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Provisional Peer-Reviewed Toxicity Values for

1-Phenyl-1-(2,4-dimethylphenyl)-ethane (PXE)
(CASRN 6165-52-2)

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
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGER

Kyoungju Choi, PhD
Center for Public Health and Environmental Assessment, Cincinnati, OH

CONTRIBUTORS

Allison L. Phillips, PhD
Center for Public Health and Environmental Assessment, Cincinnati, OH

Lucina E. Lizarraga, PhD
Center for Public Health and Environmental Assessment, Cincinnati, OH

SCIENTIFIC TECHNICAL LEAD

Lucina E. Lizarraga, PhD
Center for Public Health and Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY

SRC, Inc.
7502 Round Pond Road
North Syracuse, NY 13212

PRIMARY INTERNAL REVIEWERS

Q. Jay Zhao, PhD, MPH, DABT
Center for Public Health and Environmental Assessment, Cincinnati, OH

Jeffry L. Dean II, PhD
Center for Public Health and Environmental Assessment, Cincinnati, OH

PRIMARY EXTERNAL REVIEWERS

Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421-3136

PPRTV PROGRAM MANAGEMENT

Teresa L. Shannon
Center for Public Health and Environmental Assessment, Cincinnati, OH

Allison L. Phillips, PhD
Center for Public Health and Environmental Assessment, Cincinnati, OH

J. Phillip Kaiser, PhD, DABT
Center for Public Health and Environmental Assessment, Cincinnati, OH

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-(2,4-DIMETHYLPHENYL)-ETHANE (PXE; CASRN 6165-52-2)

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-(2,4-dimethylphenyl)-ethane (PXE), CASRN 6165-52-2, is a discrete organic chemical; it is a hydrocarbon containing both aromatic and aliphatic carbons (Figure 1). PXE is listed with the U.S. EPA Substance Registry Services and the Toxic Substances Control Act's public inventory (U.S. EPA, 2022c, d). It is listed on the European Chemicals (EC) inventory and is preregistered with Europe's Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) program (ECHA, 2022). There are no data available on the production of PXE in the United States or commercial uses reported for PXE (NLM, 2022b; U.S. EPA, 2022d). Synonyms of 1-phenyl-1-(2,4-dimethylphenyl)-ethane appearing in these databases and other sources include 2,4-dimethy-1-(1-phenylethyl)benzene, 1-phenyl-1-metaxylyl-ethane, 1-phenyl-1-(2,4-xylyl)ethane and 4-(1-phenylethyl)-*m*-xylene.

The empirical formula for PXE is $C_{16}H_{18}$. The physicochemical properties for PXE are provided in Table 1. There are no experimental physicochemical property data available for PXE; therefore, all property data presented are estimates from the U.S. EPA CompTox Chemicals Dashboard version 2.2.1 and EPI Suite™. PXE is slightly soluble in water and has moderate vapor pressure (U.S. EPA, 2012). 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 PXE has an estimated half-life of 0.5 days, based on its 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 PXE indicate the potential for sorption to soil is high. Based on its Log K_{oc} value, PXE is classified to be slightly mobile in soils by the Food & Agriculture Organization of the United Nations (FAO) (U.S. EPA, 2012). Hydrolysis is not expected to be an important fate process due to the lack of hydrolysable functional groups in this chemical.

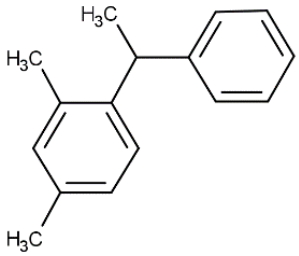


Figure 1. 1-Phenyl-1-(2,4-dimethylphenyl)-ethane (PXE) (CASRN 6165-52-2) Structure

Table 1. Physicochemical Properties of PXE (CASRN 6165-52-2)

Property (unit)	Value[a]
Molecular formula	$C_{16}H_{18}$
Molecular weight (g/mol)	210.32
Physical state	NA
Boiling point (°C)	301
Melting point (°C)	29°C
Density (g/cm^3 at 25°C)	0.962
Vapor pressure (mm Hg at 25°C)	2.7×10^{-3}
Vapor density	NA
Water solubility (mol/L)	1.46×10^{-6}
Log octanol-water partition coefficient (log K_{ow})	5.29
pKa (unitless)	NA
Henry's law constant (atm-m^3/mol at 25°C)	5.25×10^{-4}
Soil adsorption coefficient K_{oc} (L/kg)	2.29×10^3
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	2.14×10^{-11}
Atmospheric half-life (d)	0.5 (calculated using a 12-h day; 1.5×10^6 OH/cm^3)[b]
Flash point (°C)	142

[a]Unless otherwise noted, data were extracted from the U.S. EPA CompTox Chemicals Dashboard (2,4-dimethyl-1-(1-phehylethyl)benzene, CASRN 6165-52-2. https://comptox.epa.gov/dashboard/DTXSID50884231; accessed July 31, 2023). All values are predicted averages unless otherwise specified.
[b]U.S. EPA (2012) (EPI Suite™ estimates using SMILES CC(C1=CC=CC=C1)C1=CC=C(C)C=C1C.

EPI = Estimation Programs Interface; NA = not applicable; PXE = 1-phenyl-1-(2,4-dimethylphenyl)-ethane; SMILES = Simplified Molecular Input Line Entry System; U.S. EPA = U.S. Environmental Protection Agency.

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

Table 2. Summary of Available Toxicity Values for PXE (CASRN 6165-52-2)

Source (parameter)[a]	Value (applicability)	Notes	Reference[c]
Noncancer			
IRIS	NV	NA	U.S. EPA (2022b)
HEAST	NV	NA	U.S. EPA (2011b)
DWSHA	NV	NA	U.S. EPA (2018)
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)
DOE (PAC)	NV	NA	DOE (2018)
Cancer			
IRIS	NV	NA	U.S. EPA (2022b)
HEAST	NV	NA	U.S. EPA (2011b)
DWSHA	NV	NA	U.S. EPA (2018)
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; 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; WHO = World Health Organization.
[b]Parameters: PAC = protective action criteria.
[c]Reference date is the publication date for the database and not the date the source was accessed.

NA = not applicable; NV = not available; PXE = 1-phenyl-1-(2,4-dimethylphenyl)-ethane.

Literature searches were conducted in November 2018 and October 2022, and updated mostly recently in July 2023 for studies relevant to the derivation of provisional toxicity values for PXE. Searches were conducted using the U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches for the following databases: PubMed, TOXLINE[1] (including TSCATS1), Scopus, and Web of Science. The National Technical Reports Library (NTRL) was searched for government reports from 2018 through

[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 October 2022 or July 2023.

September 2020[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 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 Cooperation 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), the U.S. EPA Office of Water (OW) Drinking Water Standards and Health Advisories, 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 PXE in humans or animals exposed by oral or inhalation routes adequate for deriving provisional toxicity values were identified. 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 PXE (CASRN 6165-52-2)							
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; PXE = 1-phenyl-1-(2,4-dimethylphenyl)-ethane.

Table 3B. Summary of Potentially Relevant Cancer Data for PXE (CASRN 6165-52-2)					
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; PXE = 1-phenyl-1-(2,4-dimethylphenyl)-ethane.

2.1. HUMAN STUDIES

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

2.2. ANIMAL STUDIES

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

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

No genotoxicity or other supporting studies were identified for PXE. However, some limited data were located for mixtures containing PXE (see Table 4). Male rats treated with 100 mg/kg-day of SAS-296, a commercial preparation containing 7% PXE and 93% 1-phenyl-1-orthoxylyl-ethane, daily for 1 month showed increases in relative liver weights. Statistically significant decreases in lipid profiles (free cholesterol, total cholesterol, and/or phospholipids) in serum and the liver were observed, as were other significant increases in liver enzyme (alkaline phosphatase), and free fatty acids in serum (Hasegawa et al., 1982a). A companion toxicokinetics study performed in rats using a single oral dose showed that SAS-296 (a mixture of PXE and 1-phenyl-1-orthoxylyl-ethane) was absorbed through the gastrointestinal tract, rapidly cleared from the blood and widely distributed throughout the body, with large amounts initially found in the liver and slight accumulation in fat (Hasegawa et al., 1982b). The percent dissipation of SAS-296, enzyme kinetics, and K_M value determined by toxicokinetic experiments from the same group using rat liver microsomes supported the rapid disappearance and altered composition of SAS-296 observed in vivo. However, PXE dissipation rates were not accurately measured due to the lack of the saturation of substrate to enzymatic reaction (Hasegawa et al., 1982b).

In skin painting experiments, the test material, described only as a diaryl-alkane phenyl-xylyl-ethane synthetic fluid (and presumed to be a mixture of PXE, PXE isomers, and other structurally related compounds) was negative for tumorigenicity and carcinogenicity in two strains of SENCAR mice or *hr/hr* Oslo mice treated twice per week with 100% of diaryl-alkane phenyl-xylyl-ethane for 18 months (Iversen, 1990). Lower concentrations of diaryl-alkane phenyl-xylyl-ethane in acetone (20 or 40%) did not initiate or promote tumors in studies with dimethylbenz[*a*]anthracene or 12-*O*-tetradecanoylphorbol 13-acetate (Iversen, 1990).

Table 4. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Supporting studies in animals following oral exposure				
Short-term Mixture: SAS-296 (contains 7% PXE and 93% 1-phenyl-1-orthoxylyl-ethane)	Male JCL:SD rats (5−6/group) were administered SAS-296, via gavage (no vehicle specified) at a dose of 100 mg/kg-day for 1 mo. Body-weight change during the experiment was recorded. Rats were sacrificed ~2 h after the final dose. Blood and liver were collected for limited serum and liver biochemistry measurements (unfasted). Select organs (liver, kidney, heart, spleen, and brain) were weighed. Gross and microscopic examinations were not performed.	Reported changes included decreased body weight gain, increased relative liver weight, increased serum ALP, and lipid profile changes in serum (increased fatty acids; decreased cholesterol and phospholipids) and liver (increased phospholipids and pyruvate; decreased cholesterol, triglycerides, glycogen and glycolipids).	Repeated exposure to SAS-296 produced effects on the liver in treated rats; the potential contribution of PXE to the observed toxicologically relevant effects is unclear.	Hasegawa et al. (1982a)
Supporting studies in animals following dermal exposure				
Carcinogenicity Mixture: diaryl-alkane phenyl-xylyl-ethane (presumed to be a mixture of PXE, PXE isomers, and other structurally related compounds; mixture composition uncharacterized in the study)	In a skin painting study, *hr/hr* Oslo mice and SENCAR mice (16/sex/group; 24/sex for controls) were dermally exposed to 0% (vehicle), 20 or 40% (SENCAR mice), or 100% (Oslo mice) diaryl-alkane phenyl-xylyl-ethane in an acetone vehicle, 2 times/wk for 18 mo. A positive control group was administered 51.2 µg or 25.6 µg of DMBA. 100 µL of the test solutions were applied to the backs of mice and the applications sites were left uncovered. Mice were observed to lick each other after painting and an "oil smell" was apparent for up to 4 h; therefore, oral and inhalation exposures were also likely. Body and organ weights were not recorded. Signs of skin and general toxicity were noted but not actively monitored. Animals were monitored 1 time/wk for skin tumors. Necropsies were performed "whenever possible." Tumors in other organs were examined histologically along with areas showing skin toxicity (eczematous changes, pigmentation, or ulcerations).	No increases in incidences of skin tumors or differences in tumor rates or in overall tumor yields were observed in either *hr/hr* Oslo or SENCAR mice, compared to controls. Death rates were reported to increase in *hr/hr* mice, but data were not provided. Signs of toxicity (hyperplasia, ulcers, mast cell collections) were reported as "scant" (data were not provided).	Diaryl-alkane phenyl-xylyl ethane was nontumorigenic in *hr/hr* Oslo or SENCAR mice; the potential contribution of PXE to the lack of observed effects is unclear.	Iversen (1990)

Table 4. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Tumor initiation and promotion Mixture: diaryl-alkane phenyl-xylyl-ethane (presumed to be a mixture of PXE, PXE isomers, and structurally related compounds; mixture composition uncharacterized in the study)	Tumor promotion tests were conducted in *hr/hr* Oslo and SENCAR mice (16/sex/strain/group; 24/sex for controls). *hr/hr* Oslo mice were dermally treated: once with 51.2 µg DMBA and then with 40% diaryl-alkane phenyl-xylyl-ethane in acetone 2 times/wk for 18 mo; with 2.6 µg DMBA 2 times/wk for 10 wk followed by applications of 40% diaryl-alkane phenyl-xylyl-ethane 2 times/wk for 18 mo; with 2.6 µg DMBA alternating with 20% diaryl-alkane phenyl-xylyl-ethane in acetone 2 times/wk for 20 wk; or 100% PXE 2 times/wk for 18 mo. Negative control mice were administered acetone 2 times/wk for the duration of the experiment. Other groups of control mice received single applications of 51.2 or 25.6 µg DMBA only, 2.6 µg of DMBA 2 times/wk for 5 wk, or 2.6 µg DMBA alternating with acetone 2 times/wk for 10 wk. SENCAR mice were dermally treated: once with 51.2 µg DMBA and followed by 20% diaryl-alkane phenyl-xylyl-ethane in acetone 2 times/wk for 18 mo; once with 20% diaryl-alkane phenyl-xylyl-ethane in acetone and with 10 nmol TPA 2 times/wk for 18 mo; 2.6 µg DMBA alternating with 20% diaryl-alkane phenyl-xylyl-ethane in acetone 2 times/wk for 10wk; or 20 and 40% diaryl-alkane phenyl-xylyl-ethane in acetone 2 times/wk for 18 mo. Negative control mice were administered acetone 2 times/wk for the duration of the experiment. Other groups of control mice received single application of 51.2 µg DMBA; 2.6 µg of DMBA 2 times/wk for 10 wk; or 2.6 µg of DMBA alternating with acetone 2 times/wk for 10 wk. Body and organ weights were not recorded. Signs of skin and general toxicity were noted but not actively monitored. Animals were monitored 1 time/wk for skin tumors. Necropsies were performed “whenever possible.” Tumors in other organs were examined histologically along with areas showing skin toxicity (eczematous changes, pigmentation, or ulcerations).	Treatment with diaryl-alkane phenyl-xylyl-ethane did not enhance or diminish DMBA-induced tumorigenesis in either mouse strain in any experiment. There were no significant tumorigenic responses after initiation with 20% diaryl-alkane phenyl-xylyl-ethane in acetone and promotion with TPA in SENCAR mice.	Diaryl-alkane phenyl-xylyl ethane was not a tumor promoter or a tumor initiator; the potential contribution of PXE to the lack of observed effects is unclear.	Iversen (1990)

Table 4. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Metabolism and Toxicokinetics				
In vivo				
Distribution Mixture: SAS-296 (contains PXE and 1-phenyl-1-orthoxylyl-ethane; administered mixture composition uncharacterized in the study)	Groups of 8-wk-old male JCL-SD rats (number per group not specified) were administered SAS-296 orally either by a single dose of 100 mg/kg or daily doses of 100 mg/kg-day for 1 mo (performed simultaneously with the 1-mo toxicity study described above). Rats were sacrificed at 0, 2, 4, 24, and 48 h after the single dose, and at 2, 4, 24 h, and 7 d after the final dose in the repeated dose experiment. Multiple organs and tissues were excised at each sacrifice and analyzed by GC for SAS-296 components.	Single dose: • At 2 h: SAS-296 peaked and was primarily observed in the liver followed by fat, with smaller amounts in other organs. • At 4 h: SAS-296 was nearly absent in the liver and continued to increase in total body fat and in subcutaneous fat for 24 h. • At 48 h: SAS-296 was only present in subcutaneous fat and body fat, although at lower levels than at 24 h. • Composition of each SAS-296 component in varying in organs changed over time in comparison to material administered, which the study authors attributed to different rates of metabolism for the two components (see in vitro study, below). Repeat dose: • At 2 h: SAS-296 was primarily distributed to body fat, followed by subcutaneous fat, and to a lesser extent in the liver, heart, kidney, and brain. • SAS-296 continued to accumulate in body and subcutaneous fat and concentrations peaked at 24 h postdosing and then declined. SAS-296 was still present in fat after 7 d. Concentrations in all other organs and blood were near zero at 7 d. • SAS-296 concentrations in liver declined rapidly over time.	SAS-296 was absorbed through the gastrointestinal tract and was rapidly cleared from the blood and widely distributed throughout the body. After a single dose of SAS-296, large amounts were initially found in the liver, followed by fat. After continuous administration, SAS-296 showed some potential for accumulation in fat.	Hasegawa et al. (1982b)

Table 4. Other Studies

Test	Materials and Methods	Results	Conclusions	References
In vitro				
Rat liver microsomes Mixture: SAS-296 (contains PXE and 1-phenyl-1-orthoxylyl-ethane; mixture composition uncharacterized in the study)	In a reaction mixture, 2.5 mL of freshly prepared rat liver homogenates were incubated with SAS-296 (final concentrations of PXE at 2.6, 3.6, or 4.6 µg/mL and 1-phenyl-1-orthoxylyl-ethane at 1.1, 1.6, or 2.0 µg/mL) for 2 h at 37°C. Concentrations of PXE and 1-phenyl-1-orthoxylyl-ethane were analyzed at time zero and after 2 h and chemical dissipation rates, Michaelis constants (K_M) and maximum reaction velocities (V_{max}) were determined.	• After 2 h, PXE concentrations were reduced by 23−32%, and concentrations of 1-phenyl-1-orthoxylyl-ethane were reduced by 58−60%. • K_M and V_{max} values were 11.2 µg/mL and 3.6 µg/mL/g/h for PXE and 16.2 µg/mL and 10 µg/mL/g/h for 1-phenyl-1-orthoxylyl-ethane, reflecting the higher enzyme affinity and lower maximal velocity of enzyme-catalyzed reaction for PXE.	The percent dissipation of SAS-296 and K_M and V_{max} values are supportive of the rapid disappearance and altered isomer composition of SAS-296 in rats. However, PXE dissipation rates were not accurately measured due to the lack of the saturation of substrate to enzymatic reaction.	Hasegawa et al. (1982b)

ALP = alkaline phosphatase; DMBA = dimethylbenz[a]anthracene; GC = gas chromatography; PXE = 1-phenyl-1-(2,4-dimethylphenyl)-ethane; TPA = 12-*O*-tetradecanoylphorbol 13-acetate.

3. DERIVATION OF PROVISIONAL VALUES

3.1. DERIVATION OF ORAL REFERENCE DOSES

No studies were located regarding toxicity of PXE to humans or animals via oral exposure. Due to the lack of oral toxicity data for PXE, 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 a suitable analogue with available toxicity values was not identified (see Appendix A).

3.2. DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No studies were located regarding toxicity of PXE to humans or animals via inhalation exposure. Due to the lack of inhalation toxicity data for PXE, 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 a suitable analogue with available toxicity values was not identified (see Appendix A).

3.3. SUMMARY OF NONCANCER PROVISIONAL REFERENCE VALUES

Table 5 presents a summary of noncancer provisional reference values.

Table 5. Summary of Noncancer Reference Values for PXE (CASRN 6165-52-2)

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; PXE = 1-phenyl-1-(2,4-dimethylphenyl)-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 PXE. Under the U.S. EPA Cancer Guidelines (U.S. EPA, 2005), there is "*Inadequate Information to Assess the Carcinogenic Potential*" of PXE by oral or inhalation exposure (see Table 6).

Table 6. Cancer WOE Descriptor for PXE (CASRN 6165-52-2)			
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 PXE 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; PXE = 1-phenyl-1-(2,4-dimethylphenyl)-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 7).

Table 7 Summary of Cancer Risk Estimates for PXE (CASRN 6165-52-2)				
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; PXE = 1-phenyl-1-(2,4-dimethylphenyl)-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 PXE. 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 compound of interest are limited or unavailable. Details regarding searches and methods for analogue analysis are presented in Wang et al. (2012) and Lizarraga et al. (2023). Three types of potential analogues (structural, metabolic, and toxicity-like) are identified to facilitate the final analogue chemical 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 analogue both toxicologically and chemically.

An expanded analogue identification approach was developed to collect a comprehensive set of candidate analogues for the compounds undergoing U.S. Environmental Protection Agency (U.S. EPA) PPRTV screening-level assessment. As described below, this method includes application of a variety of tools and methods for identifying candidate analogues that are similar to the target chemical based on chemical structure and key features; metabolic relationships; or related toxic effects and mechanisms of action.

To identify structurally-related compounds, an initial pool of analogues is identified using automated tools, including ChemIDplus[3] (NLM, 2022a), the CompTox Chemicals Dashboard (U.S. EPA, 2022a), and the Organisation for Economic Co-operation and Development (OECD) Quantitative Structure-Activity Relationship (QSAR) Toolbox (OECD, 2021), to conduct structural similarity searches. Additional analogues identified as ChemIDplus-related substances, parent, salts, and mixtures, and CompTox-related substances are considered. CompTox Generalized Read-Across (GenRA) analogues are collected using the methods available on the publicly available GenRA version 3.2, which may include Morgan fingerprints, Torsion fingerprints, ToxPrints and ToxCast, Tox21, and ToxRef data. For compounds that have very few analogues identified by structure similarity using a similarity threshold of 0.8 or 80%, substructure searches in the QSAR Toolbox may be performed, or similarity searches may be rerun using a reduced similarity threshold (e.g., 70 or 60%). The compiled list of candidate analogues is batch run through the CompTox Chemicals Dashboard where QSAR-ready

[3]The National Library of Medicine (NLM) retired ChemIDplus in December 2022.

simplified molecular-input line-entry system (SMILES) notations are collected and toxicity data availability is determined (e.g., from the Agency for Toxic Substances and Disease Registry [ATSDR], Office of Environmental Health Hazard Assessment [OEHHA], California Environmental Protection Agency [CalEPA], the U.S. EPA Integrated Risk Information System [IRIS], PPRTV assessments). The batch output information is then uploaded into the Chemical Assessment Clustering Engine (ChemACE) (U.S. EPA, 2011a), which clusters the chemicals based on chemical fragments and displays the toxicity data availability for each candidate. The ChemACE output is reviewed by an experienced chemist, who narrows the list of structural analogues based on known or expected structure-toxicity relationships, reactivity, and known or expected metabolic pathways.

Toxicokinetic studies tagged as potentially relevant supplemental material during screening were used to identify metabolic analogues (metabolites and metabolic precursors). Metabolites were also identified from the two OECD QSAR Toolbox version 4.4 metabolism simulators (in vivo rat metabolism simulator and rat liver S9 metabolism simulator). Targeted PubMed searches were conducted to identify metabolic precursors and other compounds that share any of the observed or predicted metabolites identified for the target chemical. Metabolic analogues are then added to the pool of candidate analogues and toxicity data availability is determined (e.g., from ATSDR, OEHHA, CalEPA, U.S. EPA IRIS, PPRTV assessments).

In vivo toxicity data for the target chemical (if available) are evaluated to determine whether characteristic toxicity associated with a particular mechanism of toxicity was 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 version 3.2, ToxCast/Tox21, and Comparative Toxicogenomics Database (CTD) (CTD, 2022; Davis et al., 2021) were evaluated for this purpose. Data from CompTox Chemicals Dashboard ToxCast/Tox 21 are collected to determine bioactivity of the target chemical in in vitro assays that may indicate potential mechanism(s) of action. The GenRA option within the Dashboard also offers an option to search for analogues based on similarities in activity in ToxCast/Tox21 in vitro assays. Using the ToxCast/Tox21 bioactivity data, nearest neighbors identified with similarity indices of ≥0.5 may be considered potential candidate analogues. The CTD (CTD, 2022; Davis et al., 2021) is searched to identify compounds with gene interactions similar to interactions induced by the target chemical; compounds with gene interactions similar to the target chemical (with a similarity index >0.5) may be considered potential candidate analogues. These compounds are then added to the pool of candidate analogues, and toxicity data availability is determined (e.g., from ATSDR, OEHHA, CalEPA, the U.S. EPA IRIS, PPRTV assessments).

The application of a variety of different tools and methods to identify candidate analogues serves to minimize the limitations of any individual tool with respect to 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 above used for the expanded analogue approach searches were selected because they are publicly available, supported by U.S. and OECD agencies, updated regularly, and widely used.

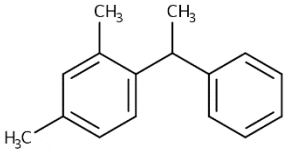
Analogue Search Results for PXE

Candidate analogues for PXE were identified based on structural, metabolic, and toxicity/mechanisms/mode-of-action (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 PXE. PXE is not a member of an existing OECD or New Chemical category. Candidate structural analogues for PXE were identified using the U.S. EPA CompTox Chemistry Dashboard, OECD QSAR Toolbox, and ChemIDplus tools. Using similarity searches, 411unique structural analogues were identified in the Dashboard version 2.2.1, GenRA version 3.2, OECD QSAR Toolbox version 4.4, and ChemIDplus.

Table A-1. Candidate Structural Analogues Identified for PXE



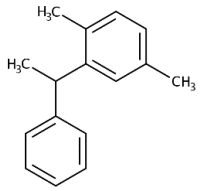
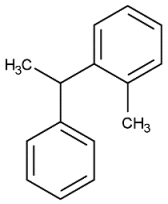
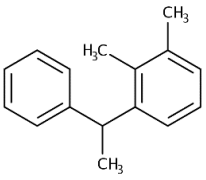
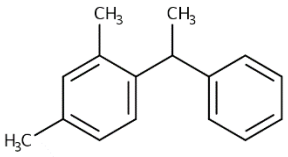
Tool (method)[a]	Analogue (CASRNs) Selected for Toxicity Value Searches[b]	Structure
Dashboard (Tanimoto) *AND* OECD QSAR Toolbox (Dice) *AND* ChemIDplus	1,4-dimethyl-2-(1-phenylethyl)benzene (6165-51-1)[b]	
Dashboard (Tanimoto) *AND* OECD QSAR Toolbox (Dice)	1-methyl-2-(1-phenylethyl)benzene (40766-30-1)	
Dashboard (Tanimoto) *AND* OECD QSAR Toolbox (Dice)	1,2-Dimethyl-3-(1-phenylethyl)benzene (40766-31-2)[b]	

Table A-1. Candidate Structural Analogues Identified for PXE



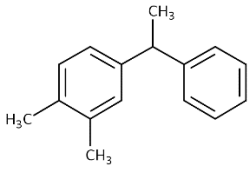
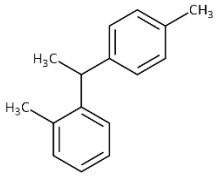
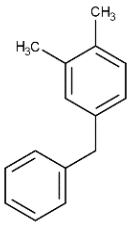
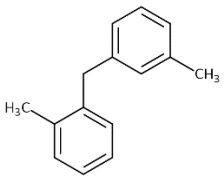
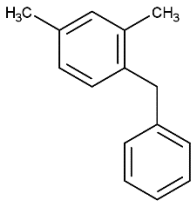
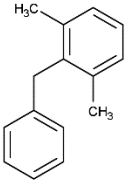
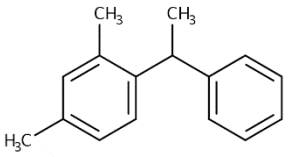
Tool (method)[a]	Analogue (CASRNs) Selected for Toxicity Value Searches[b]	Structure
Dashboard (Tanimoto) *AND* OECD QSAR Toolbox (Dice)	1,2-Dimethyl-4-(1-phenylethyl)benzene (6196-95-8)	
Dashboard (Tanimoto) only	1-Methyl-2-[1-(4-methylphenyl)ethyl]benzene (5080-10-4)	
Dashboard (Tanimoto) only	4-Benzyl-1,2-dimethylbenzene (13540-56-2)	
Dashboard (Tanimoto) only	1-Methyl-2-[(3-methylphenyl)methyl]benzene (21895-13-6)	
Dashboard (Tanimoto) only	1-Benzyl-2,4-dimethylbenzene (28122-28-3)	
Dashboard (Tanimoto) only	2-Benzyl-1,3-dimethylbenzene (28122-29-4)	

Table A-1. Candidate Structural Analogues Identified for PXE



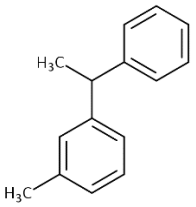
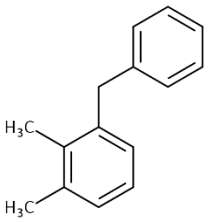
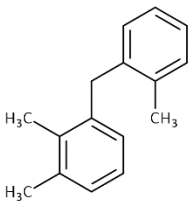
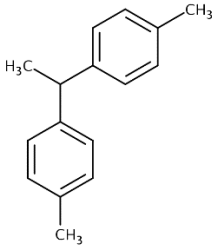
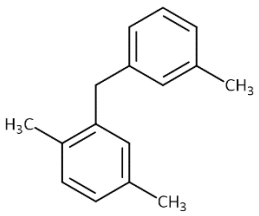
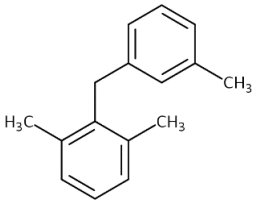
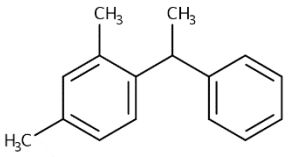
Tool (method)[a]	Analogue (CASRNs) Selected for Toxicity Value Searches[b]	Structure
Dashboard (Tanimoto) only	1-Methyl-3-(1-phenylethyl)benzene (32341-91-6)	
Dashboard (Tanimoto) only	1-Benzyl-2,3-dimethylbenzene (32518-97-1)	
Dashboard (Tanimoto) only	1,2-Dimethyl-3-[(2-methylphenyl)methyl]benzene (41888-01-1)	
Dashboard (Tanimoto) only	1-Methyl-4-[1-(4-methylphenyl)ethyl]benzene (530-45-0)	
Dashboard (Tanimoto) only	1,4-Dimethyl-2-[(3-methylphenyl)methyl]benzene (61819-81-6)	
Dashboard (Tanimoto) only	1,3-Dimethyl-2-[(3-methylphenyl)methyl]benzene (721-34-6)	

Table A-1. Candidate Structural Analogues Identified for PXE



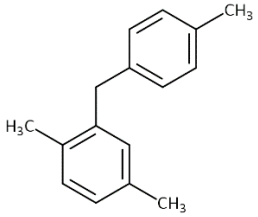
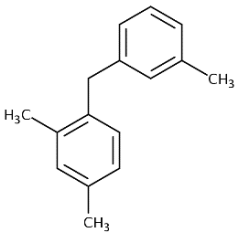
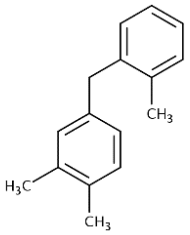
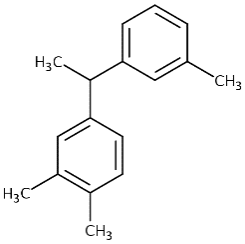
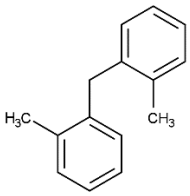
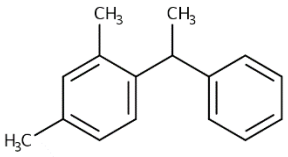
Tool (method)[a]	Analogue (CASRNs) Selected for Toxicity Value Searches[b]	Structure
Dashboard (Tanimoto) only	1,4-Dimethyl-2-[(4-methylphenyl)methyl]benzene (721-45-9)	
Dashboard (Tanimoto) only	2,4-Dimethyl-1-[(3-methylphenyl)methyl]benzene (721-54-0)	
Dashboard (Tanimoto) only	1,2-Dimethyl-4-[(2-methylphenyl)methyl]benzene (721-80-2)	
Dashboard (Tanimoto) only	1,2-Dimethyl-4-[1-(3-methylphenyl)ethyl]benzene (874811-05-9)	
Dashboard (Tanimoto) only	1-Methyl-2-[(2-methylphenyl)methyl]benzene (1335-47-3)	

Table A-1. Candidate Structural Analogues Identified for PXE



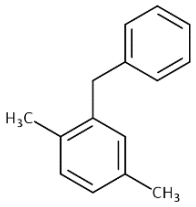
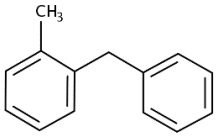
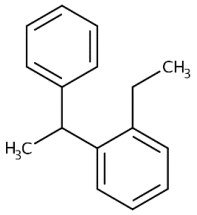
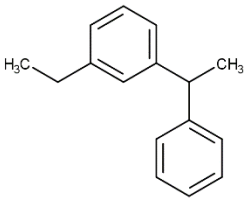
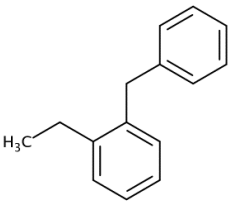
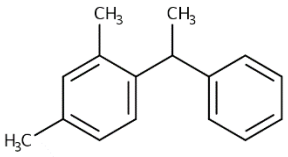
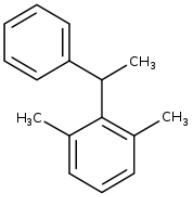
Tool (method)[a]	Analogue (CASRNs) Selected for Toxicity Value Searches[b]	Structure
Dashboard (Tanimoto) only	2-Benzyl-1,4-dimethylbenzene (13540-50-6)	
Dashboard (Tanimoto) only	1-Benzyl-2-methylbenzene (713-36-0)	
Dashboard (Tanimoto) only	1-Ethyl-2-(1-phenylethyl)benzene (18908-70-8)	
Dashboard (Tanimoto) only	1-Ethyl-3-(1-phenylethyl)benzene (18908-71-9)	
Dashboard (Tanimoto) only	1-Benzyl-2-ethylbenzene (28122-25-0)	

Table A-1. Candidate Structural Analogues Identified for PXE



Tool (method)[a]	Analogue (CASRNs) Selected for Toxicity Value Searches[b]	Structure
ChemIDplus[c] only	1,3-Dimethyl-2-(1-phenylethyl)benzene (81749-29-3)	

[a]All software tools set to 80% similarity threshold for analogue identification.
[b]OECD QSAR Toolbox reported that repeated dose toxicity data are available in the Japanese NITE database.
[c]ChemIDplus structural similarity search algorithms embedded in the software.

NITE = National Institute of Technology and Evaluation; OECD = Organisation for Economic Co-Operation and Development; PXE = 1-phenyl-1-(2,4-dimethylphenyl)-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 PXE 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 PXE, methyl groups and/or ethyl/ethynyl 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/ethynyl groups, as they are potential sites for metabolism. Of the 411 unique structural analogues identified by similarity searches, only 26 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 26 candidate structural analogues.

Identification of Toxicokinetic Precursors or Metabolites with Established Toxicity Values

PubMed searches (searching "1-phenyl-1-(2,4-dimethylphenyl)-ethane" or "6165-52-2" and "metabolite") were conducted to identify metabolic precursors to PXE. No metabolic precursors were identified. No metabolites were identified for PXE in the scientific literature. Predicted metabolites were queried with the OECD QSAR Toolbox version 4.4 using the in vivo rat metabolism simulator and the rat liver S9 metabolism simulator. PubMed was also searched to identify other compounds that are metabolized to one of the 33 predicted metabolites of PXE (searching the metabolite name [none of the metabolites had CASRNs] and "metabolite"); no

compounds that share at least one metabolite with PXE were identified. Table A-2 summarizes the 33 candidate metabolic analogues for PXE 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 PXE did not identify toxicity values for any of the predicted metabolites.

Table A-2. Candidate Metabolic Analogues of PXE

Relationship to PXE	Compound[a]
Metabolic precursor	None identified
Predicted metabolite	[3-methyl-4-(1-methyl-1-phenylethyl)phenyl]methanol [5-methyl-2-(1-phenylethyl)phenyl]methanol 2-(2,4-dimethyl-phenyl)-2-phenyl)ethanol
	5-[1-(4-hydroxyphenyl)ethyl]-2,4-dimethylphenol
	3-[1-(2,4-dimethylphenyl)ethyl]phenol
	2,4-dimethyl-5-(1-phenylethyl)phenol
	2,6-dimethyl-3-(1phenylethyl)phenol
	4-[1-(2,4-dimethylphenyl)ethyl]phenol
	4-[1-(2,hydroxymethyl-4-methylphenyl)-ethyl]-phenol
	4-[1-[2-methyl-4-(hydroxymethyl)phenyl]ethylphenol
	4-[1-(2,4-dimethylphenyl)-2-hydroxy]ethylphenol
	3-methyl-4-(1-phenylethyl)benzoic acid
	3-methyl-4-(1-phenylethyl)benzaldehyde
	5-methyl-2-(1-phenylethyl)benzoic acid
	5-methyl-2-(1-phenylethyl)benzaldehyde
	2-(2,4-dimethylphenyl)-2-phenylacetic acid
	2-(2,4-dimethyl-phenyl)-2-phenylacetaldehyde
	4-(2-hydroxy-1-phenylethyl)-3-methylbenzaldehyde
	2-(4-hydroxymethyl-2-methylphenyl)-2-phenylacetaldehyde
	2-(4-hydroxymethyl-2-methylphenyl)-2-phenylethanol
	(2-hydroxymethyl-4-methylphenyl)-2-phenylacetaldehyde
	2-(2-hydroxy-1-phenylethyl)-5-methylbenzaldehyde
	2-(2-hydroxymethyl-4-methylphenyl)-2-phenylethanol
	4-hydroxy-5-methyl-2-(1-phenylethyl)benzaldehyde
	4-hydroxymethyl-2-methyl-5-(1-phenylethyl)phenol
	2-hydroxy-5-methyl-4-(1-phenylethyl)benzaldehyde
	2-hydroxymethyl-4-methyl-5-(1-phenyl-ethyl)-phenol
	5-(2-hydroxy-1-phenylethyl)-2,4-dimethylphenol
	2-hydroxymethyl-5-(2-hydroxy-1-phenyl-ethyl)-4-methyl-phenol
	4-hydroxymethyl-5-(2-hydroxy-1-phenylethyl)-2-methylphenol
	4-[1-(2,4-dimethylphenyl)ethyl]-benzene-1,2-diol
	2-(1-phenylethyl)-3,5-dimethylphenol

Table A-2. Candidate Metabolic Analogues of PXE	
Relationship to PXE	**Compound[a]**
	2-(5-hydroxy-2,4-dimethylphenyl)-2-phenylacetaldehyde
	1-(2,4-dimethylphenyl)-1-phenylethane-1-hydroperoxide[b]
	2-(1-phenylethyl)-2,5-dimethylphenol
Shares common metabolite(s)	None identified

[a]No CASRNs are available for these metabolites.
[b]Chemical structure is unstable or otherwise unsuitable for use as PXE analogue.

PXE = 1-phenyl-1-(2,4-dimethylphenyl)-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 PXE were identified in the scientific literature. The GenRA option version 3.2 within the 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 PXE, so this was not further investigated. The CTD did not have an entry for PXE.

Summary

Searches for metabolic, structural, and toxicity/mechanistic analogues for PXE yielded a total of 59 unique candidate analogues: 33 metabolism-related analogues and 26 structural 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 Subchronic and Chronic Screening Provisional Reference Doses

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 Subchronic and Chronic Screening Provisional Reference Concentrations

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

APPENDIX B. REFERENCES

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