United States
Environmental Protection
Agency

EPA/690/R-24/002F | August 2024 | FINAL

Provisional Peer-Reviewed Toxicity Values for

1-Phenyl-1-(4-methylphenyl)-ethane (PTE)
(CASRN 3717-68-8)

U.S. EPA Office of Research and Development
Center for Public Health and Environmental Assessment

United States Environmental Protection Agency

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https://www.epa.gov/pprtv

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Center for Public Health and Environmental Assessment
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Questions regarding the content of this PPRTV assessment should 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.

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COMMONLY USED ABBREVIATIONS AND ACRONYMS

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	benchmark concentration
BMCL	benchmark concentration lower confidence limit
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service registry number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPHEA	Center for Public Health and Environmental Assessment
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
ER	estrogen receptor
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-*S*-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	*N*-acetyl-β-D-glucosaminidase
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure-activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_C	composite uncertainty factor
UF_D	database uncertainty factor
UF_H	intraspecies uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
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.

DRAFT PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 1-PHENYL-1-(4-METHYLPHENYL)-ETHANE (PTE; CASRN 3717-68-8)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund program. PPRTVs are derived after a review of the relevant scientific literature using established 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 the 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

1-Phenyl-1-(4-methylphenyl)-ethane (PTE), CASRN 3717-68-8, is a discrete organic chemical; it is a hydrocarbon containing both aromatic and aliphatic moieties (see Figure 1). PTE is not listed with the U.S. EPA Substance Registry Services or the Toxic Substances Control Act (TSCA) public inventory (U.S. EPA, 2022c, d). It is not listed on the European Chemicals (EC) inventory and is not preregistered within Europe's Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) program (ECHA, 2022). There are no data available on the production of PTE in the United States or commercial uses reported for PTE (NLM, 2022b; U.S. EPA, 2022d). Synonyms of PTE appearing in these databases and in other sources include 1-methyl-4-(1-phenylethyl)benzene, 1-phenyl-1-(p-tolyl)-ethane, 4-(1-phenylethyl)toluene, and methylphenyl-p-tolylmethan.

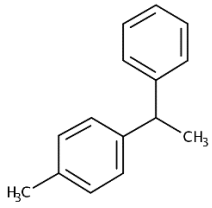

Figure 1. 1-Phenyl-1-(4-methylphenyl)-ethane (PTE) (CASRN 3717-68-8) Structure

The empirical formula for PTE is $C_{15}H_{16}$. Table 1 summarizes the physicochemical properties for PTE. There are no experimental physicochemical property data available for PTE; therefore, all property data presented are estimates from the U.S. EPA CompTox Chemicals Dashboard version 2.2.1 and the Estimation Programs Interface Suite (EPI Suite™). PTE has low water solubility and moderate vapor pressure. Its moderate vapor pressure indicates that it may volatilize from dry soil surfaces and will exist in the vapor phase in air. In the atmosphere, vapor-phase PTE has an estimated half-life of 0.8 days, based on the estimated rate of reaction with photochemically-produced hydroxyl radicals (U.S. EPA, 2012). At ambient temperatures, the potential for volatilization from water surfaces or moist soil surfaces is expected to be moderate, based on its estimated Henry's law constant. The estimated soil adsorption coefficient (K_{oc}) values for PTE indicate that the potential for sorption to soil is high. Based on its log K_{oc} value, PTE is classified to be hardly mobile in soils by the Food and Agriculture Organization of the United Nations (FAO) (U.S. EPA, 2012, 2009). Hydrolysis is not expected to be an important fate process due to the lack of hydrolysable functional groups in this chemical.

Table 1. Physicochemical Properties of PTE (CASRN 3717-68-8)

Property (unit)	Value[a]
Molecular formula	$C_{15}H_{16}$
Physical state	NA
Boiling point (°C)	291[b]
Melting point (°C)	21.0 (predicted)
Density (g/cm^3 at 25°C)	NA
Vapor pressure (mm Hg at 25°C)	2.0×10^{-3} [b]
Vapor density	NA
Acid dissociation constant (pKa) (unitless)	NA
Solubility in water (mol/L at 25°C)	4.5[b]
Octanol-water partition coefficient (log K_{ow})	4.7[b]
Henry's law constant (atm-m^3/mol at 25°C)	5.25×10^{-4} (predicted)
Soil adsorption coefficient (K_{oc}) (L/kg)	1.15×10^3 (predicted)
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	2.09×10^{-11} (predicted)
Atmospheric half-life (d)	0.8 (calculated using a 12-h day; 1.5×10^6 OH/cm^3)[b]
Molecular weight (g/mol)	196.29
Flash point (°C)	2.00 (predicted)

[a]Data were extracted from the U.S. EPA CompTox Chemicals Dashboard (1-phenyl-1-(4-methylphenyl)-ethane, CASRN 3717-68-8. https://comptox.epa.gov/dashboard/chemical/details/DTXSID101027177; accessed May 21, 2024). All values are experimental averages unless otherwise specified.
[b]Values are from U.S. EPA (2012) EPI Suite™ estimates using SMILES CC(C1=CC=CC=C1)C1=CC=C(C)C=C1.

EPI = Estimation Programs Interface; NA = not applicable; PTE = 1-phenyl-1-(4-methylphenyl)-ethane; SMILES = Simplified Molecular Input Line Entry System; U.S. EPA = U.S. Environmental Protection Agency.

A summary of available toxicity values for PTE from U.S. EPA and other agencies/ organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values and Qualitative Conclusions Regarding Carcinogenicity for PTE (CASRN 3717-68-8)

Source (parameter)[a]	Value (applicability)	Notes	Reference[b]
Noncancer			
IRIS	NV	NA	U.S. EPA (2024)
HEAST	NV	NA	U.S. EPA (2011c)
DWSHA	NV	NA	U.S. EPA (2018a)
ATSDR	NV	NA	ATSDR (2022)
WHO	NV	NA	WHO (2022); IPCS (2021)
CalEPA	NV	NA	CalEPA (2022, 2020)
OSHA	NV	NA	OSHA (2020, 2017a, 2017b)
NIOSH	NV	NA	NIOSH (2018)
ACGIH	NV	NA	ACGIH (2022)
Cancer			
IRIS	NV	NA	U.S. EPA (2024)
HEAST	NV	NA	U.S. EPA (2011c)
DWSHA	NV	NA	U.S. EPA (2018a)
NTP	NV	NA	NTP (2021)
IARC	NV	NA	IARC (2022)
CalEPA	NV	NA	CalEPA (2022, 2020)
ACGIH	NV	NA	ACGIH (2022)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; 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; WHO = World Health Organization.
[b]Reference date is the publication date for the database and not the date the source was accessed.

NA = not applicable; NV = not available; PTE = 1-phenyl-1-(4-methylphenyl)-ethane.

Literature searches were conducted in November 2018 and September 2020, and updated most recently in February 2024 for studies relevant to the derivation of provisional toxicity values for PTE. Search results were stored in the U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature (https://heronet.epa.gov/heronet/index.cfm/project/page/project_id/2776). HERO was used to store results from the following databases: PubMed, Web of Science, Scopus and TOXLINE[1] (including TSCATS1), Scopus, and Web of Science. The National Technical Reports Library

[1]Note that this version of TOXLINE is no longer updated (https://www.nlm.nih.gov/databases/download/toxlinesubset.html); therefore, it was not included in the literature search update from September 2020 or February 2024.

(NTRL) was searched for government reports from 2018 through February 2024[2]. The following resources were searched outside of HERO for health-related values: American Conference of Governmental Industrial Hygienists (ACGIH), U.S. 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 Health Effects Assessment Summary Tables (HEAST), the U.S. EPA Integrated Risk Information System (IRIS), the U.S. EPA Office of Water (OW) Drinking Water Standards and Health Advisories, the U.S. EPA TSCATS2/TSCATS8e, the U.S. EPA High Production Volume (HPV) Challenge database, International Agency for Research on Cancer (IARC), 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, U.S. National Institute for Occupational Safety and Health (NIOSH), U.S. National Toxicology Program (NTP), U.S. Occupational Safety and Health Administration (OSHA), and World Health Organization (WHO).

[2]NTRL was a subset of TOXLINE until December 2019 when TOXLINE was discontinued. Searches of NTRL were conducted starting in 2018 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)

As summarized in Tables 3A and 3B, no short-term, subchronic, chronic, or reproductive/developmental toxicity studies of PTE in humans or animals exposed by oral or inhalation routes adequate for deriving provisional toxicity values were identified.

Table 3A. Summary of Potentially Relevant Noncancer Data for PTE (CASRN 3717-68-8)							
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry**	**Critical Effects**	**NOAEL**	**LOAEL**	**Reference (comments)**	**Notes**
Human							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
ND							
Animal							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
ND							

LOAEL = lowest-observed-adverse-effect level; ND = no data; NOAEL = no-observed-adverse-effect level; PTE = 1-phenyl-1-(4-methylphenyl)-ethane.

Table 3B. Summary of Potentially Relevant Cancer Data for PTE (CASRN 3717-68-8)					
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Duration**	**Dosimetry**	**Critical Effects**	**Reference (comments)**	**Notes**
Human					
1. Oral (mg/kg-d)					
ND					
2. Inhalation (mg/m^3)					
ND					
Animal					
1. Oral (mg/kg-d)					
ND					
2. Inhalation (mg/m^3)					
ND					

ND = no data; PTE = 1-phenyl-1-(4-methylphenyl)-ethane.

2.1. HUMAN STUDIES

No studies were located regarding the toxicity or carcinogenicity of PTE in humans after oral or inhalation exposure.

2.2. ANIMAL STUDIES

No studies were located regarding the toxicity or carcinogenicity of PTE in animals after oral or inhalation exposure.

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

No genotoxicity data or other supporting studies, including mode-of-action (MOA)/ mechanistic or metabolism/toxicokinetics studies, were identified for PTE. However, preliminary unpublished experiments suggest that exposure to sediments contaminated with PTE (and other chemicals) produced neurotoxic effects in zebrafish and mice (Hewett et al., 2017).

3. DERIVATION OF PROVISIONAL VALUES

3.1. DERIVATION OF ORAL REFERENCE DOSES

No studies were located regarding toxicity of PTE to humans or animals via oral exposure. Due to the lack of oral toxicity data for PTE, subchronic and chronic provisional reference doses (p-RfDs) could not be derived directly. Instead, the derivation of oral toxicity values was attempted using an alternative analogue approach, but no suitable analogue with available toxicity values was identified (see Appendix A).

3.2. DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No studies were located regarding toxicity of PTE to humans or animals via inhalation exposure. Due to the lack of inhalation toxicity data for PTE, subchronic and chronic provisional reference concentrations (p-RfCs) could not be derived directly. Instead, the derivation of inhalation toxicity values was attempted using an alternative analogue approach, but no suitable analogue with available toxicity values was identified (see Appendix A).

3.3. SUMMARY OF NONCANCER PROVISIONAL REFERENCE VALUES

Table 4 presents a summary of noncancer provisional reference values.

Table 4. Summary of Noncancer Reference Values for PTE (CASRN 3717-68-8)

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD (HED/HEC)	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	NDr						
Chronic p-RfD (mg/kg-d)	NDr						
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

HEC = human equivalent concentration; HED = human equivalent dose; NDr = not determined; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; PTE = 1-phenyl-1-(4-methylphenyl)-ethane; UF_C = composite uncertainty factor.

3.4. CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

No oral or inhalation studies have been conducted to assess the carcinogenicity of PTE. Under the U.S. EPA Cancer Guidelines (U.S. EPA, 2005), there is "*Inadequate Information to Assess the Carcinogenic Potential*" of PTE by oral or inhalation exposure (see Table 5).

Table 5. Cancer WOE Descriptor for PTE (CASRN 3717-68-8)

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	The available data do not support this descriptor.
"Likely to be Carcinogenic to Humans"	NS	NA	The available data do not support this descriptor.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	The available data do not support this descriptor.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**No adequate information is available to assess the carcinogenic potential of PTE by the inhalation or oral routes of exposure.**
"Not Likely to be Carcinogenic to Humans"	NS	NA	The available data do not support this descriptor.

NA = not applicable; NS = not selected; PTE = 1-phenyl-1-(4-methylphenyl)-ethane; WOE = weight of evidence.

3.5. DERIVATION OF PROVISIONAL CANCER RISK ESTIMATES

Due to a lack of carcinogenicity data, derivation of cancer risk estimates is precluded (see Table 6).

Table 6. Summary of Cancer Risk Estimates for PTE (CASRN 3717-68-8)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Risk Estimate	Principal Study
p-OSF $(mg/kg\text{-}d)^{-1}$	NDr			
p-IUR $(mg/m^3)^{-1}$	NDr			

NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor; PTE = 1-phenyl-1-(4-methylphenyl)-ethane.

APPENDIX A. SCREENING NONCANCER 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 1-phenyl-1-(4-methylphenyl)-ethane (PTE). However, some information is available for this chemical, which although insufficient to support derivation of a provisional toxicity value under current guidelines, may be of limited use to risk assessors. In such cases, the 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 deriving 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.

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 B. 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 Organisation for Economic Co-operation and Development (OECD) agencies, updated regularly, and widely used.

To identify structurally-related compounds, an initial pool of analogues is identified using automated tools, including ChemIDplus[3] (NLM, 2022a), the CompTox Chemicals Dashboard[4] (U.S. EPA, 2022a), and the OECD Quantitative Structure-Activity Relationship (QSAR) Toolbox[5] (OECD, 2021). Additional analogues identified as ChemIDplus-related substances, mixtures, and CompTox "related substances[6]" are also considered. CompTox General Read-Across (GenRA)[7] 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 structure 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 analogues are clustered using the Chemical Assessment Clustering Engine (ChemACE)[8] (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-toxicity 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.

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[3]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 Dec. 2022.

[4]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).

[5]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).

[6]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).

[7]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, 2022b).

[8]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).

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[9], and Comparative Toxicogenomics Database (CTD)[10] (CTD, 2022) are also evaluated for this purpose. ToxCast/Tox 21 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 similarities and activity in ToxCast/Tox21 in vitro assays or ToxRef data (10 analogues collected from each neighbors dataset). 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 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.

[9]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).

[10]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).

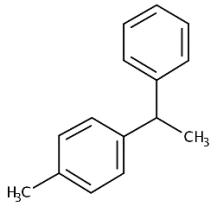
Analogue Search Results for PTE

Candidate analogues for PTE 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 oral and inhalation toxicity values. Details are provided below.

Identification of Structural Analogues with Established Toxicity Values

Table A-1 summarizes the candidate structural analogues for PTE. PTE is not a member of an existing OECD or New Chemical category. Candidate structural analogues for PTE were identified using the U.S. EPA CompTox Chemicals Dashboard and the OECD QSAR Toolbox. A total of 395 unique structural analogues were identified for PTE in the Dashboard version 2.2.1, GenRA version 3.2, and OECD QSAR Toolbox version 4.4.

Table A-1. Candidate Structural Analogues Identified for PTE



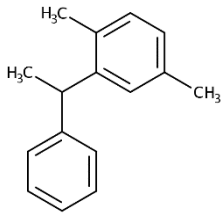
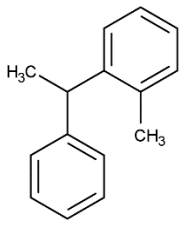
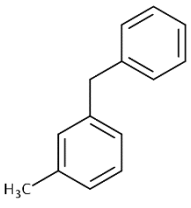
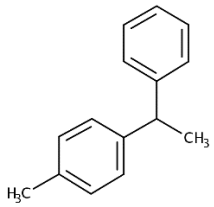
Tool (method)[a]	Analogue (CASRNs) Selected for Toxicity Value Searches[b]	Structure
Dashboard (Tanimoto) *and* OECD QSAR Toolbox (Dice)	2-(1-Phenylethyl)-*p*-xylene (6165-51-1)[b]	
Dashboard (Tanimoto) *and* OECD QSAR Toolbox (Dice)	1-Methyl-2-(1-phenylethyl)benzene (40766-30-1)	
Dashboard (Tanimoto)	3-Methyldiphenylmethane (620-47-3)	

Table A-1. Candidate Structural Analogues Identified for PTE



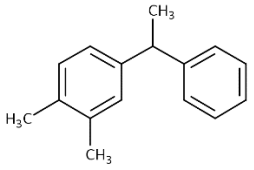
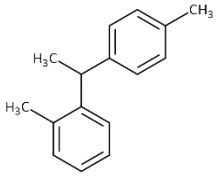
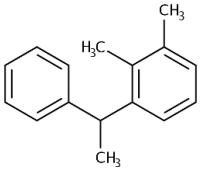
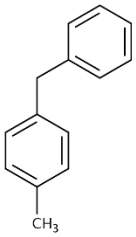
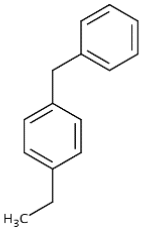
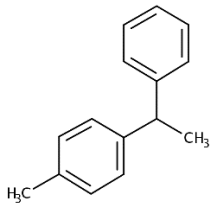
Tool (method)[a]	Analogue (CASRNs) Selected for Toxicity Value Searches[b]	Structure
Dashboard (Tanimoto)	1,2-Dimethyl-4-(1-phenylethyl)benzene (6196-95-8)	
Dashboard (Tanimoto)	1-Methyl-2-[1-(4-methylphenyl)ethyl]benzene (5080-10-4)	
Dashboard (Tanimoto) *AND* OECD QSAR Toolbox (Dice)	1,2-Dimethyl-3-(1-phenylethyl)benzene (40766-31-2)[b]	
Dashboard (Tanimoto)	1-Methyl-4-(phenylmethyl)benzene (620-83-7)	
Dashboard (Tanimoto)	1-Ethyl-4-(phenylmethyl)benzene (620-85-9)	

Table A-1. Candidate Structural Analogues Identified for PTE



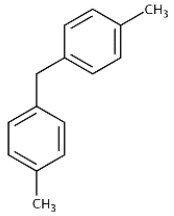
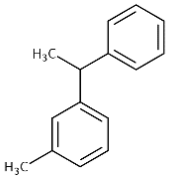
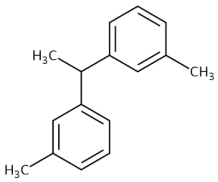
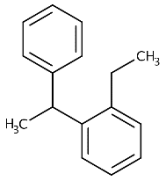
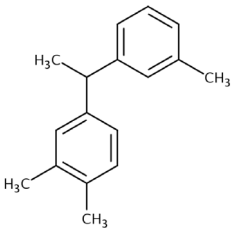
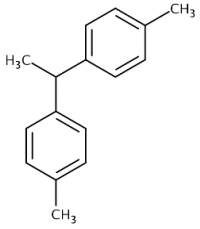
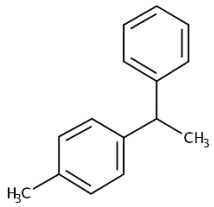
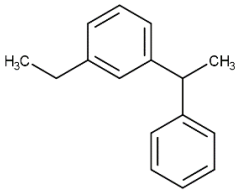
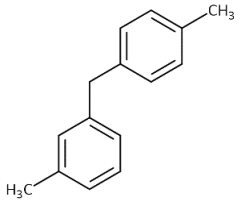
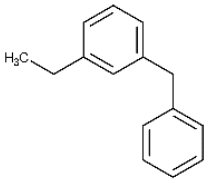
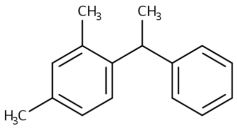
Tool (method)[a]	Analogue (CASRNs) Selected for Toxicity Value Searches[b]	Structure
Dashboard (Tanimoto)	1-Methyl-4-[(4-methylphenyl)methyl]benzene (4957-14-6)	
Dashboard (Tanimoto)	1-Methyl-3-(1-phenylethyl)benzene (32341-91-6)	
Dashboard (Tanimoto)	1,1'-(Ethane-1,1-diyl)bis(3-methylbenzene) (89881-30-1)	
Dashboard (Tanimoto)	1-Ethyl-2-(1-phenylethyl)benzene (18908-70-8)	
Dashboard (Tanimoto)	1,2-Dimethyl-4-[1-(3-methylphenyl)ethyl]benzene (874811-05-9)	
Dashboard (Tanimoto)	1-Methyl-4-[1-(4-methylphenyl)ethyl]benzene (530-45-0)	

Table A-1. Candidate Structural Analogues Identified for PTE



Tool (method)[a]	Analogue (CASRNs) Selected for Toxicity Value Searches[b]	Structure
Dashboard (Tanimoto)	1-Ethyl-3-(1-phenylethyl)benzene (18908-71-9)	
Dashboard (Tanimoto)	1-Methyl-3-[(4-methylphenyl)methyl]benzene (21895-16-9)	
Dashboard (Tanimoto)	1-Benzyl-3-ethylbenzene (28122-24-9)	
Dashboard (Tanimoto) *AND* OECD QSAR Toolbox (Dice)	1-Phenyl-1-(2,4-dimethylphenyl)-ethane (6165-52-2)	

[a]All software tools set to 80% similarity threshold for analogue identification, unless otherwise noted.
[b]OECD QSAR Toolbox reported that repeated-dose toxicity data are available in the Japanese NITE database.

NITE = National Institute of Technology and Evaluation; OECD = Organisation for Economic Co-operation and Development; PTE = 1-phenyl-1-(4-methylphenyl)-ethane; QSAR = quantitative structure-activity relationship.

After eliminating analogues containing metals or deuterated compounds, the remaining list of analogues was reviewed by a chemist with expertise in read-across. The following criteria for determining PTE analogues were applied as part of the expert review: (1) the presence of a methylene or 1,1-ethylidene bridge connecting the two aromatic rings (compounds with other hydrocarbon moieties connecting the two aromatic rings were excluded because additional substitutions would impact the steric rotation of the molecule and would block the bridge atom from metabolism [or reactivity in general]); (2) compounds with any other atom (such as oxygen or sulfur) at the bridge or substituted on the structure were excluded because this could change the activation/reactivity of the aromatic rings; (3) consistent with the structure of PTE, methyl groups and/or an ethyl group on the rings were limited to no more than two per ring or one per

ring, respectively, because more or larger substitutions would result in steric hinderance, decrease the solubility, and increase the log K_{ow} of the compound; and (4) the presence of methyl or ethyl groups was required as they are potential sites for metabolism. Of the 395 unique structural analogues identified by similarity searches, only 18 met the criteria above and were carried forward as candidate structural analogues (see Table A-1). No toxicity values were identified for any of the 18 candidate structural analogues.

Identification of Toxicokinetic Precursors or Metabolites with Established Toxicity Values

PubMed searches (searching "1-phenyl-1-(4-methylphenyl)-ethane" or "3717-68-8" and "metabolite") were conducted to identify metabolic precursors to PTE. No metabolic precursors were identified. No metabolites were identified for PTE in the scientific literature. Predicted metabolites were queried using the OECD QSAR Toolbox version 4.4 using the in vivo rat metabolism simulator and rat liver S9 metabolism simulator. PubMed was also searched to identify other compounds that are metabolized to one of the predicted metabolites of PTE (searching the metabolite name [none of the metabolites had CASRNs] and "metabolite"); no compounds that share at least one metabolite with PTE were identified. Table A-2 summarizes the 22 candidate metabolic analogues for PTE identified by the OECD QSAR Toolbox. Searches for relevant toxicity values available from the U.S. EPA, ATSDR, or CalEPA for the candidate metabolic analogues of PTE did not identify toxicity values for any of the predicted metabolites.

Table A-2. Candidate Metabolic Analogues of PTE	
Relationship to PTE	**Compound[a]**
Metabolic precursor	None identified
Predicted metabolites	4-[1-(4-Methylphenyl)ethyl]benzene-1,2-diol
	4-[1-(4-Methylphenyl)ethyl]phenol
	3-[1-(4-Methylphenyl)ethyl]phenol
	2-[1-(4-Hydroxyphenyl)ethyl]-5-methylphenol
	4-[1-(4-Hydroxyphenyl)ethyl]benzaldehyde
	4-[1-(4-Hydroxyphenyl)ethyl]benzyl alcohol
	2-Methyl-5-(1-phenylethyl)phenol
	5-Methyl-2-(1-phenylethyl)phenol
	4-(1-Phenylethyl)benzaldehyde
	[4-(1-Phenylethyl)phenyl]methanol
	4-(1-Phenylethyl)benzoic acid
	2-(4-Methylphenyl)-2-phenylacetic acid
	2-(4-Hydroxyphenyl)-2-(4-methylphenyl)acetaldehyde
	2-(4-Methylphenyl)-2-phenylacetaldehyde
	2-(4-Hydroxyphenyl)-2-(4-methylphenyl)
	2-(4-Methylphenyl)-2-phenylethan-1-ol
	4-[2-Hydroxy-1-[4-(hydroxymethyl)phenyl]ethyl]phenol
	4-(1-Phenyl-2-hydroxyethyl)benzaldehyde
	2-[4-(Hydroxymethyl)phenyl]-2-phenylethan-1-ol
	4-(1-Phenyl-2-hydroxyethyl)benzoic acid
	2-[4-(Hydroxymethyl)phenyl]-2-phenylacetic acid
	2-[4-(Hydroxymethyl)phenyl]-2-phenylacetaldehyde
Shares common metabolite(s)	None identified

[a]No CASRNs are available for these metabolites.

PTE = 1–phenyl-1-(4-methylphenyl)-ethane.

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

No toxicity or mechanistic/MOA data relevant for identifying candidate analogues for PTE were identified in the scientific literature. The GenRA option version 3.2 within the U.S. EPA CompTox Dashboard version 2.2.1 offers the ability to search for analogues based on similarities in activity in ToxCast/Tox21 in vitro assays; however, there were no bioactivity data for PTE, so this was not further investigated. The CTD did not have an entry for PTE.

Candidate Analogues Moving Forward for Evaluation

Searches for structural, metabolic, and toxicity/mechanistic analogues for PTE yielded a total of 40 unique candidate analogues: 18 structural analogues and 22 metabolism-related analogues. No candidate analogues were identified on the basis of having similar characteristic toxicity or mechanisms/MOAs.

None of the candidate analogues have oral or inhalation toxicity values from the U.S. EPA, ATSDR, or CalEPA. Therefore, no suitable candidate analogues were identified to calculate screening oral or inhalation toxicity values.

ORAL NONCANCER TOXICITY VALUES

Derivation of Screening Subchronic and Chronic Provisional Reference Doses

Screening subchronic and chronic provisional reference doses could not be derived due to the lack of an appropriate analogue having oral toxicity values.

INHALATION NONCANCER TOXICITY VALUES

Derivation of Screening Subchronic and Chronic Provisional Reference Concentrations

Screening subchronic and chronic provisional reference concentrations could not be derived due to the lack of an appropriate analogue having inhalation toxicity values.

APPENDIX B. PARAMETERS OF TOOLS USED FOR READ ACROSS

Table B-1. Parameters of Tools Used for Read-Across Evaluation of PTE

Similarity Context [417][a]	Tool Name [4]	Settings/Parameters	Searched by (date)
Structural [395]	The U.S. EPA CompTox Chemicals Dashboard [371]	Tanimoto similarity threshold of 0.8 and related substances	CASRN (April 2023)
	GenRA Beta version (in the U.S. EPA CompTox Chemicals Dashboard) [23]	Collect 10 nearest neighbors by each similarity setting and combination available: • Morgan Fingerprints • Torsion Fingerprints • ToxPrints • Morg2Tor1Bio1 • CT1:Bio3 Using each of the following data sources: ToxCast, Tox 21, and ToxRef	
	OECD QSAR Toolbox [1]	Similarity search with ≥80% similarity threshold using default settings: • Dice similarity • Atom centered fragments • Hologram calculation • All features combined • Atom characteristics: atom type, count H attached, and hybridization	
Metabolic [22]	OECD QSAR Toolbox Metabolism Simulators [22]	No settings or parameters; results obtained from: • Rat liver S9 metabolism simulator version 3.7 • in vivo rat metabolism simulator version 3.5	SMILES[b] (April 2023)
Toxicity/mechanistic [0]	GenRA Beta version (in the U.S. EPA CompTox Chemicals Dashboard) [0]	Collected 10 nearest neighbors using the ToxCast similarity settings. • Nearest neighbors with a similarity index ≥0.5 considered for use as analogue.	CASRN (April 2023)
	Comparative Toxicogenomics Database (CTD) [0]	Identify compounds with gene interactions similar to those induced by PTE: • Used the interacting genes comparison search. • A similarity index of ≥0.5 is considered for use as a mechanistic analogue	(April 2023)

[a]Unique analogues identified using analogue identification search tools.
[b]Phenyl-1-(4-methylphenyl)-ethane; SMILES: CC(C1=CC=CC=C1)C1=CC=C(C)C=C1) (CASRN 3717-68-8).

GenRA = General Read-Across; NA = not applicable; OECD = Organisation for Economic Co-operation and Development; PTE = 1-phenyl-1-(4-methylphenyl)-ethane; QSAR = quantitative structure-activity relationship; SMILES = Simplified Molecular Input Line Entry System; U.S. EPA = U.S. Environmental Protection Agency.

APPENDIX C. REFERENCES

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