (decreased fetal body weight and increased fetal malformations [i.e., cleft palate]) at  $\geq 2,060$  mg/kg-day accompanied by maternal toxicity (decreased uterine weight) and subchronic oral studies in rats and mice that reported no effects on reproductive organ weights or histopathology up to 1,429 mg/kg-day.



**Figure A-7. Reproductive and Developmental Effects Following Inhalation Exposure to *p*-Isopropyltoluene Candidate Analogues**



**Figure A-8. Reproductive and Developmental Effects Following Oral Exposure to *p*-Isopropyltoluene and Candidate Analogues**

Figure A-9 illustrates that respiratory irritation occurs following acute inhalation exposure to *p*-isopropyltoluene and isopropylbenzene in animals and acute/short-term inhalation exposure to xylene in humans. Correspondingly, sensory irritation RD<sub>50</sub> values (i.e., the concentration that elicits a respiratory rate decrease of 50%) in mice were similar for isopropylbenzene (2,058 ppm or 10,117 mg/m<sup>3</sup>) and xylene (1,300–2,440.2 ppm or 5,645–10,595 mg/m<sup>3</sup>) (see Figure A-10). No RD<sub>50</sub> data are available for the target compound. The inhalation LC<sub>50</sub> values in rodents (see Table A-9) were similar for the target compound and both candidate analogues, suggesting low acute inhalation toxicity following exposure to these compounds (19,500–24,000 mg/m<sup>3</sup> for *p*-isopropyltoluene; 10,000–39,000 mg/m<sup>3</sup> for isopropyltoluene; and 17,000–29,000 mg/m<sup>3</sup> for xylene).

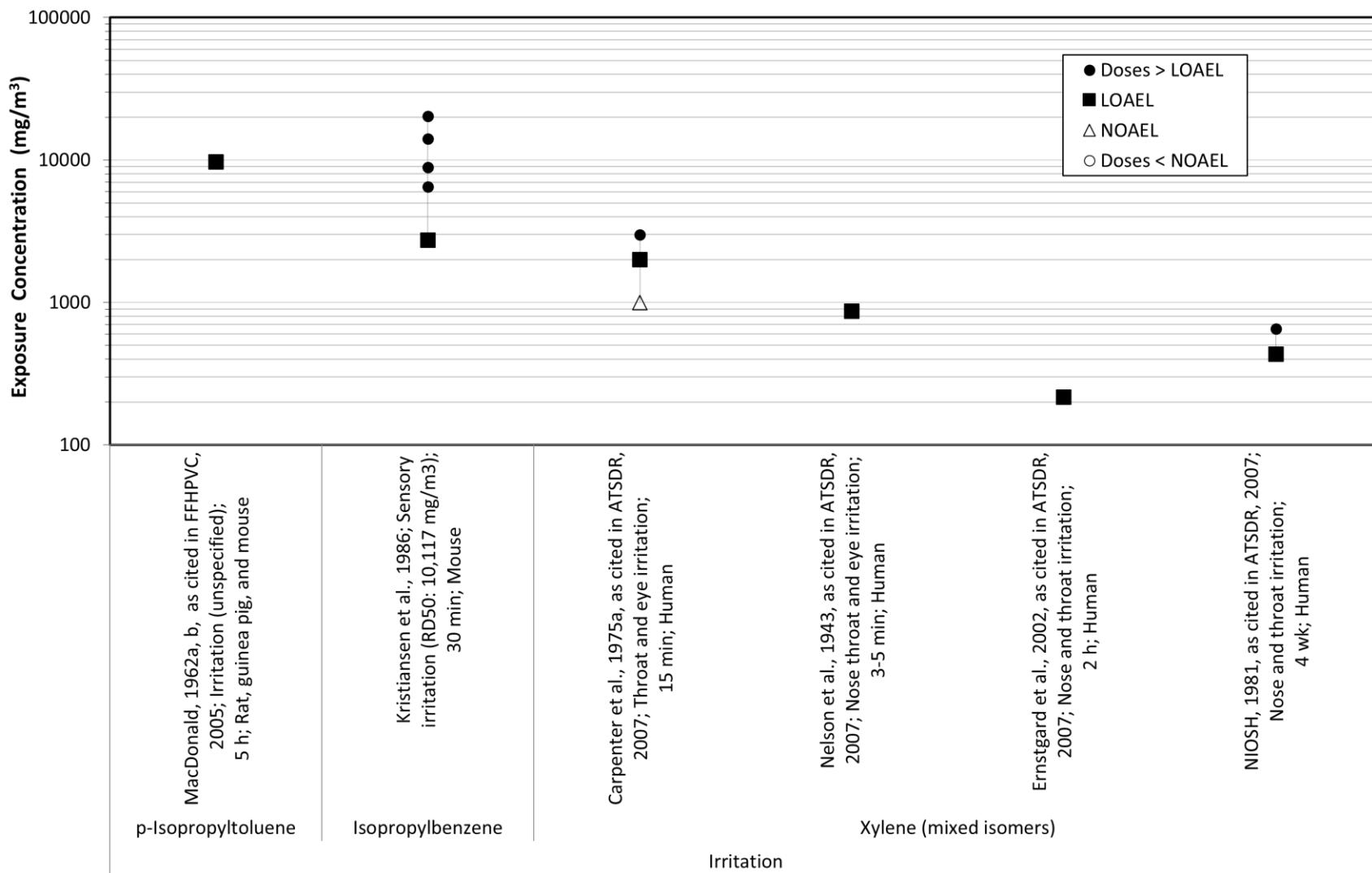


Figure A-9. Irritation Effects Following Inhalation Exposure to *p*-Isopropyltoluene and Candidate Analogues

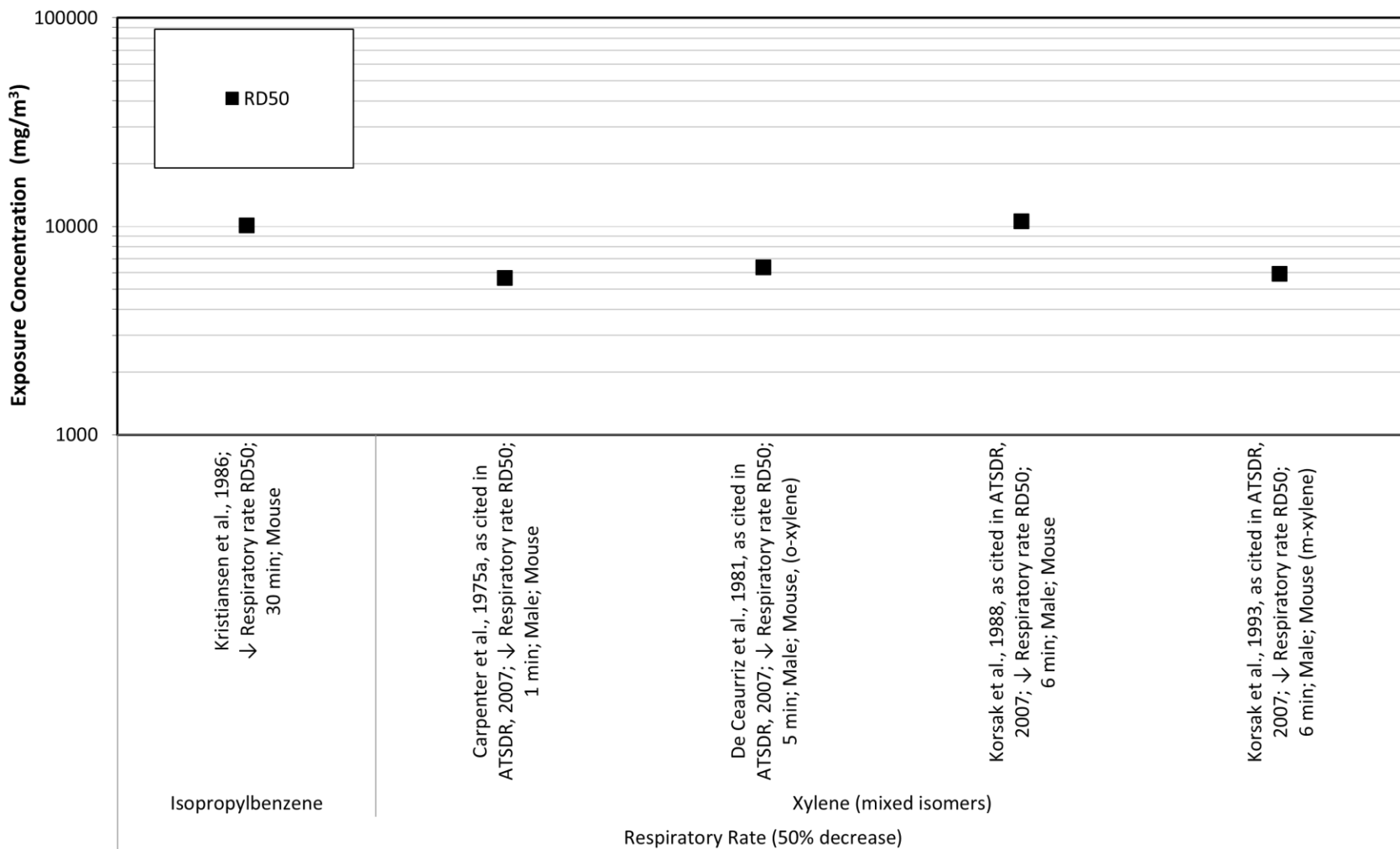


Figure A-10. Inhalation RD<sub>50</sub> Values for *p*-Isopropyltoluene Candidate Analogues

Although there is limited toxicity data on *p*-isopropyltoluene to clearly identify or rule out suitable analogues based on toxicity comparisons, the available evidence suggests some commonalities between the target compound and candidate analogues. For example, all three compounds target the liver, kidney, and developmental systems to some extent after repeated-dose inhalation and/or oral exposures, albeit at different potencies. Further, *p*-isopropyltoluene and its candidate analogues induce acute/short-term neurological effects, respiratory irritation, and low acute lethality following inhalation exposure.

### Weight-of-Evidence Approach

A WOE approach is used to evaluate information available for candidate analogues as described by [Wang et al. \(2012\)](#) and [Lizarraga et al. \(2023\)](#). Similarities between candidate analogues and the target chemical are identified across three major categories of evidence: structural/physicochemical properties; toxicokinetics (absorption, distribution, metabolism, excretion; ADME) and toxicodynamics (toxicity or MOA). Evidence of toxicological and/or toxicokinetic similarity is prioritized over evidence of similarity in structural/physicochemical properties. Candidate analogues are excluded if they demonstrate substantial differences from the pool of candidate analogues as a whole and/or the target chemical in any of the three categories of evidence. From the remaining pool of candidate analogues, the most suitable analogue (i.e., the analogue that displays the closest biological or toxicological similarity to the target chemical) with the greatest structural similarity and/or most health-protective point-of-departure is selected. Additional considerations include preference for evidence from existing U.S. EPA assessments and suitability of study duration (i.e., chronic studies are preferred over subchronic studies when selecting an analogue for the derivation of a chronic value).

*p*-Isopropyltoluene and both candidate analogues (isopropylbenzene and xylene [mixed isomers]) share important structural features expected to influence toxicokinetics and/or toxicity (i.e., a single benzene ring containing one or two methyl and/or isopropyl substituents). Similarities in physicochemical properties (i.e., vapor pressure, water solubility,  $K_{oc}$ , and  $\log K_{ow}$ ) suggest that the target compound and candidate analogues are expected to be bioavailable by the oral and inhalation routes. *p*-Isopropyltoluene and candidate analogues showed similar structural alerts for protein binding, reproductive and developmental toxicity, and metabolism by CYP. In summary, similarities in structural features, physicochemical properties, and structural alerts suggest that both isopropylbenzene and xylene are suitable structural analogues for *p*-isopropyltoluene.

The target compound and candidate analogues share similarities in absorption, metabolism, and distribution based on available *in vivo* data from experimental animals. Indeed, all three compounds exhibit extensive absorption by multiple exposure routes (including by inhalation) and are primarily metabolized through the oxidation of side-chain substituents in laboratory animals (i.e., methyl and/or isopropyl substituents) and excreted via the urine as glycine-, glucuronide-, and sulfate-conjugated metabolites. No *in vivo* distribution data are available for *p*-isopropyltoluene; however, based on the  $\log K_{ow}$  value  $>4$ , it is expected to accumulate in fatty tissues, similar to the candidate analogue compounds. Taken together, these data suggest that both isopropylbenzene and xylene are suitable analogues for *p*-isopropyltoluene based on toxicokinetic properties.

There are limited toxicity data, particularly by the inhalation route, to draw comparisons between *p*-isopropyltoluene and the candidate analogues and to clearly identify or rule out suitable analogues based on toxicodynamic properties. Additionally, comparison of toxicities by

the oral route may or may not inform toxicities by the inhalation route. However, the available evidence suggests that these compounds may share some common toxicity targets (i.e., liver, kidney, and developmental system) after repeated-dose exposure via inhalation and/or oral routes and induce neurological effects, respiratory irritation, and low acute lethality potency after acute/short-term inhalation exposure.

In summary, both isopropylbenzene and xylene (mixed isomers) are considered suitable analogues for *p*-isopropyltoluene on the basis of structural and toxicokinetic properties and limited toxicity data. Xylene provides the only subchronic inhalation toxicity value ([U.S. EPA, 2009](#)) and the more health-protective chronic inhalation toxicity value ([U.S. EPA, 2003](#)). ATSDR Minimal Risk Levels (MRLs) for xylene are available for both intermediate and chronic durations ([ATSDR, 2007](#)); however, the [U.S. EPA \(2009, 2003\)](#) values for this analogue are more health-protective than the ATSDR values. Therefore, the subchronic and chronic p-RfC values for xylene (mixed isomers) ([U.S. EPA, 2009, 2003](#)) will be used to derive the screening p-RfC values for *p*-isopropyltoluene.

### Derivation of a Screening Subchronic Provisional Reference Concentration

Based on the overall analogue approach presented in this PPRTV assessment, xylene (mixed isomers) is selected as the analogue for *p*-isopropyltoluene for derivation of screening subchronic and chronic p-RfCs. The principal study used for the screening subchronic and chronic p-RfC values for *p*-isopropyltoluene is a 3-month inhalation study of *m*-xylene in rats [Korsak et al. (1994) as cited in ([U.S. EPA, 2009, 2003](#))]<sup>14</sup>. The PPRTV assessment for xylenes (CASRN 1330-20-7) provided the following summary:

*Korsak et al. (1994) exposed groups of 12 male Wistar rats by inhalation to 0, 50 or 100 ppm m-xylene or n-butyl alcohol or a 1:1 mixture (purity of chemicals not provided) for 6 hours per day, 5 days per week for 3 months and evaluated similar endpoints as in the earlier study (Korsak et al., 1992). Rotarod performance and spontaneous motor activity were assayed. The report does not specify the timing of the neurologic examinations; however, given that the 1994 study was conducted by the same group of investigators as a 1992 study (Korsak et al., 1992) and that one of the tests (rotarod performance) was the same in both studies, it appears reasonable to assume that the tests were administered 24 hours after termination of exposure. The rotarod test was used as a measure of motor coordination disturbances from exposure to m-xylene. The rotarod test involves placing the subject animals on a rotating rod and evaluating their ability to remain on the rod for a period of 2 minutes. The animals were trained to perform the task, exposed to chemical or control gas and evaluated at defined intervals. By the time interval after exposure, considerable proportions of absorbed xylenes are expected to have been eliminated from the body (see Toxicological Review, U.S. EPA, 2003). Body weights and weights of seven organs were measured. Blood for clinical biochemistry (e.g., alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, alkaline phosphatase and total protein) and hematologic analysis (erythrocyte counts, hemoglobin concentration, hematocrit, leukocyte count and differential leukocyte counts) was collected 24 hours after termination of exposure. Statistical evaluations (using a*

<sup>14</sup>Korsak, Z; Wisniewska-Knypl, J; Swiercz, R. 1994. Toxic effects of subchronic combined exposure to n-butyl alcohol and m-xylene in rats. *Int J Occup Med Environ Health* 7:155-166. [as cited in [U.S. EPA \(2009, 2003\)](#)].

$p = 0.05$  level of significance) of the collected data included analysis of variance, Dunnett's test and Fisher's exact test.

No statistically significant exposure-related changes were noted in body-weight gain, absolute or relative organ weights, hepatic activities of microsomal monooxygenases, lipid peroxidation or levels of triglycerides in the liver (Korsak et al., 1994). Statistically significant decreases in erythrocyte number were seen in animals exposed to 50 ppm (93% of controls) or 100 ppm (80.5% of controls) of *m*-xylene alone. Similarly, decreased levels of hemoglobin were reported in both groups (92% of controls for both groups). At 100 ppm, a statistically significant increase in leukocyte number (35% increase over controls) was reported. Exposure to 50 or 100 ppm *m*-xylene alone also resulted in decreased rotarod performance starting at 1 month of exposure, which remained at the same level until the end of the 3-month exposure. Decreases were statistically significant in the 100 ppm group when compared with the controls. The results were presented in graphical form; the actual numerical data are not provided. The decreases in performance were roughly 8% and 33% for the 50 and 100 ppm groups, respectively, versus 0% for the controls.

Sensitivity to pain was assessed using the hot plate behavior test, in which the animals are placed on a hot (54°C) surface and the time interval between being placed on the plate and licking of the paws is measured (Korsak et al., 1994). Rats exposed to 50 or 100 ppm *m*-xylene alone had statistically significantly increased sensitivity to pain at the end of the 3-month exposure (latency of the paw-lick response was 8.7 and 8.6 seconds, respectively, vs. 12.2 seconds for the controls). The LOAEL is 100 ppm, based on decreased rotarod performance and decreased latency in the paw-lick response in the hot-plate test and the NOAEL is 50 ppm.

The NOAEL<sub>HEC</sub> based on impaired motor coordination in rats (decreased rotarod performance) used to derive the subchronic p-RfC value for xylene (mixed isomers), is described by [U.S. EPA \(2009, 2003\)](#) as follows:

The NOAEL of 50 ppm (217 mg/m<sup>3</sup>) was duration adjusted as follows:

$$\begin{aligned} \text{NOAEL}_{\text{ADJ}} &= \text{NOAEL} \times (5 \text{ days}/7 \text{ days}) \times (6 \text{ hrs}/\text{day} / 24 \text{ hrs}/\text{day}) \\ &= 217 \text{ mg}/\text{m}^3 \times 5/7 \times 6/24 \\ &= 39 \text{ mg}/\text{m}^3 \end{aligned}$$

The NOAEL<sub>[ADJ]</sub> was used to derive a human equivalent concentration (HEC), as described in U.S. EPA (1994b). Xylene is considered a category 3 gas because of its low water solubility and its potential for accumulation in blood during exposure and because its most sensitive effect is an extrarrespiratory effect. The NOAEL<sub>[HEC]</sub> was calculated using the equation

$$\begin{aligned} (H_{b/g})_A / (H_{b/g})_H &= 46.0/26.4 = 1.7 \\ \text{NOAEL}_{\text{HEC}} &= \text{NOAEL}_{\text{adj}} \times (H_{b/g})_A / (H_{b/g})_H \\ &= 39 \text{ mg}/\text{m}^3 \times 1 \\ &= 39 \text{ mg}/\text{m}^3 \end{aligned}$$

where  $H_{b/g}$  = blood/gas partition coefficient for the species in question, animal (A) or human (H)

Tardif et al. (1995) reported an  $(H_{b/g})_H$  of 26.4 for *m*-xylene, and an earlier study from the same group (Tardif et al., 1993a) reported an  $(H_{b/g})_A$  of 46.0 for *m*-xylene in the rat.

However, when  $(H_{b/g})_A > (H_{b/g})_H$ , a value of 1 is used for the ratio (U.S. EPA, 1994b).

To derive the screening subchronic p-RfC for *p*-isopropyltoluene, the same POD (NOAEL<sub>HEC</sub>) of 39 mg/m<sup>3</sup> based on impaired motor coordination (decreased rotarod performance) in rats exposed to *m*-xylene is adopted. Persistent neurological effects have been associated with exposure to individual xylene isomers and mixed xylenes as described by [U.S. EPA \(2009, 2003\)](#). A U<sub>F</sub>C of 300 is applied to the POD to account for residual interspecies differences after default NOAEL<sub>HEC</sub> dosimetric adjustments (U<sub>F</sub>A of 3), database uncertainties due to the absence of adequate repeated-dose inhalation toxicity data for *p*-isopropyltoluene (U<sub>F</sub>D of 10), and human variability and sensitive populations (U<sub>F</sub>H of 10).

$$\begin{aligned} \text{Screening Subchronic p-RfC} &= \text{Analogue POD (HEC)} \div \text{U}_{F_C} \\ &= 39 \text{ mg/m}^3 \div 300 \\ &= 1 \times 10^{-1} \text{ mg/m}^3 \end{aligned}$$

Table A-10 summarizes the uncertainty factors for the screening subchronic p-RfC for *p*-isopropyltoluene.

<b>Table A-10. Uncertainty Factors for the Screening Subchronic p-RfC for <i>p</i>-Isopropyltoluene (CASRN 99-87-6)</b>		
<b>UF</b>	<b>Value</b>	<b>Justification</b>
U <sub>F</sub> A	3	A U <sub>F</sub> A of 3 (10 <sup>0.5</sup> ) is applied to account for uncertainty associated with extrapolating from animals to humans when cross-species dosimetric adjustment (HEC calculation) is performed.
U <sub>F</sub> D	10	A U <sub>F</sub> D of 10 is applied to reflect database limitations for the target compound, <i>p</i> -isopropyltoluene. For <i>p</i> -isopropyltoluene, there were no adequate subchronic or chronic inhalation toxicity studies or any repeated-dose studies evaluating developmental/reproductive toxicity.
U <sub>F</sub> H	10	A U <sub>F</sub> H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of <i>p</i> -isopropyltoluene in humans.
U <sub>F</sub> L	1	A U <sub>F</sub> L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
U <sub>F</sub> S	1	A U <sub>F</sub> S of 1 is applied because the POD was derived from a subchronic 3-month study.
U <sub>F</sub> C	300	Composite UF = U <sub>F</sub> A × U <sub>F</sub> D × U <sub>F</sub> H × U <sub>F</sub> L × U <sub>F</sub> S.

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; UF = uncertainty factor; U<sub>F</sub>A = interspecies uncertainty factor; U<sub>F</sub>C = composite uncertainty factor; U<sub>F</sub>D = database uncertainty factor; U<sub>F</sub>H = intraspecies uncertainty factor; U<sub>F</sub>L = LOAEL-to-NOAEL uncertainty factor; U<sub>F</sub>S = subchronic-to-chronic uncertainty factor.

### Derivation of a Screening Chronic Provisional Reference Concentration

The NOAEL<sub>HEC</sub> 39 mg/m<sup>3</sup> based on impaired motor coordination in rats used in the derivation of the chronic p-RfC for xylene (mixed isomers) [Korsak et al. (1992) as cited in [U.S.](#)

[EPA \(2009, 2003\)](#)] is also selected as the POD for the derivation of the screening chronic p-RfC for *p*-isopropyltoluene. The screening chronic p-RfC for *p*-isopropyltoluene is derived by applying a UF<sub>C</sub> of 1,000 to the POD (HEC) of 39 mg/m<sup>3</sup>. The UF<sub>C</sub> of 1,000 was derived by applying a UF<sub>A</sub> of 3, a UF<sub>D</sub> of 10, a UF<sub>H</sub> of 10, and a UF<sub>S</sub> of 3. A factor of 10 is not used for duration extrapolation from subchronic to chronic because the changes in rotarod performance associated with xylene inhalation exposure did not increase with time from 1 to 3 months, and they were similar to those described in a separate study of 6 months in duration [Korsak et al. (1992) as cited in [U.S. EPA \(2009, 2003\)](#)]. The same rationale and UFs of 3 was used in the [U.S. EPA \(2003\)](#) assessment to derive the chronic RfC for xylene.

$$\begin{aligned} \text{Screening Chronic p-RfC} &= \text{Analogue POD (HEC)} \div \text{UF}_C \\ &= 39 \text{ mg/m}^3 \div 1,000 \\ &= 4 \times 10^{-2} \text{ mg/m}^3 \end{aligned}$$

Table A-11 summarizes the uncertainty factors for the screening chronic p-RfC for *p*-isopropyltoluene.

<b>Table A-11. Uncertainty Factors for the Screening Chronic p-RfC for <i>p</i>-Isopropyltoluene (CASRN 99-87-6)</b>		
<b>UF</b>	<b>Value</b>	<b>Justification</b>
UF <sub>A</sub>	3	A UF <sub>A</sub> of 3 (10 <sup>0.5</sup> ) is applied to account for uncertainty associated with extrapolating from animals to humans when cross-species dosimetric adjustment (HEC calculation) is performed.
UF <sub>D</sub>	10	A UF <sub>D</sub> of 10 is applied to reflect database limitations for the target compound, <i>p</i> -isopropyltoluene. For <i>p</i> -isopropyltoluene, there were no adequate subchronic or chronic inhalation toxicity studies or any repeated-dose studies evaluating developmental/reproductive toxicity.
UF <sub>H</sub>	10	A UF <sub>H</sub> of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of <i>p</i> -isopropyltoluene in humans.
UF <sub>L</sub>	1	A UF <sub>L</sub> of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF <sub>S</sub>	3	A UF <sub>S</sub> of 3 is applied because the POD was derived from a subchronic 3-mo study. A factor of 10 was not used because the changes in rotarod performance did not increase with time from 1 to 3 mo, and they were similar to those described in a separate study of a 6-mo duration [Korsak et al (1992) as cited in <a href="#">U.S. EPA (2009, 2003)</a> ].
UF <sub>C</sub>	1,000	Composite UF = UF <sub>A</sub> × UF <sub>D</sub> × UF <sub>H</sub> × UF <sub>L</sub> × UF <sub>S</sub> .

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor; UF<sub>A</sub> = interspecies uncertainty factor; UF<sub>C</sub> = composite uncertainty factor; UF<sub>D</sub> = database uncertainty factor; UF<sub>H</sub> = intraspecies uncertainty factor; UF<sub>L</sub> = LOAEL-to-NOAEL uncertainty factor; UF<sub>S</sub> = subchronic-to-chronic uncertainty factor.

## APPENDIX B. DATA TABLES

<b>Table B-1. Select Functional Observational Battery Findings in Male Sprague Dawley Rats Exposed to <i>p</i>-Isopropyltoluene via Gavage for up to ~35 Days<sup>a</sup></b>				
	<b>Males: ~35 Days [HED] (mg/kg-d)<sup>b</sup></b>			
	<b>0 (control)</b>	<b>50 [14]</b>	<b>100 [28.1]</b>	<b>200 [56.2]</b>
Number of animals	5	5	5	5
Forelimb grip strength (g)	1,401.7 ± 346.3 <sup>c</sup>	1,109.3 ± 413.1 (-21%) <sup>d</sup>	1,143.7 ± 261.7 (-18%)	984.4 ± 231.9 (-30%)
Hindlimb grip strength (g)	837.7 ± 284.5	680.5 ± 54.2 (-19%)	628.2 ± 152.0 (-25%)	541.6 ± 227.7* (-35%)

<sup>a</sup>[Symrise \(2018\)](#).

<sup>b</sup>ADDs (mg/kg-day) were reported by the study authors; calculated HEDs appear in brackets.

<sup>c</sup>Data are mean ± SD.

<sup>d</sup>Value in parentheses is % change relative to control =  $([\text{treatment mean} - \text{control mean}] \div \text{control mean}) \times 100$ .

\*Significantly different from control ( $p < 0.05$ ) as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; SD = standard deviation.

<b>Table B-2. Select Hematology, Coagulation, and Serum Chemistry Findings in Sprague Dawley Rats Exposed to <i>p</i>-Isopropyltoluene via Gavage for up to ~35 Days (Males) or ~63 Days (Females)<sup>a</sup></b>				
<b>Endpoint</b>	<b>Males: ~35 Days [HED] (mg/kg-d)<sup>b</sup></b>			
	<b>0 (control)</b>	<b>50 [14]</b>	<b>100 [28.1]</b>	<b>200 [56.2]</b>
<b>Hematology and coagulation</b>				
Number of animals	4	5	5	5
Retic ( $\times 10^9/L$ )	163.4 $\pm$ 9.51 <sup>c</sup>	166.3 $\pm$ 20.02 (+2%) <sup>d</sup>	151.8 $\pm$ 15.96 (-7%)	211.7 $\pm$ 36.29** (+30%)
RDW (%)	12.5 $\pm$ 0.19	12.7 $\pm$ 0.49 (+2%)	12.3 $\pm$ 0.36 (-2%)	13.4 $\pm$ 0.8* (+7%)
PT (sec)	18 $\pm$ 0.76	18.7 $\pm$ 0.54 (+4%)	19.5 $\pm$ 0.77** (+8%)	19.6 $\pm$ 0.4** (+9%)
<b>Serum chemistry</b>				
Number of animals	5	5	5	5
ALP (U/L)	160 $\pm$ 23.5	166 $\pm$ 43.5 (+4%)	184 $\pm$ 22.8 (+15%)	232 $\pm$ 61.4* (+45%)
BUN (mg/dL)	12 $\pm$ 0 <sup>e</sup>	13 $\pm$ 0.9 (+8%)	14 $\pm$ 1.3 (+17%)	18 $\pm$ 1.8** (+50%)
Triglyceride (mg/dL)	86 $\pm$ 14.4	69 $\pm$ 38.1 (-20%)	45 $\pm$ 9.1* (-48%)	43 $\pm$ 18.1** (-50%)
Na <sup>+</sup> (mEq/L)	143 $\pm$ 1.4	143 $\pm$ 0.8 (0%)	143 $\pm$ 0.5 (0%)	141 $\pm$ 0.5* (-1%)
Cl <sup>-</sup> (mEq/L)	103 $\pm$ 1.1	102 $\pm$ 1.2* (-1%)	102 $\pm$ 0.9* (-1%)	102 $\pm$ 0.8* (-1%)
PHOS (mg/dL)	8.5 $\pm$ 0.41	7.9 $\pm$ 0.5 (-7%)	7.8 $\pm$ 0.11* (-8%)	8.5 $\pm$ 0.43 (0%)
<b>Endpoint</b>	<b>Mated Females: ~63 Days [HED] (mg/kg-d)</b>			
	<b>0 (control)</b>	<b>50 [13]</b>	<b>100 [25.6]</b>	<b>200 [51.2]</b>
<b>Serum chemistry</b>				
Number of animals	5	5	4	0
ALT (U/L)	183 $\pm$ 39	124 $\pm$ 25.9** (-32%)	93 $\pm$ 14** (-49%)	NA
ALP (U/L)	151 $\pm$ 19.8	210 $\pm$ 70.9 (+39%)	270 $\pm$ 119.1* (+79%)	NA
Cholesterol (mg/dL)	120 $\pm$ 30.8	95 $\pm$ 12 (-21%)	85 $\pm$ 5.4* (-29%)	NA
Albumin (g/dL)	3.5 $\pm$ 0.29	3.5 $\pm$ 0.15 (0%)*	3.2 $\pm$ 0.21* (-9%)	NA

<sup>a</sup>Symrise (2018).

<sup>b</sup>ADDs (mg/kg-day) were reported by the study authors; calculated HEDs appear in brackets.

<sup>c</sup>Data are mean  $\pm$  SD.

<sup>d</sup>Value in parentheses is % change relative to control =  $([\text{treatment mean} - \text{control mean}] \div \text{control mean}) \times 100$ .

\*Significantly different from control ( $p < 0.05$ ) as reported by the study authors.

\*\*Significantly different from control ( $p < 0.01$ ) as reported by the study authors.

ADD = adjusted daily dose; ALP = alkaline phosphatase; ALT = alanine aminotransferase; BUN = blood urea nitrogen; Cl<sup>-</sup> = chloride; HED = human equivalent dose; Na<sup>+</sup> = sodium; NA = not available; PHOS = inorganic phosphate; PT = prothrombin time; RDW = red blood cell distribution width; RETIC = reticulocyte count; SD = standard deviation.

**Table B-3. Select Organ Weights (Percent Difference Relative to Controls) in Sprague Dawley Rats Exposed to *p*-Isopropyltoluene via Gavage for ~35 Days (Males) or ~63 Days (Females)<sup>a</sup>**

Endpoint <sup>c</sup>	Males: ADD [HED] (mg/kg-d) <sup>b</sup>		
	50 [14]	100 [28.1]	200 [56.2]
Testes weight			
Absolute (%)	–	–	–14*
Relative to body weight (%)	–	–	–8
Relative to brain weight (%)	–	–	–12
Epididymides			
Absolute (%)	–	–	–14*
Relative to body weight (%)	–	–	–8
Relative to brain weight (%)	–	–	–14*
Levator ani/bulbocavernosus muscle			
Absolute (%)	–	–	–14
Relative to body weight (%)	–	–	–9
Relative to brain weight (%)	–	–	–15
Seminal vesicles/coagulating glands			
Absolute (%)	–19	–23	–22
Relative to body weight (%)	–20	–22	–14
Relative to brain weight (%)	–16	–23	–18
Prostate			
Absolute (%)	–26	2	–24*
Relative to body weight (%)	–27*	5	–16
Relative to brain weight (%)	–23	3	–20
Liver			
Absolute (%)	8	6	27*
Relative to body weight (%)	6	8*	41*
Relative to brain weight (%)	13	6	35*

**Table B-3. Select Organ Weights (Percent Difference Relative to Controls) in Sprague Dawley Rats Exposed to *p*-Isopropyltoluene via Gavage for ~35 Days (Males) or ~63 Days (Females)<sup>a</sup>**

Endpoint <sup>c</sup>	Females: ADD [HED] (mg/kg-d) <sup>b</sup>		
	50 [13]	100 [25.6]	200 [51.2]
Liver weight			
Absolute (%)	16	26*	NA
Relative to body weight (%)	14	22*	NA
Relative to brain weight (%)	14	22	NA

<sup>a</sup>[Symrise \(2018\)](#).

<sup>b</sup>ADDs (mg/kg-day) were reported by the study author; calculated HEDs appear in brackets.

<sup>c</sup>Data are percent difference relative to controls [actual measurement data for control and treatment groups were not available in the study report ([ECHA, 2019b](#))]; number of animals = 5; organs were not weighed in females that failed to deliver a litter).

\*Significantly different ( $p < 0.05$ ) between mean values for treated and control groups, as reported by the study authors.

– = reported in ECHA as not test item-related; ADD = adjusted daily dose; ECHA = European Chemicals Agency; HED = human equivalent dose; NA = not available; no organ weights were taken for females that failed to deliver a litter.

**Table B-4. Histopathology Findings in Liver and Kidney of Adult P<sub>0</sub> Sprague Dawley Rats Exposed to *p*-Isopropyltoluene via Gavage for ~35 Days (Males) or ~63 Days (Females)<sup>a</sup>**

Lesions <sup>c</sup>	Dose Group, mg/kg-d [HED] <sup>b</sup>							
	P <sub>0</sub> Males				P <sub>0</sub> Females			
	0	50 [14]	100 [28.1]	200 [56.2]	0	50 [13]	100 [25.6]	200 [51.2]
Liver								
Hepatocellular hypertrophy	0/5 (0%)	0/5 (0%)	0/5 (0%)	2/5 <sup>+</sup> (40%)	0/6 (0%)	1/6 <sup>+</sup> (17%)	0/10 (0%)	1/10 <sup>+</sup> (10%) <sup>d</sup>
Kidney								
Tubular dilation	1/5 <sup>++</sup> (20%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	1/5 <sup>++</sup> (20%)	0/4 (0%)	NA
Tubular epithelium vacuolation	0/5 (0%)	0/5 (0%)	0/5 (0%)	2/5 <sup>+</sup> (40%)	0/5 (0%)	0/5 (0%)	0/4 (0%)	NA
Hyaline droplets accumulation	1/5 <sup>+</sup> (20%)	1/5 <sup>+</sup> (20%)	0/5 (0%)	3/5 <sup>++</sup> (60%) <sup>e</sup>	0/5 (0%)	0/5 (0%)	0/4 (0%)	NA
Tubular basophilia	0/5 (0%)	1/5 <sup>+</sup> (20%)	1/5 <sup>+</sup> (20%)	1/5 <sup>+</sup> (20%)	0/5 (0%)	0/5 (0%)	0/4 (0%)	NA

<sup>a</sup>[Symrise \(2018\)](#).

<sup>b</sup>ADDs (mg/kg-day) were reported by the study author; calculated HEDs appear in brackets.

<sup>c</sup>Values denote number of animals showing changes / total number of animals examined; severity of lesions indicated by + (minimal) and ++ (slight).

<sup>d</sup>The number of livers examined includes those from nonpregnant females that were euthanized during the gestation period.

<sup>e</sup>2/5 had minimal severity and 1/5 had slight severity.

HED = human equivalent dose; NA = not available; kidneys from females in the 200-mg/kg-day group were not examined.

<b>Table B-5. Select Histological Findings in Reproductive Organs of Male Sprague Dawley Rats Administered <i>p</i>-Isopropyltoluene via Gavage for ~35 Days<sup>a</sup></b>				
<b>Lesions<sup>c</sup></b>	<b>Dose Group, mg/kg-d [HED]<sup>b</sup></b>			
	<b>0 (control)</b>	<b>50 [14]</b>	<b>100 [28.1]</b>	<b>200 [56.2]</b>
Testis				
Degeneration/depletion, germ cell				
Minimal	0/10 (0%)	0/10 (0%)	0/10 (0%)	1/10 (10%)
Slight	0/10 (0%)	0/10 (0%)	0/10 (0%)	5/10 (50%)*
Moderate	0/10 (0%)	0/10 (0%)	0/10 (0%)	1/10 (10%)
Total	0/10 (0%)	0/10 (0%)	0/10 (0%)	7/10 (70%)*
Depletion, germ cell				
Minimal	0/10 (0%)	0/10 (0%)	0/10 (0%)	2/10 (20%)
Total	0/10 (0%)	0/10 (0%)	0/10 (0%)	2/10 (20%)
Retention, spermatid				
Minimal	0/10 (0%)	0/10 (0%)	7/10 (70%)*	2/10 (20%)
Slight	0/10 (0%)	0/10 (0%)	0/10 (0%)	7/10 (70%)*
Total	0/10 (0%)	0/10 (0%)	7/10 (70%)*	9/10 (90%)*
Epididymides				
Sperm, reduced, luminal				
Minimal	0/10 (0%)	0/10 (0%)	1/10 (10%)	0/10 (0%)
Slight	0/10 (0%)	0/10 (0%)	1/10 (10%)	4/10 (40%)*
Moderate	0/10 (0%)	0/10 (0%)	0/10 (0%)	5/10 (50%)*
Marked	0/10 (0%)	0/10 (0%)	0/10 (0%)	1/10 (10%)
Total	0/10 (0%)	0/10 (0%)	2/10 (20%)	10/10 (100%)*
Cribriform change				
Minimal	0/10 (0%)	0/10 (0%)	0/10 (0%)	2/10 (20%)
Slight	0/10 (0%)	0/10 (0%)	1/10 (10%)	3/10 (30%)
Total	0/10 (0%)	0/10 (0%)	1/10 (10%)	5/10 (50%)*

**Table B-5. Select Histological Findings in Reproductive Organs of Male Sprague Dawley Rats Administered *p*-Isopropyltoluene via Gavage for ~35 Days<sup>a</sup>**

Lesions <sup>c</sup>	Dose Group, mg/kg-d [HED] <sup>b</sup>			
	0 (control)	50 [14]	100 [28.1]	200 [56.2]
Cell debris, luminal				
Minimal	0/10 (0%)	0/10 (0%)	0/10 (0%)	2/10 (20%)
Slight	0/10 (0%)	0/10 (0%)	0/10 (0%)	3/10 (30%)
Moderate	0/10 (0%)	0/10 (0%)	0/10 (0%)	4/10 (40%)*
Total	0/10 (0%)	0/10 (0%)	0/10 (0%)	9/10 (90%)*

<sup>a</sup>[Symrise \(2018\)](#).

<sup>b</sup>ADDs (mg/kg-day) were reported by the study author; calculated HEDs appear in brackets.

<sup>c</sup>Values denote number of animals showing changes / total number of animals examined (% incidence); all changes were bilateral.

\*Statistically significant from control ( $p < 0.05$ ) based on one-tailed Fisher's exact test performed for this review.

HED = human equivalent dose.

**Table B-6. Select Estrous Cycle Evaluations in Female Sprague Dawley Rats Exposed to *p*-Isopropyltoluene via Gavage for ~63 Days<sup>a</sup>**

Endpoints <sup>c</sup>	Dose Group, mg/kg-d [HED] <sup>b</sup>			
	0	50 [13]	100 [25.6]	200 [51.2]
Females with regular cycles <sup>d</sup>	6/10 (60%)	7/10 (70%)	7/10 (70%)	4/10 (40%)
Females with irregular cycles <sup>e</sup>	4/10 (40%)	3/10 (30%)	3/10 (30%)	6/10 (60%)
Females with extended estrus <sup>f</sup>	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
Acyclic females <sup>g</sup>	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
Total number of pregnant females	10	10	10	10

<sup>a</sup>[Symrise \(2018\)](#).

<sup>b</sup>ADDs (mg/kg-day) were reported by the study author; calculated HEDs appear in brackets.

<sup>c</sup>Values denote number of animals with estrus cycle observations / total number of animals examined (% incidence).

<sup>d</sup>All regular cycles (4, 4/5, and 5 days).

<sup>e</sup>At least one cycle of <4 or >5 days.

<sup>f</sup>At least 4 consecutive days of estrus.

<sup>g</sup>At least 10 days without estrus.

HED = human equivalent dose.

**Table B-7. Select Fertility and Offspring Survival Parameters in Sprague Dawley Rats Exposed to *p*-Isopropyltoluene via Gavage for Gavage for ~35 Days (Males) or ~63 Days (Females)<sup>a</sup>**

Endpoints	Dose Group, mg/kg-d [HED]			
	0	50 [13]	100 [25.6]	200 [51.2]
Mating and fertility				
Number of females paired with males	10	10	10	10
Number mated	10	10	10	9
Mating index (%) <sup>b</sup>	100	100	100	90
Total number pregnant females	9	9	4	0
Fertility index (%) <sup>c</sup>	90	90	40	0
Reproductive and offspring survival indices				
Number	9	9	4	
Gestation length (days)	21.8 ± 0.44	21.7 ± 0.50	21.3 ± 0.58 <sup>d</sup>	–
Number of corpora lutea	16.3 ± 2.40	14.9 ± 3.06	17.3 ± 1.89	–
Number of implantations	16.0 ± 2.06	14.0 ± 3.08	16.0 ± 1.41	–
Preimplantation loss (%) <sup>e</sup>	1.8 ± 3.64	5.9 ± 6.81	7.1 ± 1.94	–
Postimplantation survival index (%) <sup>f</sup>	95 ± 6.55	97.7 ± 4.65	87.3 ± 14.50	–
Live birth index (%) <sup>g</sup>	100 ± 0	97.7 ± 4.77	94.3 ± 4.17*	–
Viability index, Day 4 (%) <sup>h</sup>	100 ± 0	100 ± 0	98.3 ± 3.33	–
Viability index, Day 7 (%) <sup>h</sup>	86.7 ± 1.24	84.3 ± 4.28	82.5 ± 4.33	–
Viability index, Day 13 (%) <sup>h</sup>	84.5 ± 3.27	84.3 ± 4.28	82.5 ± 4.33	–

**Table B-7. Select Fertility and Offspring Survival Parameters in Sprague Dawley Rats Exposed to *p*-Isopropyltoluene via Gavage for Gavage for ~35 Days (Males) or ~63 Days (Females)<sup>a</sup>**

Endpoints	Dose Group, mg/kg-d [HED]			
	0	50 [13]	100 [25.6]	200 [51.2]
Mean body weight for offspring (g)				
Number	9	9	4	
Males, Day 1	6.8 ± 0.62	6.8 ± 0.91 (0%)	6.1 ± 0.44 (-10.3%)	NA
Males, Day 4	8.9 ± 0.89	9.8 ± 1.61 (10.1%)	8.7 ± 0.50 (-2.2%)	NA
Males, Day 7	13.1 ± 1.31	14.8 ± 2.68 (13.0%)	13.4 ± 0.78 (2.3%)	NA
Males, Day 11	20.4 ± 2.08	23.0 ± 4.77 (12.7%)	21.2 ± 1.58 (3.9%)	NA
Males, Day 13	24.5 ± 2.70	26.8 ± 5.22 (9.4%)	25.1 ± 1.72 (2.4%)	NA
Females, Day 1	6.6 ± 0.66	6.3 ± 0.84 (-4.5%)	6.0 ± 0.3 (-9.1%)	NA
Females, Day 4	8.4 ± 0.90	9.0 ± 1.75 (7.1%)	8.6 ± 0.53 (2.4%)	NA
Females, Day 7	12.7 ± 1.51	14.0 ± 2.8 (10.2%)	12.8 ± 0.81 <sup>d</sup> (0.8%)	NA
Females, Day 11	20.0 ± 2.74	22.2 ± 4.85 (11.0%)	19.9 ± 1.04 <sup>d</sup> (-0.5%)	NA
Females, Day 13	23.7 ± 3.25	26.0 ± 5.53 (9.7%)	23.7 ± 1.16 <sup>d</sup> (0%)	NA

<sup>a</sup>[Symrise \(2018\)](#).

<sup>b</sup>Mating index = (number of females with confirmed mating + number of pregnant females without evidence of mating) / (number of females placed with males) × 100.

<sup>c</sup>Fertility index = ([number pregnant] / [number copulated]) × 100.

<sup>d</sup>*n* = 3 for Days 7–13 in the 100-mg/kg-day group.

<sup>e</sup>Preimplantation loss (%) = (number of corpora lutea – number of implantation sites) / (number of corpora lutea) × 100.

<sup>f</sup>Postimplantation survival index = ([number of implantation sites – total number of live pups on Day 1] / [number of implantation sites]) × 100.

<sup>g</sup>Live birth index = ([total number of live pups on Day 1] / [total number of pups born]) × 100.

<sup>h</sup>Viability index = ([number of pups alive on the specified day] / [total number of live pups on Day 1]) × 100.

\*Significantly different from controls, as reported by study authors (*p*-level was not specified).

HED = human equivalent dose; NA = not available.

## APPENDIX C. BENCHMARK DOSE MODELING RESULTS

### MODELING PROCEDURE FOR NONCANCER EFFECTS

#### Continuous Data

The benchmark dose (BMD) modeling of continuous data was conducted with the U.S. Environmental Protection Agency (U.S. EPA) Benchmark Dose Software (BMDS) (version 3.3). For these data, the Exponential, Linear, Polynomial, Hill, and Power continuous models available within the software were used. The continuous models available within the software were fit using a benchmark response (BMR) of 1 standard deviation (SD) or alternative BMRs may be used where appropriate as outlined in the Benchmark Dose Technical Guidance (U.S. EPA, 2012a). A standard BMR of 1 SD was used for increased alkaline phosphatase (ALP) in P<sub>0</sub> male and female rats. For developmental effects (i.e., decreased female offspring body weight), a BMR of 5% relative deviation (RD) is considered a minimally biologically significant response during growth/development in gestational studies (e.g., fetal weight) and was applied in this assessment for BMD modeling purposes. An adequate fit was judged based on the  $\chi^2$  goodness-of-fit *p*-value (*p* > 0.1), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination was made as to whether the variance across dose groups was constant. If a constant variance model was deemed appropriate (i.e., Test 2 in BMDS; *p*-value > 0.05), the final BMD results were estimated from a constant variance model. If the test for homogeneity of variance was rejected (*p*-value < 0.05), the model was run again while modeling the variance as a power function of the mean to account for this nonconstant variance. If this nonconstant variance model did not adequately fit the data (i.e., Test 3 in BMDS; *p*-value < 0.05), the data set was considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest lower confidence limit on the benchmark dose (BMDL) is selected if the BMDLs estimated from different models varied less than threefold; otherwise, the BMDL from the model with the lowest Akaike's information criterion (AIC) is selected as a potential point of departure (POD) from which to derive the screening provisional reference values.

#### Dichotomous Data

The BMD modeling of dichotomous data was conducted with the U.S. EPA's BMDS (version 3.3). The Gamma, Logistic, Log-Logistic, Probit, Log-Probit, Hill, Multistage, and Weibull dichotomous models available within the software were fit using a standard BMR of 10% extra risk (ER). In general, the BMR should be near the low end of the observable range of increased risk in the study. BMRs that are too low can result in widely disparate BMDL estimates from different models (i.e., model dependence is high). Adequacy of model fit was judged on the basis of the  $\chi^2$  goodness-of-fit *p*-value (*p* > 0.1), magnitude of scaled residuals (absolute value < 2.0), and visual inspection of the model fit. Among all models providing adequate fit, the BMDL from the model with the lowest AIC is selected as a potential POD, if the BMDLs are sufficiently close (less than approximately threefold); if the BMDLs are not sufficiently close (greater than approximately threefold), model dependence is indicated, and the model with the lowest reliable BMDL is selected.

## BMD MODELING TO IDENTIFY POTENTIAL PODS FOR DERIVATION OF SCREENING SUBCHRONIC AND CHRONIC PROVISIONAL REFERENCE DOSES

### Increased ALP in P<sub>0</sub> Male Sprague Dawley Rats After Oral Exposure to *p*-Isopropyltoluene for ~35 Days (ECHA, 2019b; Symrise, 2018)

The procedure outlined above for continuous data was applied to the data for increased ALP in P<sub>0</sub> male Sprague Dawley rats orally exposed to *p*-isopropyltoluene for ~35 days (ECHA, 2019b; Symrise, 2018). The constant variance model provided an adequate fit to the variance data, and the Exponential (degree 3), Polynomial (degree 2), Power, and Linear models provided adequate fit to the means. Visual inspection of the dose-response curves suggested adequate fit, BMDLs were not 10 times lower than the lowest nonzero dose, and scaled residuals did not exceed  $\pm 2$  units at the data point closest to the predefined BMR. BMDLs for models providing adequate fit were sufficiently close (differed by less than threefold), so the model with the lowest AIC was selected (Linear). The estimated human equivalent BMD<sub>1SD</sub> and BMDL<sub>1SD</sub> values of 28 and 18 mg/kg-day, respectively, were selected from this model. The results of the BMD modeling are summarized in Table C-1. Figure C-1 shows the fit of the Linear model to the data.

Model	Variance <i>p</i> -Value <sup>b</sup>	Means <i>p</i> -Value <sup>c</sup>	Scaled Residual at Dose Nearest BMD	AIC	BMD <sub>1SD</sub> (HED, (mg/kg-d))	BMDL <sub>1SD</sub> (HED, (mg/kg-d))
Exponential (model 3) <sup>d</sup>	0.07737514	0.9003972	0.065709363	208.883831	37.08159	21.43453
Exponential (model 5) <sup>d</sup>	0.07737514	NA	7.5654E-08	210.8681661	35.42935	30.92168
Hill	0.07737514	NA	-8.85231E-07	210.8681661	35.53358	14.59477
Polynomial (3-degree) <sup>e</sup>	0.07737514	NA	-0.002490259	211.208119	45.13184	18.04798
Polynomial (2-degree) <sup>e</sup>	0.07737514	0.8023287	-0.0530054	208.9308334	34.25201	18.41255
Power <sup>e</sup>	0.07737514	0.9244079	0.048369367	208.8771688	36.6691	31.59494
<b>Linear<sup>d,f</sup></b>	<b>0.07737514</b>	<b>0.7738805</b>	<b>-0.371230114</b>	<b>207.3808417</b>	<b>27.85133</b>	<b>17.83316</b>

<sup>a</sup>Symrise (2018).

<sup>b</sup>Values <0.05 fail to meet conventional goodness-of-fit criteria.

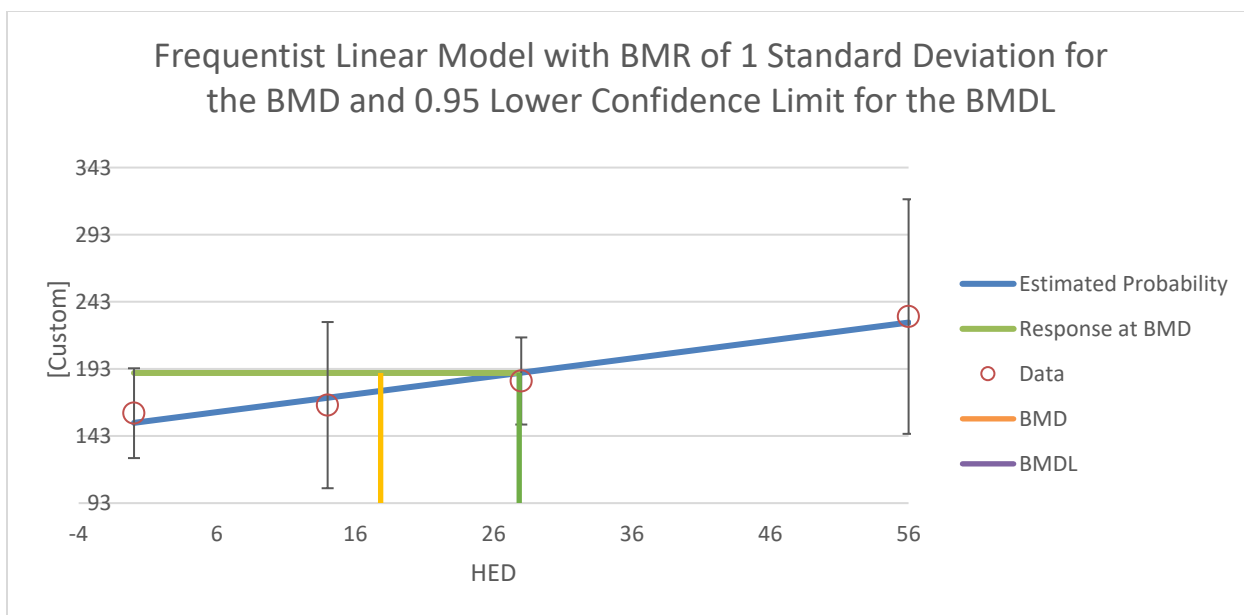
<sup>c</sup>Values <0.1 fail to meet conventional goodness-of-fit criteria.

<sup>d</sup>Power restricted to be  $\geq 1$ .

<sup>e</sup>Coefficients restricted to be positive.

<sup>f</sup>Selected model.

AIC = Akaike's information criterion; ALP = alkaline phosphatase; BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 1SD = dose associated with 1 standard deviation from the control); BMR = benchmark response; NA = test for fit is not valid; HED = human equivalent dose.



**Figure C-1. Fit of Linear Model to Data for Increased Alkaline Phosphatase in P<sub>0</sub> Male Sprague Dawley Rats After Oral Exposure to *p*-Isopropyltoluene for ~35 Days (ECHA, 2019b; Symrise, 2018)**

**BMD Model Output for Linear Model to Data for Increased ALP in P<sub>0</sub> Male Sprague Dawley Rats After Oral Exposure to *p*-Isopropyltoluene for ~35 Days (ECHA, 2019b; Symrise, 2018)**

*Data*

Increased ALP in P0 males			
Dose	N	Mean	Std. Dev.
HED (mg/kg-day)	[Custom]	[Custom]	[Custom]
0	5	160	23.5
14	5	166	43.5
28	5	184	22.8
56	5	232	61.4

*Model Results*

Benchmark Dose	
BMD	27.85132587
BMDL	17.83316026
BMDU	62.79187172
AIC	207.3808417
Test 4 p-Value	0.773880476
D.O.F.	2

Model Parameters				
# of Parameters	3			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	152.8000008	12.87668371	127.562164	178.037837
beta	1.334693861	0.401408791	0.54794708	2.12144064
alpha	1381.831454	603824.1589	-1182091.8	1184855.45

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	5	152.8000008	160	160	37.1729936	23.5	23.5	0.433101723
14	5	171.4857149	166	166	37.1729936	43.5	43.5	-0.329982339
28	5	190.1714289	184	184	37.1729936	22.8	22.8	-0.371230114
56	5	227.5428571	232	232	37.1729936	61.4	61.4	0.268110626

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-100.434083	5	210.868166
A2	-97.0169938	8	210.033988
A3	-100.434083	5	210.868166
fitted	-100.6904209	3	207.380842
R	-105.0905624	2	214.181125

\*Includes additive constant of -18.37877. This constant was not included in the LL derivation prior to BMD5 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-Value
1	16.14713719	6	0.01298564
2	6.834178449	3	0.07737514
3	6.834178449	3	0.07737514
4	0.512675682	2	0.77388048

### Increased ALP in P<sub>0</sub> Female Sprague Dawley Rats After Oral Exposure to *p*-Isopropyltoluene for ~63 Days (ECHA, 2019b; Symrise, 2018)

The procedure outlined above for continuous data was applied to the data for increased ALP in P<sub>0</sub> female Sprague Dawley rats orally exposed to *p*-isopropyltoluene for ~63 days (ECHA, 2019b; Symrise, 2018). The constant variance model did not provide an adequate fit to the variance data ( $p < 0.05$ ; see Table C-2). Data were modeled using a nonconstant variance model, which provided an adequate fit to the variance data (see Table C-3). The Exponential (model 3), and Power models provided adequate fit to the means. Visual inspection of the dose-response curves suggested adequate fit, BMDLs were not 10 times lower than the lowest nonzero dose, and scaled residuals did not exceed  $\pm 2$  units at the data point closest to the predefined

BMR. BMDLs for models providing adequate fit were sufficiently close (differed by less than threefold), so the model with the lowest AIC was selected (Exponential degree 3). The estimated human equivalent BMD<sub>1SD</sub> and BMDL<sub>1SD</sub> values of 5.6 and 3.6 mg/kg-day, respectively, were selected from this model. The results of the BMD modeling are summarized in Table C-3. Figure C-2 shows the fit of the Exponential (degree 3) model to the data.

<b>Table C-2. BMD Modeling Results (Constant Variance) for Increased ALP in P<sub>0</sub> Female Sprague Dawley Rats Orally Exposed to <i>p</i>-Isopropyltoluene for ~63 Days<sup>a</sup></b>						
<b>Model</b>	<b>Variance <i>p</i>-Value<sup>b</sup></b>	<b>Means <i>p</i>-Value<sup>c</sup></b>	<b>Scaled Residual at Dose Nearest BMD</b>	<b>AIC</b>	<b>BMD<sub>1SD</sub> (HED, (mg/kg-d))</b>	<b>BMDL<sub>1SD</sub> (HED, (mg/kg-d))</b>
Exponential (model 3) <sup>d</sup>	0.00472624	0.8340455	0.164569433	163.8104955	16.67688	11.32402
Exponential (model 5) <sup>d</sup>	0.00472624	NA	-9.855E-09	167.7665986	14.20689	0.208399
Hill	0.00472624	NA	3.89928E-08	167.7665986	14.2768	0
Polynomial (2-degree) <sup>e</sup>	0.00472624	NA	-0.008198238	165.7667504	14.78772	8.693893
Power <sup>e</sup>	0.00472624	NA	0.000329145	165.7665988	14.90258	8.692696
Linear <sup>d</sup>	0.00472624	0.9894642	-0.010564001	163.766773	14.80401	8.693664

<sup>a</sup>[Symrise \(2018\)](#).

<sup>b</sup>Values <0.05 fail to meet conventional goodness-of-fit criteria.

<sup>c</sup>Values <0.1 fail to meet conventional goodness-of-fit criteria.

<sup>d</sup>Power restricted to be ≥1.

<sup>e</sup>Coefficients restricted to be positive.

AIC = Akaike's information criterion; ALP = alkaline phosphatase; BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 1SD = dose associated with 1 standard deviation from the control); BMR = benchmark response; NA = test for fit is not valid; HED = human equivalent dose.

**Table C-3. BMD Modeling Results (Nonconstant Variance) for Increased ALP in P<sub>0</sub> Female Sprague Dawley Rats Orally Exposed to *p*-Isopropyltoluene for ~63 Days<sup>a</sup>**

Model	Variance <i>p</i> -Value <sup>b</sup>	Means <i>p</i> -Value <sup>c</sup>	Scaled Residual at Dose Nearest BMD	AIC	BMD <sub>1SD</sub> (HED, (mg/kg-d))	BMDL <sub>1SD</sub> (HED, (mg/kg-d))
<b>Exponential (model 3)<sup>d,e</sup></b>	<b>0.65440701</b>	<b>0.5701245</b>	<b>0.107050508</b>	<b>154.3815366</b>	<b>5.615738</b>	<b>3.608899</b>
Exponential (model 5) <sup>e</sup>	0.65440701	NA	0.324414859	160.1941198	0.089199	0.032063
Hill	0.65440701	NA	0.278150212	159.8411931	5.403369	0.405075
Polynomial (2-degree) <sup>f</sup>	–	–	–	–	–	–
Power <sup>f</sup>	0.65440701	0.4169571	0.236217929	155.9166117	4.331736	2.568022
Linear <sup>d</sup>	–	–	–	–	–	–

<sup>a</sup>[Symrise \(2018\)](#).

<sup>b</sup>Values <0.05 fail to meet conventional goodness-of-fit criteria.

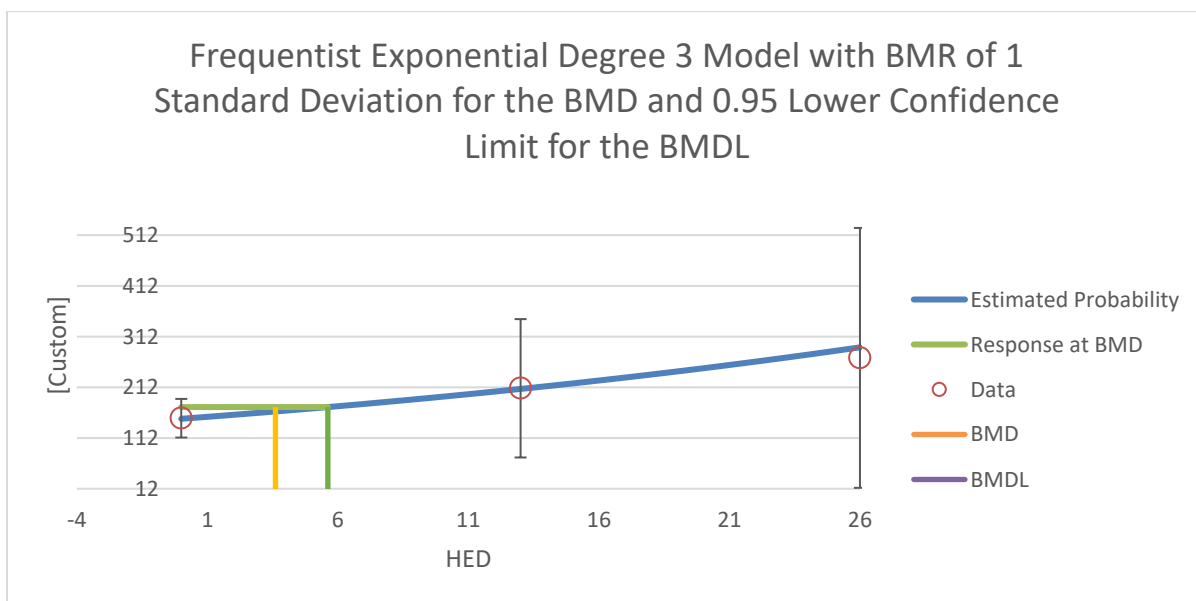
<sup>c</sup>Values <0.1 fail to meet conventional goodness-of-fit criteria.

<sup>d</sup>Coefficients restricted to be positive.

<sup>e</sup>**Selected model.**

<sup>f</sup>Power restricted to be ≥1.

AIC = Akaike's information criterion; ALP = alkaline phosphatase; BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 1SD = dose associated with 1 standard deviation from the control); BMR = benchmark response; NA = test for fit is not valid; HED = human equivalent dose.



**Figure C-2. Fit of Exponential (Degree 3) Model to Data for Increased Alkaline Phosphatase in P<sub>0</sub> Female Sprague Dawley Rats After Oral Exposure to *p*-Isopropyltoluene for ~63 Days ([ECHA, 2019b](#); [Symrise, 2018](#))**

**BMD Model Output for Exponential (Degree 3) Model to Data for Increased ALP in P<sub>0</sub> Female Sprague Dawley Rats After Oral Exposure to *p*-Isopropyltoluene for ~63 Days (ECHA, 2019b; Symrise, 2018)**

**Data**

Increased ALP in P <sub>0</sub> females			
Dose	N	Mean	Std. Dev.
HED	[Custom]	[Custom]	[Custom]
0	5	151	19.8
13	5	210	70.9
26	4	270	119.1

**Model Results**

Benchmark Dose	
BMD	5.615737565
BMDL	3.608899049
BMDU	12.47634342
AIC	154.3815366
Test 4 p-Value	0.570124523
D.O.F.	2

Model Parameters				
# of Parameters	5			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
a	149.8959152	9.323998674	131.621213	168.170617
b	0.025483328	5.72E-03	0.01426484	0.03670182
d	Bounded	NA	NA	NA
rho	4.845641848	9.54E-02	4.65873323	5.03255047
log-alpha	Bounded	NA	NA	NA

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	5	149.8959152	151	151	23.0620926	19.8	19.8	0.107050508
13	5	208.768173	210	210	51.4613106	70.9	70.9	0.053524656
26	4	290.7627603	270	270	114.832012	119.1	119.1	-0.361619725

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-78.88329932	4	165.766599
A2	-73.52867333	6	159.057347
A3	-73.62886784	5	157.257736
fitted	-74.19076832	3	154.381537
R	-81.68323444	2	167.366469

\*Includes additive constant of -12.86514. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-Value
1	16.30912223	4	0.00263122
2	10.70925199	2	0.00472624
3	0.200389036	1	0.65440701
4	1.123800961	2	0.57012452

**Increased Incidence of Reduced Epididymal Luminal Sperm in P<sub>0</sub> Male Sprague Dawley Rats After Oral Exposure to *p*-Isopropyltoluene for ~35 Days ([ECHA, 2019b](#); [Symrise, 2018](#)).**

The procedure outlined above for dichotomous data was applied to the data for reduced epididymal luminal sperm in P<sub>0</sub> male Sprague Dawley rats orally exposed to *p*-isopropyltoluene for ~35 days ([ECHA, 2019b](#); [Symrise, 2018](#)). The BMD modeling results are summarized in Table C-4 and Figure C-3. The Dichotomous Hill, Gamma, Log-Logistic, Multistage (degree 3 and 2), Weibull, Logistic, Log-Probit and Probit models provided adequate fit to the means (*p*-value > 0.1). The BMDLs for the models providing adequate fit were sufficiently close (differed by less than threefold), so the model with the lowest AIC (Log-Logistic) was selected. For reduced epididymal luminal sperm, the BMDL<sub>10ER</sub> of 20 mg/kg-day from this model was selected.

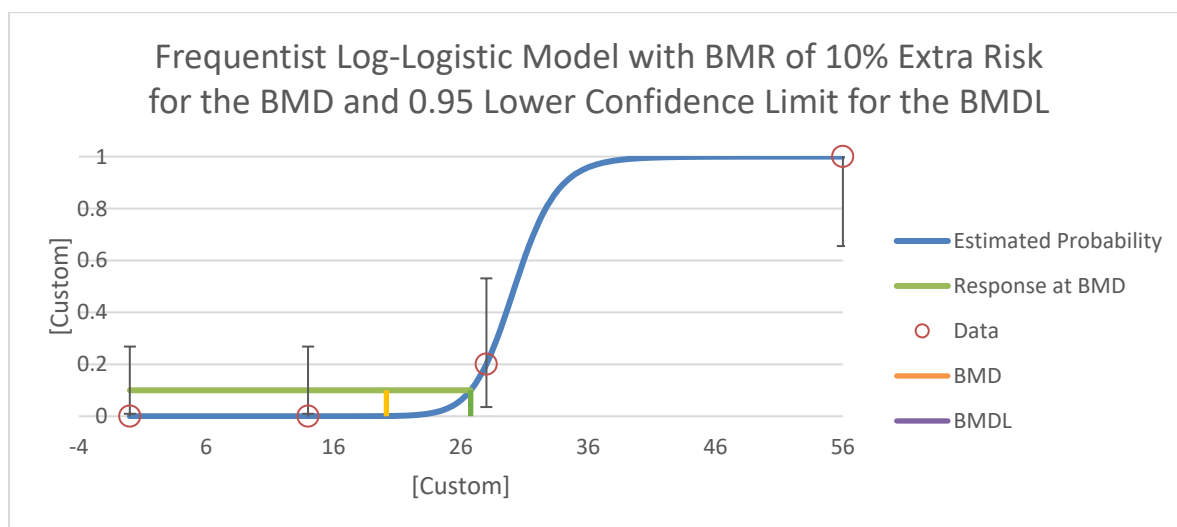
<b>Table C-4. BMD Modeling Results for Increased Incidence of Reduced Epididymal Luminal Sperm in P<sub>0</sub> Male Sprague Dawley Rats Orally Exposed to <i>p</i>-Isopropyltoluene for ~35 Days<sup>a</sup></b>					
Model	<i>p</i> -Value <sup>b</sup>	Scaled Residual at Dose Nearest BMD	AIC	BMD <sub>10ER</sub> (HED, (mg/kg-d))	BMDL <sub>10ER</sub> (HED, (mg/kg-d))
Dichotomous Hill	0.9999994	-0.000113059	12.00837362	26.76641	20.14922
Gamma	0.9876456	-0.148364038	12.2508008	24.56389	18.72623
<b>Log-Logistic<sup>c</sup></b>	<b>0.9999994</b>	<b>-0.000113087</b>	<b>12.00837331</b>	<b>26.76641</b>	<b>20.14922</b>
Multistage 3	0.6691959	-0.680591644	14.60019152	18.5518	12.49361
Multistage 2	0.2254552	-1.117668833	19.1047269	13.24523	8.821077
Multistage 1	0.0170617	-0.000390256	27.83415841	5.442348	3.421249
Weibull	0.9999067	0.007002091	12.01795831	25.72946	0
Logistic	0.9999959	0.000240027	12.00928765	26.6336	18.55289
Log-Probit	0.9999998	3.73132E-09	14.00804908	26.91278	19.8688
Probit	0.9999998	1.14334E-06	14.00804939	26.63133	17.75566
Quantal Linear	0.0170617	-0.000390256	27.83415841	5.442347	3.421303

<sup>a</sup>[Symrise \(2018\)](#).

<sup>b</sup>Values <0.10 fail to meet conventional goodness-of-fit criteria.

<sup>c</sup>Selected model (bold). Lowest AIC among models with adequate fit was selected (Hill).

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10ER = dose associated with 10% extra risk from the control); BMR = benchmark response.



**Figure C-3. Fit of Log-Logistic Model to Data for Reduced Epididymal Luminal Sperm in P<sub>0</sub> Male Sprague Dawley Rats After Oral Exposure to *p*-Isopropyltoluene for ~35 Days ([ECHA, 2019b](#); [Symrise, 2018](#))**

**BMD Model Output for Log-Logistic Model to Data for Reduced Epididymal Luminal Sperm in P<sub>0</sub> Male Sprague Dawley Rats After Oral Exposure to *p*-Isopropyltoluene for ~35 Days (ECHA, 2019b; Symrise, 2018)**

**Data**

Reduced luminal sperm		
Dose	N	Incidence
[Custom]	[Custom]	[Custom]
0	10	0
14	10	0
28	10	2
56	10	10

**Model Results**

Benchmark Dose	
BMD	26.76641336
BMDL	20.14922027
BMDU	29.75486686
AIC	12.00837331
p-Value	0.999999449
D.O.F.	3
Chi <sup>2</sup>	0.000162429

Model Parameters				
# of Parameters	3			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
a	-61.36588622	0.790507797	-62.915253	-59.816519
b	Bounded	NA	NA	NA

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.52301E-08	1.52301E-07	0	10	-0.0003903
14	9.68989E-07	9.68989E-06	0	10	-0.0031129
28	0.200014305	2.000143049	2	10	-0.0001131
56	0.999984743	9.999847428	10	10	0.0123521

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test df	p-Value
Full Model	-5.004024235	4	–	–	NA
Fitted Model	-5.004186657	1	0.00032484	3	0.9999984
Reduced Model	-24.43457208	1	38.8610957	3	<0.0001

**Increased Incidence of Epididymal Sperm with Cribriform Changes in P<sub>0</sub> Male Sprague Dawley Rats After Oral Exposure to *p*-Isopropyltoluene for ~35 Days (ECHA, 2019b; Symrise, 2018)**

The procedure outlined above for dichotomous data was applied to the data for epididymal sperm with cribriform changes in P<sub>0</sub> male Sprague Dawley rats orally exposed to *p*-isopropyltoluene for ~35 days (ECHA, 2019b; Symrise, 2018). The BMD modeling results are summarized in Table C-5 and Figure C-4. All models provided adequate fit to the means (*p*-value > 0.1). The BMDLs for the models providing adequate fit were sufficiently close (differed by less than threefold), so the model with the lowest AIC (Multistage Degree 3) was selected. For epididymal sperm with cribriform changes, the BMDL<sub>10ER</sub> of 14 mg/kg-day from this model was selected.

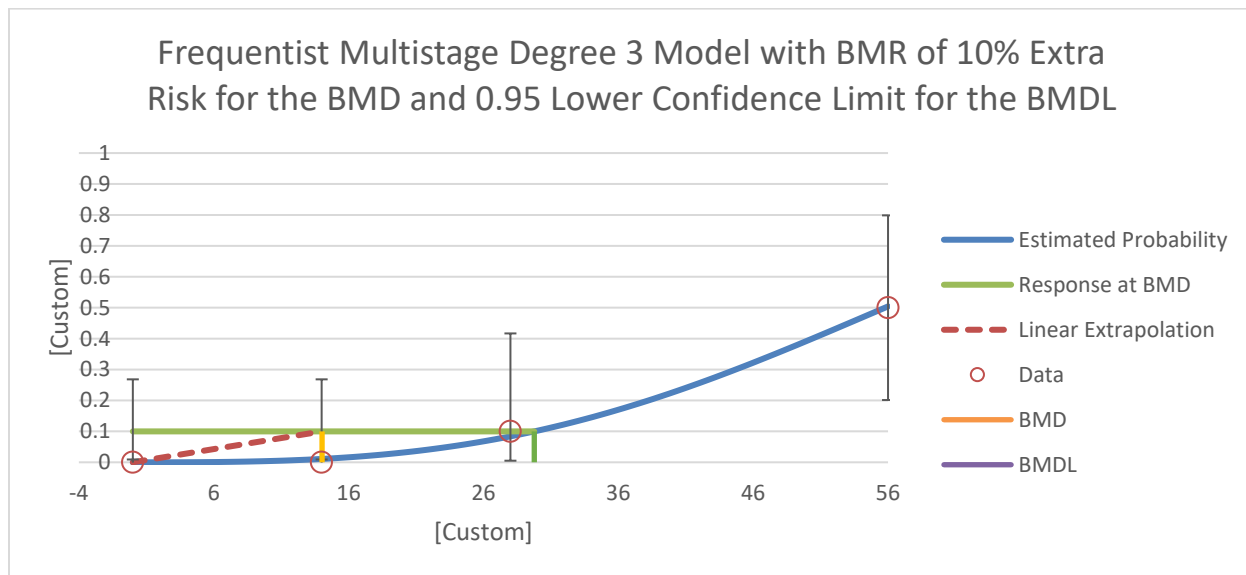
Table C-5. BMD Modeling Results for Increased Incidence of Epididymal Sperm with Cribriform Changes in P <sub>0</sub> Male Sprague Dawley Rats Orally Exposed to <i>p</i> -Isopropyltoluene for ~35 Days <sup>a</sup>					
Model	<i>p</i> -Value <sup>b</sup>	Scaled Residual at Dose Nearest BMD	AIC	BMD <sub>10ER</sub> (HED, (mg/kg-d))	BMDL <sub>10ER</sub> (HED, (mg/kg-d))
Dichotomous Hill	0.9999975	5.60817E-06	24.36461322	28.00001	16.06515
Gamma	0.9545159	0.174487442	24.5156259	29.46519	15.36218
Log-Logistic	0.9429148	0.183751807	24.56091147	29.59281	15.43774
<b>Multistage 3<sup>c</sup></b>	<b>0.9860244</b>	<b>0.182964274</b>	<b>22.61622846</b>	<b>29.76698</b>	<b>14.03198</b>
Multistage 2	0.8929701	-0.332772397	23.34733897	23.76345	12.22134
Multistage 1	0.431135	-1.041320469	26.10691469	14.32795	7.791204
Weibull	0.9265372	0.2231386	24.61371866	30.11822	14.91087
Logistic	0.8045946	0.45253127	24.9917569	33.31747	21.77432
Log-Probit	0.9755454	0.115685467	24.44800513	28.89839	16.02347
Probit	0.866618	0.363213801	24.78200744	31.66984	20.41978
Quantal Linear	0.431135	-1.041320478	26.10691469	14.32795	7.791332

<sup>a</sup>Symrise (2018).

<sup>b</sup>Values <0.10 fail to meet conventional goodness-of-fit criteria.

<sup>c</sup>Selected model (bold). Lowest AIC among models with adequate fit was selected (Hill).

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10ER = dose associated with 10% extra risk from the control); BMR = benchmark response.



**Figure C-4. Fit of Multistage (Degree 3) Model to Data for Epididymal Sperm with Cribriform Changes in P<sub>0</sub> Male Sprague Dawley Rats After Oral Exposure to *p*-Isopropyltoluene for ~35 Days ([ECHA, 2019b](#); [Symrise, 2018](#))**

**BMD Model Output for Multistage (Degree 3) Model to Data for Epididymal Sperm with Cribriform Changes in P<sub>0</sub> Male Sprague Dawley Rats After Oral Exposure to *p*-Isopropyltoluene for ~35 Days ([ECHA, 2019b](#); [Symrise, 2018](#))**

*Data*

Sperm with cribriform changes		
Dose	N	Incidence
[Custom]	[Custom]	[Custom]
0	10	0
14	10	0
28	10	1
56	10	5

**Model Results**

Benchmark Dose	
BMD	29.7669847
BMDL	14.03198061
BMDU	38.44259094
AIC	22.61622846
p-Value	0.986024401
D.O.F.	3
Chi <sup>2</sup>	0.14438555
Slope Factor	0.007126578

Model Parameters				
# of Parameters	4			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
b1	Bounded	NA	NA	NA
b2	Bounded	NA	NA	NA
b3	3.9946E-06	0.291299158	-0.57093187	0.57093986

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	1.523E-07	0	10	-0.0003903
14	0.010901344	0.109013436	0	10	-0.3319863
28	0.083954719	0.839547191	1	10	0.1829643
56	0.504166826	5.04166826	5	10	-0.0263542

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test df	p-Value
Full Model	-10.18230154	4	-	-	NA
Fitted Model	-10.30811423	1	0.25162538	3	0.9688539
Reduced Model	-16.90836351	1	13.4521239	3	0.0037542

**Decreased Body Weight in F<sub>1</sub> Female Sprague Dawley Rats on Postnatal Day (PND) 1 After Exposure to *p*-Isopropyltoluene During Gestation and Lactation until PND 13 (ECHA, 2019b; Symrise, 2018)**

The procedure outlined above for continuous data was applied to the data for decreased body weight in F<sub>1</sub> female Sprague Dawley rats on postnatal day (PND) 1 after exposure to *p*-Isopropyltoluene during gestation and lactation until PND 13 (ECHA, 2019b; Symrise, 2018). The constant variance model provided an adequate fit to the variance data. The Linear model

provided adequate fit to the means. Visual inspection of the dose-response curve suggested adequate fit, the BMDL was not 10 times lower than the lowest nonzero dose, and scaled residual did not exceed  $\pm 2$  units at the data point closest to the predefined BMR. Therefore, the  $BMDL_{0.05RD}$  value of 7.1 mg/kg-day was selected from this model. The results of the BMD modeling are summarized in Table C-6. Figure C-5 shows the fit of the Linear model to the data.

<b>Table C-6. BMD Modeling Results (Constant Variance) for Decreased Body Weight in F<sub>1</sub> Female Sprague Dawley Rats on PND 1 Exposed to <i>p</i>-Isopropyltoluene During Gestation and Lactation until PND 13<sup>a</sup></b>						
<b>Model</b>	<b>Variance <i>p</i>-Value<sup>b</sup></b>	<b>Means <i>p</i>-Value<sup>c</sup></b>	<b>Scaled Residual at Dose Nearest BMD</b>	<b>AIC</b>	<b>BMD<sub>0.05RD</sub> (HED, (mg/kg-d))</b>	<b>BMDL<sub>0.05RD</sub> (HED, (mg/kg-d))</b>
Exponential (model 3) <sup>d</sup>	0.09017585	NA	4.23952E-06	51.72503846	14.28686	6.722934
Exponential (model 5) <sup>d</sup>	0.09017585	NA	-3.56272E-07	53.72503846	14.27673	0.470149
Hill	0.09017585	NA	-3.96764E-07	53.72503846	14.256	0.0096
Polynomial (2-degree) <sup>e</sup>	0.09017585	NA	-0.034757938	51.72713056	14.79179	7.146885
Power <sup>e</sup>	0.09017585	NA	-0.000293854	51.72503862	14.30375	7.147386
<b>Linear<sup>d,f</sup></b>	<b>0.09017585</b>	<b>1</b>	<b>-5.60327E-09</b>	<b>49.72503846</b>	<b>14.3</b>	<b>7.147205</b>

<sup>a</sup>[Symrise \(2018\)](#).

<sup>b</sup>Values <0.05 fail to meet conventional goodness-of-fit criteria.

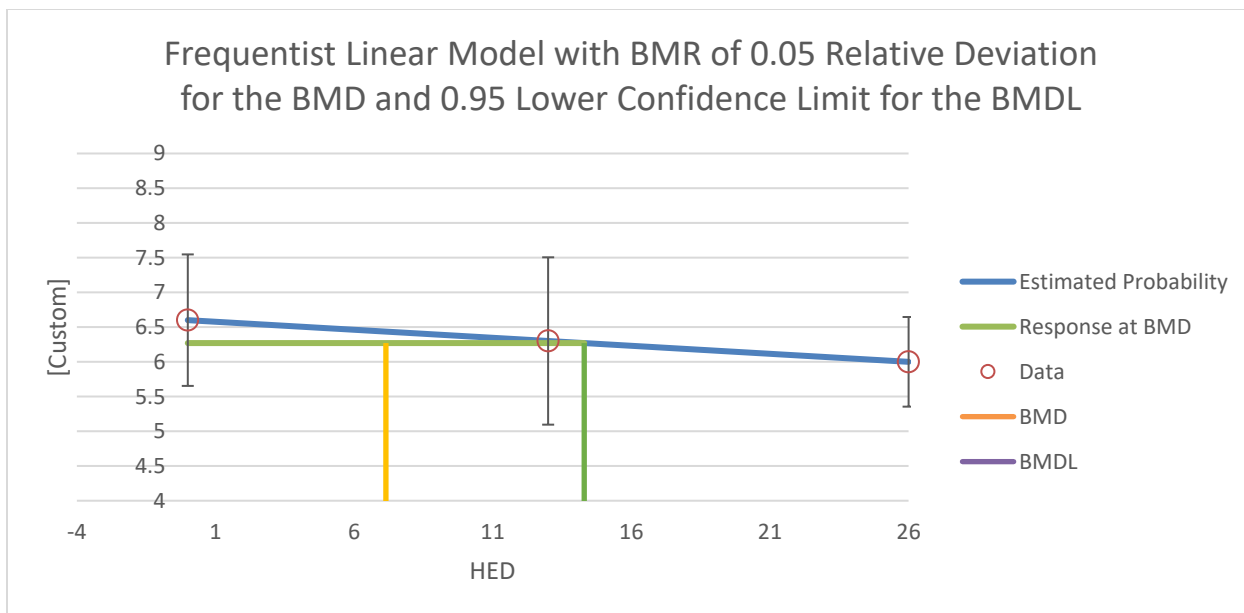
<sup>c</sup>Values <0.1 fail to meet conventional goodness-of-fit criteria.

<sup>d</sup>Power restricted to be  $\geq 1$ .

<sup>e</sup>Coefficients restricted to be positive.

<sup>f</sup>**Selected model.**

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 0.05 RD = dose associated with 5% relative deviation from the control); BMR = benchmark response; NA = test for fit is not valid; HED = human equivalent dose; PND = postnatal day.



**Figure C-5. Fit of Linear Model to Data for Decreased Body Weight in F<sub>1</sub> Female Sprague Dawley Rats on Postnatal Day (PND 1) After Exposure to *p*-Isopropyltoluene During Gestation and Lactation until PND 13 ([ECHA, 2019b](#); [Symrise, 2018](#))**

**BMD Model Output for Linear Model to Data for Decreased Body Weight in F<sub>1</sub> Female Sprague Dawley Rats on Postnatal Day (PND 1) After Exposure to *p*-Isopropyltoluene During Gestation and Lactation until PND 13 ([ECHA, 2019b](#); [Symrise, 2018](#))**

*Data*

Decreased body weight in F <sub>1</sub> females on PND 1			
Dose	N	Mean	Std. Dev.
HED	[Custom]	[Custom]	[Custom]
0	9	6.6	0.66
13	9	6.3	0.84
26	4	6	0.3

*Model Results*

Benchmark Dose	
BMD	14.29999876
BMDL	7.147205466
BMDU	Infinity
AIC	49.72503846
Test 4 p-value	1
D.O.F.	1

Model Parameters				
# of Parameters	3			
Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	6.599999989	0.202291962	6.20351503	6.99648495
beta	-0.023076922	1.46E-02	-0.05168652	0.00553268
alpha	0.427254548	5.50E-02	0.31938096	0.53512813

Goodness of Fit								
Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	9	6.599999989	6.6	6.6	0.65364711	0.66	0.66	4.85877E-08
13	9	6.300000001	6.3	6.3	0.65364711	0.84	0.84	-5.60327E-09
26	4	6.000000013	6	6	0.65364711	0.3	0.3	-3.98628E-08

Likelihoods of Interest			
Model	Log Likelihood*	# of Parameters	AIC
A1	-21.86251923	4	51.7250385
A2	-19.45652557	6	50.9130511
A3	-21.86251923	4	51.7250385
fitted	-21.86251923	3	49.7250385
R	-23.04602664	2	50.0920533

\*Includes additive constant of -20.21665. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest			
Test	-2*Log(Likelihood Ratio)	Test df	p-Value
1	7.179002137	4	0.12672578
2	4.811987326	2	0.09017585
3	4.811987326	2	0.09017585
4	0	1	1

## APPENDIX D. PARAMETERS OF TOOLS USED FOR READ-ACROSS

<b>Table D-1. Parameters of Tools Used for Read-Across Evaluation of p-Isopropyltoluene</b>			
<b>Similarity Context</b> [569] <sup>a</sup>	<b>Tool Name</b> [4]	<b>Settings/Parameters</b>	<b>Searched by (date)</b>
Structural [547]	U.S. EPA CompTox Chemicals Dashboard [489]	Tanimoto similarity threshold of 0.8 and related substances	CASRN (December 2021– February 2, 2022)
	ChemIDplus [2]	ChemIDplus similarity search (default method) with $\geq 80\%$ threshold and related substances, parent (or exact structure match), salts, and mixtures <sup>b</sup>	
	GenRA Beta version (in the U.S. EPA CompTox Chemicals Dashboard) [56]	Collect 10 nearest neighbors by each similarity setting and combination available: <ul style="list-style-type: none"> <li>• Morgan Fingerprints</li> <li>• Torsion Fingerprints</li> <li>• ToxPrints</li> <li>• Morg2Tor1Bio1</li> <li>• CT1:Bio3</li> </ul> Using each of the following data sources: ToxCast, Tox21, and ToxRef	
	OECD QSAR Toolbox [10]	Similarity search with $\geq 80\%$ similarity threshold using default settings: <ul style="list-style-type: none"> <li>• Dice similarity</li> <li>• Atom centered fragments</li> <li>• Hologram calculation</li> <li>• All features combined</li> <li>• Atom characteristics: atom type, count H attached, and hybridization</li> </ul>	
	QSAR Toolbox Profilers <sup>c</sup>	No settings or parameters; results obtained from: <ul style="list-style-type: none"> <li>• DART scheme</li> <li>• DNA binding by OECD</li> </ul>	SMILES <sup>d</sup> (December 2021)
	ToxAlerts <sup>c</sup>	No settings or parameters; structural alerts obtained from: <ul style="list-style-type: none"> <li>• Cytochrome P450-mediated drug metabolism alert</li> <li>• Idiosyncratic toxicity (Arenes alert)</li> </ul>	SMILES <sup>d</sup> (December 2021)
Toxtree <sup>c</sup>	No settings or parameters; results obtained from: <ul style="list-style-type: none"> <li>• Protein binding</li> <li>• DNA binding</li> </ul>	SMILES <sup>d</sup> (December 2021)	

**Table D-1. Parameters of Tools Used for Read-Across Evaluation of p-Isopropyltoluene**

Similarity Context [569] <sup>a</sup>	Tool Name [4]	Settings/Parameters	Searched by (date)
	OECD QSAR Toolbox Metabolism Simulators [22]	No settings or parameters; results obtained from: <ul style="list-style-type: none"> <li>• Rat liver S9 metabolism simulator version 3.7</li> <li>• in vivo rat metabolism simulator version 3.5</li> </ul>	SMILES <sup>e</sup> (January 2022)
Toxicity/mechanistic [0]	GenRA beta version (in the U.S. EPA CompTox Chemicals Dashboard) [0]	Collected 10 nearest neighbors using the ToxCast similarity settings. <ul style="list-style-type: none"> <li>• Nearest neighbors with a similarity index <math>\geq 0.5</math> considered for use as analogue</li> </ul>	CASRN (February 2022)
	Comparative Toxicogenomics Database (CTD) [0]	Compounds identified with gene interactions similar to those induced by p-isopropyltoluene: <ul style="list-style-type: none"> <li>• Used the interacting genes comparison search</li> <li>• A similarity index of <math>\geq 0.5</math> is considered for use as a mechanistic analogue</li> <li>• The number of gene interactions is also considered for use as a mechanistic analogue if similarity index is <math>\geq 0.5</math></li> </ul>	

<sup>a</sup>Unique analogues identified using analogue identification search tools.

<sup>b</sup>For more information, see [https://www.nlm.nih.gov/pubs/techbull/ma06/ma06\\_technote.html](https://www.nlm.nih.gov/pubs/techbull/ma06/ma06_technote.html).

<sup>c</sup>Tool used for candidate analogue evaluation.

<sup>d</sup>SMILES collected from the U.S. EPA CompTox Chemicals Dashboard batch search of the structural analogues CASRN.

<sup>e</sup>p-Isopropyltoluene SMILES: CC(C)C1=CC=C(C)C=C1 (CASRN: 99-87-6).

DART = developmental and reproductive toxicity; DNA = deoxyribonucleic acid; GenRA = General Read-Across; OECD = Organisation for Economic Co-operation and Development; QSAR = quantitative structure-activity relationship; SMILES = simplified molecular input line entry system; U.S. EPA = U.S. Environmental Protection Agency.

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