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Provisional Peer-Reviewed Toxicity Values for

Perylene
(CASRN 198-55-0)

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	glutamic oxaloacetic transaminase, also known as AST
SGPT	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.

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DRAFT PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR PERYLENE (CASRN 198-55-0)

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 adverse 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 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 adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. 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

Perylene, CASRN 198-55-0, is a polycyclic aromatic hydrocarbon (PAH) compound that occurs in coal tar and fossil fuels and is found as a byproduct of incomplete combustion (NLM, 2022c). Its structure consists of five fused aromatic rings and can be described as a dinaphthalene. Perylene is preregistered with Europe's Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) program (ECHA, 2022) and is listed on the U.S. EPA's Toxic Substances Control Act (TSCA) public inventory (NLM, 2022c; U.S. EPA, 2021).

Perylene is used as a fluorescent lipid probe in membrane cytochemistry and in the production of organic semiconductors (NLM, 2022c). Perylene is not produced commercially in the United Sates; it can be produced by the condensation of naphthalene in the presence of mixed Lewis acid and protic acid catalysts or by reaction of phenanthrene with acrolein in anhydrous hydrofluoric acid (NLM, 2022c).

The empirical formula for perylene is $C_{20}H_{12}$; its structure is shown in Figure 1. Table 1 provides physicochemical properties for perylene. Perylene is a yellow to colorless crystalline solid. Its negligible water solubility and negligible vapor pressure indicate that this substance is hydrophobic and nonvolatile and will exist predominantly in the particulate phase in air. Additionally, volatilization from water surfaces or moist soil surfaces is expected to be low based upon the predicted Henry's law constant of 1.06×10^{-6} atm-m^3/mole. In the atmosphere, perylene has an estimated half-life of 3.7 hours, calculated from a predicted rate constant of 3.45×10^{-11} cm^3/molecule-second at 25°C for reaction with photochemically-produced hydroxyl radicals (U.S. EPA, 2012). The estimated soil adsorption coefficient (K_{oc}) for perylene indicates minimal potential for mobility in soil; therefore, perylene has low potential for migration into groundwater (U.S. EPA, 2012). Perylene is not expected to undergo hydrolysis due to its lack of hydrolysable functional groups.

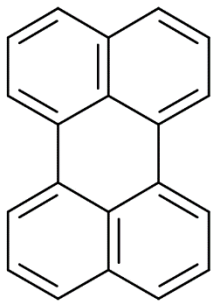


Figure 1. Perylene (CASRN 198-55-0) Structure

Table 1. Physicochemical Properties of Perylene (CASRN 198-55-0)

Property (unit)	Value[a]
Molecular weight (g/mol)	252.32
Physical state	Solid
Boiling point (°C)	>350 (estimated, range 443–487); 350−400 (sublimes)[b,c]
Melting point (°C)	274
Density (g/cm^3 at 25°C)	1.28 (predicted average)
Vapor pressure (mm Hg at 25°C)	5.25×10^{-9}
pH (unitless)	NA
pKa (unitless)	NA
Solubility in water (mg/L at 25°C)	4.0×10^{-4} (reported as 1.58×10^{-9} mol/L)
Octanol-water partition coefficient (log K_{ow})	6.04
Henry's law constant (atm-m^3/mol at 20°C)	1.06×10^{-6} (predicted average)
Soil adsorption coefficient (K_{oc}) (L/kg)	4.07×10^{5} (predicted average)
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	3.45×10^{-11} (predicted average)
Atmospheric half-life (d)	0.31 d (3.7 h)[d]
Relative vapor density (air = 1)	NA
Flash point (open cup in °C)	230 (predicted average)

[a]Data were extracted from the U.S. EPA CompTox Chemicals Dashboard (perylene; CASRN 198-55-0) (U.S. EPA, 2022c). Accessed on January 18, 2023. All values are experimental averages unless otherwise specified.
[b]NLM (2022c).
[c]NIST (2022); Goldfarb and Suuberg (2008).
[d]Calculated half-life in troposphere; $t_{1/2} = 0.693/k_{OH}$ [OH] where $k_{OH} = 3.45 \times 10^{-11}$ and [OH] = 1.5×10^{6} molecules/cm^3.

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

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

Table 2. Summary of Available Toxicity Values for Perylene (CASRN 198-55-0)

Source/Parameter[a,b]	Value (applicability)	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2022e)
HEAST	NV	NA	U.S. EPA (2011b)
DWSHA	NV	NA	U.S. EPA (2018)
ATSDR	NV	NA	ATSDR (2021); ATSDR (1995)
IPCS	NV	NA	IPCS (2020)
CalEPA	NV	NA	CalEPA (2022); CalEPA (2020)
OSHA	NV	NA	OSHA (2021a); OSHA (2021b); OSHA (2021c)
NIOSH	NV	NA	NIOSH (2018)
ACGIH	NV	NA	ACGIH (2021)
TCEQ (RfD)	0.02 mg/kg-d	Basis for RfD not specified; value developed with TECQ's protocol (TCEQ, 2015).	TCEQ (2022)
Cancer			
IRIS	NV	NA	U.S. EPA (2022e)
HEAST	NV	NA	U.S. EPA (2011b)
DWSHA	NV	NA	U.S. EPA (2018)
NTP	NV	NA	NTP (2021)
IARC (WOE)	Group 3, not classifiable as to its carcinogenicity to humans	Inadequate data to permit an evaluation of the carcinogenicity of perylene in experimental animals	IARC (2010)
CalEPA	NV	NA	CalEPA (2022); CalEPA (2020)
ACGIH	NV	NA	ACGIH (2021)

[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; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; TCEQ = Texas Commission of Environmental Quality.
[b]Parameters: RfD = reference dose; WOE = weight of evidence.

NA = not applicable; NV = not available.

Literature searches were conducted in June 2019 and updated in January 2023 for studies relevant to the derivation of provisional toxicity values for perylene, CASRN 198-55-0. Searches were conducted using the U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, Web of Science, TOXLINE[1] (including TSCATS1), and Web of Science. The National Technical Reports Library (NTRL) was searched for government reports from 2018 through September 2020. The following resources were searched outside of HERO for health-related values: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (CalEPA), Defense Technical Information Center (DTIC), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), European Chemicals Agency (ECHA), the U.S. EPA Chemical Data Access Tool (CDAT), the U.S. EPA ChemView, the U.S. EPA Integrated Risk Information System (IRIS), the U.S. EPA Health Effects Assessment Summary Tables (HEAST), the U.S. EPA Office of Water (OW), International Agency for Research on Cancer (IARC), the U.S. EPA TSCATS2/TSCATS8e, the U.S. EPA High Production Volume (HPV), Chemicals via International Programme on Chemical Safety (IPCS) INCHEM, Japan Existing Chemical Data Base (JECDB), Organisation for Economic Co-operation and Development (OECD) Screening Information Data Sets (SIDS), OECD International Uniform Chemical Information Database (IUCLID), OECD HPV, National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), Occupational Safety and Health Administration (OSHA), and World Health Organization (WHO).

Following the literature search, literature was screened and categorized using systematic review methods to identify studies pertinent to understanding the potential human health hazard of perylene. The resulting relevant literature was developed into a systematic evidence map (SEM) using the methods outlined in Thayer et al. (2022). A description of how the SEM was used during assessment development can be found in Appendix A.

[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 January 2023.

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 perylene in humans or animals exposed by oral or inhalation routes adequate for deriving provisional toxicity values have been identified. The phrase "statistical significance," used throughout the document, indicates a *p*-value of < 0.05 unless otherwise specified.

Table 3A. Summary of Potentially Relevant Noncancer Data for Perylene (CASRN 198-55-0)							
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.

Table 3B. Summary of Potentially Relevant Cancer Data for Perylene (CASRN 198-55-0)					
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study 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.

2.1. HUMAN STUDIES

Studies directly examining the toxicity or carcinogenicity of perylene in humans were not located. Perylene is a component of complex PAH-containing combustion product mixtures, several of which are known or suspected to be carcinogenic in humans (e.g., coal tars, soot, and tobacco smoke and products) (IARC, 1998, 1983). However, results from studies of these mixtures do not provide adequate exposure data for dose-response assessment to derive toxicity values for perylene or other individual PAH components.

2.2. ANIMAL STUDIES

No studies were located regarding cancer or noncancer effects in animals after oral or inhalation exposure.

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

Available toxicity data for perylene are limited to dermal and injection studies in laboratory animals evaluating immunotoxicity and carcinogenicity. Other available data include toxicokinetic studies and genotoxicity assays.

2.3.1. Genotoxicity

The genotoxicity of perylene has been examined in numerous in vitro studies and a very limited number of in vivo studies. Available studies are summarized in Table 4A. The data indicate that perylene is mutagenic in bacteria in the presence of metabolic activation and is usually less mutagenic in the absence of metabolic activation. In cultured human cell lines, perylene was not mutagenic with endogenous or exogenous metabolic activity. In general, perylene did not cause chromosomal damage in vitro or in host-mediated assays, and there is no evidence that perylene directly damages or binds deoxyribonucleic acid (DNA). Perylene induced cell transformation in metabolically competent mouse cells but did not induce cell transformation in hamster cells in the absence of metabolic activation (see Table 4A).

Table 4A. Summary of Perylene Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Genotoxicity studies in prokaryotic organisms						
Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1538	4–2,500 µg/plate	NDr	+ (TA1535, TA100) – (TA98, TA1538)	Plate incorporation method. Perylene was positive in TA1535 and TA100 in the presence of metabolic activation under conditions in which background lawn indicated at least 10% survival. The maximum increase in revertants observed was a 20-fold increase at 100 µg/plate in TA1535 and a 5-fold increase at 4 µg/plate in TA100 (quantitative data not reported at other concentrations). Perylene was negative in TA98 and TA1538. No details were provided regarding compound solubility in the test medium.	Anderson and Styles (1978)
Reverse mutation	*S. typhimurium* TA98	NS	–	–	Plate incorporation method. No increase in revertants was observed with or without metabolic activation. No details were provided regarding cytotoxicity or compound solubility in the test medium.	Anderson et al. (1987)
Reverse mutation	*S. typhimurium* TA98, TA100	50 µg/plate	NDr	+	Plate incorporation method. Perylene was positive with metabolic activation in TA98 and TA100. Mutagenic activity increased with increasing concentration of rat liver S9 (ranged from 5 to 420 µL/plate) with a >twofold increase in revertants at S9 concentrations ≥60 µL/plate. No cytotoxicity was observed. No details were provided regarding compound solubility in the test medium.	Carver et al. (1985)
Reverse mutation	*S. typhimurium* TA100	5, 10, 15 µg/plate	NDr	+	Plate incorporation method. Perylene was positive with metabolic activation. Mutagenic activity increased with increasing rat and hamster liver S9, with a >twofold increase in revertants at all S9 concentrations (ranged from 50 to 400 µL/plate). Perylene-specific data on cell survival or compound solubility in the test medium were not reported, but the study authors indicated that compounds were tested to limit of solubility, of cytotoxicity, or to 1,000 µg/plate.	Carver et al. (1986)

Table 4A. Summary of Perylene Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	NS (serial twofold dilution series starting at a high concentration of solubility or toxicity limit)	NDr	+ (TA98, TA1537, TA1538) ± (TA100) – (TA1535)	Plate incorporation method. Perylene was positive in TA98, TA1537, and TA1538 (>2-fold increase in revertants) and weakly positive in TA100 (1.5- to 2-fold increase in revertants) in the presence of metabolic activation. Perylene was negative in TA1535. Perylene-specific data on cell survival or compound solubility in the test medium were not reported, but the study authors indicated that the highest dose tested was based on solubility or toxicity limit.	De Flora et al. (1984)
Reverse mutation	*S. typhimurium* TA97, TA98, TA100, TA1535, TA1537, TA1538	40–80 nmol/plate	± TA100 – (TA97, TA98, TA1535, TA1537, TA1538)	± (strain[s] NS)	Plate incorporation method. Perylene was weakly positive (1.9-fold increase in revertants) in TA100 without metabolic activation. The addition of metabolic activation was “borderline activating” (no additional details or strain-specific information were reported). Perylene-specific data on cell survival or compound solubility in the test medium were not reported, but the study authors indicated that the highest dose tested was based on solubility or toxicity limit.	De Flora (1981)
Reverse mutation	*S. typhimurium* TA98, TA100	Up to 0.75 µmol/plate	± (strain NS)	+ (TA98) – (TA100)	Plate incorporation method. Perylene was positive in TA98 and negative in TA100 with metabolic activation. Perylene was noted to be “weakly mutagenic” without metabolic activation, but the magnitude of response and strain were not specified. No details were provided regarding cytotoxicity or compound solubility in the test medium.	Florin et al. (1980)
Reverse mutation	*S. typhimurium* TA97	Up to 400 nmol/plate	NDr	–	Liquid test and plate incorporation methods. No increase in revertants was observed with metabolic activation by either method. No details were provided regarding cytotoxicity or compound solubility in the test medium.	Hera and Pueyo (1988)

Table 4A. Summary of Perylene Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Reverse mutation	*S. typhimurium* TA98	0.001-0.020 mg/plate	NDr	+	Plate incorporation method. Revertants were increased two- to sixfold in TA98 in the presence of metabolic activation. No cytotoxicity was observed. No details were provided regarding compound solubility in the test medium.	Ho et al. (1981)
Reverse mutation	*S. typhimurium* TA100, TA98	10 or 20 µg/plate	NDr	+ (TA100) – (TA98)	Plate incorporation method. Revertants were increased two- to threefold in TA100 in the presence of metabolic activation. No evidence of mutagenicity was observed in TA98 with metabolic activation. No cytotoxicity was observed. No details were provided regarding compound solubility in the test medium.	Lavoie et al. (1979)
Reverse mutation	*S. typhimurium* TA98, TA100	1–40 µg/plate	–	+	Plate incorporation method. Perylene was positive in TA98 and TA100 in the presence of metabolic activation and negative in the absence of metabolic activation. No details were provided regarding cytotoxicity or compound solubility in the test medium.	Lofroth et al. (1984)
Reverse mutation	*S. typhimurium* TA97, TA98, TA100	1–50 µg/plate	–	+	Plate incorporation method. Revertants increased >twofold at all concentrations in TA97 and at ≥4 µg/plate in TA98 and TA100 with metabolic activation. No evidence of mutagenicity was observed without S9 activation. No cytotoxicity was observed. No details were provided regarding compound solubility in the test medium.	Sakai et al. (1985)
Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	0.1–1,000 µg/plate	–	–	Plate incorporation method. Revertants were increased <twofold in all strains with or without metabolic activation. Perylene-specific data on cell survival or compound solubility in the test medium were not reported, but (when observed) the study authors discussed cytotoxicity and solubility issues identified with other tested compounds.	Salamone et al. (1979)
Forward mutation	*S. typhimurium* BA9	Up to 400 nmol/plate	NDr	+	L-arabinose resistance assay. Perylene significantly increased the frequency of L-arabinose-resistant mutants in strain BA9 in the presence of a high concentration (33%) of S9; findings were not significant at 3% S9. No details were provided regarding cytotoxicity or compound solubility in the test medium.	Hera and Pueyo (1988)

Table 4A. Summary of Perylene Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Forward mutation	*S. typhimurium* TM677	1.1 µM	NDr	+	8-Azaguanine resistance assay. Perylene was mutagenic at the $8AG^s/8AG^r$ locus. No cytotoxicity was observed. No details were provided regarding compound solubility in the test medium.	Kaden et al. (1979)
Forward mutation	*S. typhimurium* TM677	2.6–40 µM	–	+	8-Azaguanine resistance assay. Perylene increased mutation rates for 8-azaguanine resistance in the presence of metabolic activation. Cell survival was >80% at all tested concentrations. No details were provided regarding compound solubility in the test medium.	Penman et al. (1980)
Forward mutation	*S. typhimurium* TM677	Up to 80 µM	NDr	+	8-Azaguanine resistance assay. Perylene increased mutation rates for 8-azaguanine resistance in the presence of metabolic activation. No cytotoxicity was observed. No details were provided regarding compound solubility in the test medium.	Thilly et al. (1983)
DNA damage	*Escherichia coli* PQ37	0.156–10 µg/assay	–	–	SOS chromotest. Perylene was negative for DNA damage with or without metabolic activation. No cytotoxicity was observed. No details were provided regarding compound solubility in the test medium.	Mersch-Sundermann et al. (1992)
DNA damage	*E. coli* PQ37	Three to five concentrations at half-log intervals up to limit of solubility or 100 mM	–	NDr	SOS chromotest. Criterion for positive response was not reported. Perylene was negative for DNA damage without metabolic activation. Perylene-specific data on cell survival or compound solubility in the test medium were not reported, but the study authors indicated that the highest dose tested was based on solubility limit (up to 100 mM).	von der Hude et al. (1988)
DNA repair	*E. coli* WP2, WP67, CM871	≤50 µg (eight twofold dilutions)	–	–	Liquid micromethod. The minimal inhibitory concentration was >50 µg with or without metabolic activation. Perylene-specific data on cell survival or compound solubility in the test medium were not reported, but the study authors indicated that the highest dose tested was based on solubility or toxicity limit.	De Flora et al. (1984)
DNA repair	*E. coli* WP2, WP67, CM871	≤50 µg/10^3 bacteria	–	±	2-H preincubation assay (treat-and-plate method). Survival did not differ between repair-deficient and wild-type strains without metabolic activation. Findings were equivocal with metabolic activation. No details were provided regarding compound solubility in the test medium.	De Flora et al. (1984)

Table 4A. Summary of Perylene Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Genotoxicity studies in mammalian cells—in vitro						
Mutation	Human lymphoblast cell line (AHH-1)	10 or 20 µM	–	NA	Forward mutation assay (6-thioguanine-resistance assay). There was no evidence of mutagenicity without exogenous metabolic activation (AHH-1 cells have endogenous metabolic capabilities). No cytotoxicity was observed. Concentrations >20 µM were not tested due to solubility issues.	Crespi and Thilly (1984)
Mutation	Human lymphoblast cell line (h1A1v2)	1–10,000 ng/mL	–	NA	Forward mutation assay (thymidine kinase locus). There was no evidence of mutagenicity without exogenous metabolic activation (h1A1v2 cells constitutively express cytochrome P4501A1). Cell survival was >75% at all tested concentrations. No details were provided regarding compound solubility in the test medium.	Durant et al. (1996)
Mutation	Human diploid lymphoblast cells	11 or 22 µM	NDr	–	Forward mutation assay (6-thioguanine-resistance assay). There was no evidence of mutagenicity with exogenous metabolic activation. No details were provided regarding compound solubility in the test medium.	Penman et al. (1980)
Mutation	Human diploid lymphoblast cells	11 or 22 µM	NDr	–	Forward mutation assay (thymidine kinase locus). There was no evidence of mutagenicity with exogenous metabolic activation. No details were provided regarding compound solubility in the test medium.	Penman et al. (1980)
CAs	Human peripheral leukocytes	10 µg/mL	–	NDr	There was no induction of CAs without metabolic activation. Of the metaphases scored in cells exposed to perylene, 0/200 showed chromosomal G bands (no other aberration types were scored). No cytotoxicity was observed. No details were provided regarding compound solubility in the test medium.	DiPaolo and Popescu (1974)
CAs	SHE cells	10 µg/mL	–	NDr	There was no induction of CAs without metabolic activation. Of the metaphases scored in cells exposed to perylene, 0/200 showed chromosomal G bands (no other aberration types were scored). No cytotoxicity was observed. No details were provided regarding compound solubility in the test medium.	DiPaolo and Popescu (1974)

Table 4A. Summary of Perylene Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
CAs	Chinese hamster V79 cells	10 µg/mL	+	NDr	Perylene increased the frequency of CAs (dicentric chromosomes, chromatid gaps, chromatid interchanges) without metabolic activation. The number of cell metaphases showing at least one aberration was 9/20 for perylene, compared to 0/20 for control. No details were provided regarding cytotoxicity or compound solubility in the test medium.	Popescu et al. (1977)
SCE	Chinese hamster V79 cells	10 µg/mL	–	NDr	There was no induction of SCE without metabolic activation. No details were provided regarding cytotoxicity or compound solubility in the test medium.	Popescu et al. (1977)
Unscheduled DNA synthesis	SHE cells	20 µg/mL	–	NDr	There was no induction of unscheduled DNA synthesis without metabolic activation. No details were provided regarding cytotoxicity or compound solubility in the test medium.	Casto et al. (1976)
DNA synthesis	Sprague Dawley rat primary hepatocytes	0.01–100 nM	–	NDr	3H-thymidine incorporation assay. Perylene did not induce DNA synthesis. Perylene was not tested at concentrations >100 nM due to cytotoxicity. No details were provided regarding compound solubility in the test medium.	Zhao and Ramos (1995)
Cell transformation	Bhas 42 cells (v-Ha-*ras*-transfected BALB/c 3T3 cell line)	0.01–10 µg/mL	+	NA	Initiation/promotion transformation assay. Perylene significantly increased the number of transformation foci/well in both the initiation stage of the assay (2-d treatment of low-density cells; ≥1 µg/mL) and promotion stage of the assay (12-d treatment of near confluent cells; ≥0.1 µg/mL) without exogenous metabolic activation (Bhas 42 cells have endogenous metabolic capabilities). No cytotoxicity was observed. No details were provided regarding compound solubility in the test medium.	Asada et al. (2005)
Cell transformation	SHE cells	Up to 20 µg/mL	–	NDr	Pretreatment with perylene did not increase transformation frequency associated with adenovirus infection. No cytotoxicity was observed. No details were provided regarding compound solubility in the test medium.	Casto et al. (1973)

Table 4A. Summary of Perylene Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Cell transformation	SHE cells	20 µg/mL	–	NDr	Perylene did not increase transformation frequency. When a promotor (TPA) was added 48 h after incubation with perylene, the percentage of transformed colonies was 0.54%. Cloning efficiency was comparable to control. No details were provided regarding compound solubility in the test medium.	Popescu et al. (1980)
DNA adducts/ binding	Human peripheral blood lymphocytes	30 µM	–	NDr	^{32}P-postlabeling analysis. No DNA adducts were detected in cells after perylene exposure. No details were provided regarding cytotoxicity or compound solubility in the test medium.	Gupta et al. (1988)
Genotoxicity studies—mammalian species in vivo						
SCE	Chinese hamster V79 cells implanted in mouse (C3H/St) peritoneal cavity; mice were injected with perylene after implantation	NS	–	NA	Host-mediated SCE assay. V79 cells were contained in diffusion chambers implanted in the peritoneal cavities of mice; V79 cells were examined for SCE frequencies after perylene injection (additional treatment details not reported). No increases of SCE frequency were detected with perylene compared to controls.	Sirianni and Huang (1978)
DNA adducts	Female BALB/c mice exposed via four topical applications at 0, 6, 30, and 54 h; sacrificed 24 h after last treatment	1.2 µmol	–	NA	^{32}P-postlabeling analysis. No adducts were detected in mouse skin.	Reddy et al. (1984)

[a]+ = positive; ± = weakly positive/equivocal; – = negative.

CA = chromosomal aberration; DNA = deoxyribonucleic acid; NA = not applicable; NDr = not determined; NS = not specified; SHE = Syrian hamster embryo; SCE = sister chromatid exchange; TPA = 12-*O*-tetradecanoylphorbol 13-acetate.

Mutagenicity

Of the available reverse mutation studies in *Salmonella typhimurium*, 10/13 reported that perylene was at least weakly mutagenic in the presence of metabolic activation in one or more strains (Carver et al., 1986, 1985; Sakai et al., 1985; De Flora et al., 1984; Lofroth et al., 1984; De Flora, 1981; Ho et al., 1981; Florin et al., 1980; Lavoie et al., 1979; Anderson and Styles, 1978) (see Table 4A). In general, perylene induced borderline or low reverse mutation rates in comparison to other mutagens (e.g., other PAHs) (Hera and Pueyo, 1988; Carver et al., 1986; De Flora et al., 1984; Lofroth et al., 1984; De Flora, 1981; Ho et al., 1981; Florin et al., 1980; Anderson and Styles, 1978). Three studies indicated that perylene was not mutagenic with metabolic activation (Hera and Pueyo, 1988; Anderson et al., 1987; Salamone et al., 1979). Two of these studies [Anderson et al. (1987) and Hera and Pueyo (1988)] used low concentrations of S9 (2−3%), which may have been inadequate to promote metabolic transformation; however, Salamone et al. (1979) reported negative results with 10% S9. Perylene also induced forward mutations in *S. typhimurium* strains in the presence of metabolic activation (Hera and Pueyo, 1988; Thilly et al., 1983; Penman et al., 1980; Kaden et al., 1979). In contrast to reverse mutations, the forward mutagenic potential of perylene in the 8-azaguanine resistance assay was similar or more potent compared to other PAHs (e.g., benzo[*a*]pyrene [BaP]) (Thilly et al., 1983; Penman et al., 1980; Kaden et al., 1979). In the absence of metabolic activation, perylene did not induce reverse mutations in *S. typhimurium* in four of six assays (Anderson et al., 1987; Sakai et al., 1985; Lofroth et al., 1984; Salamone et al., 1979) and was weakly mutagenic in one or more strains in two of six assays (De Flora, 1981; Florin et al., 1980). Perylene did not induce forward mutations in *S. typhimurium* in the absence of metabolic activation (Penman et al., 1980).

Perylene was not mutagenic in metabolically competent human cell lines (Durant et al., 1996; Crespi and Thilly, 1984) or in human cell lines with exogenous metabolic activation (Penman et al., 1980).

Clastogenicity

Evidence from in vitro studies in mammalian cells regarding clastogenicity is mostly negative. Sister chromatid exchanges (SCEs) were not observed in Chinese hamster V79 cells in the absence of metabolic activation (Popescu et al., 1977). Similarly, chromosomal aberrations (CAs), specifically chromosomal G bands, were not observed during metaphase in human peripheral lymphocytes or Syrian hamster embryonic (SHE) cells in the absence of metabolic activation (Popescu et al., 1977; DiPaolo and Popescu, 1974). However, the frequency of CAs was increased in Chinese hamster V79 cells without metabolic activation, including dicentric chromosomes, chromatid gaps, and chromatid interchanges (Popescu et al., 1977). None of the in vitro clastogenicity studies were conducted in the presence of metabolic activation. In a host-mediated assay, SCEs were not observed in Chinese hamster V79 cells implanted into the peritoneal cavity of mice prior to perylene injection (Sirianni and Huang, 1978).

DNA Damage and Repair

Findings were generally negative in in vitro assays of DNA damage and repair. In *Escherichia coli*, perylene did not induce DNA damage or repair without metabolic activation; with activation, findings were negative or equivocal/borderline (Mersch-Sundermann et al., 1992; von der Hude et al., 1988; De Flora et al., 1984). In mammalian cells, perylene did not induce DNA synthesis in Sprague Dawley rat primary hepatocytes or unscheduled DNA synthesis in SHE cells in the absence of metabolic activation; assays were not conducted in the presence of metabolic activation (Zhao and Ramos, 1995; Casto et al., 1976).

Perylene did not form DNA adducts in cultured human peripheral blood lymphocytes (Gupta et al., 1988). Similarly, no DNA adducts were identified in mouse skin following repeated topical application of perylene to shaved skin of mice (four exposures over 54 hours) (Reddy et al., 1984).

Cell Transformation

Perylene did not induce cell transformation in SHE cells in the absence of metabolic activation (Popescu et al., 1977; Casto et al., 1973). In an assay specifically designed to evaluate tumor initiation and promotion potentials of compounds, perylene induced transformation foci in metabolically competent Bhas 42 cells (derived from BALB/c mouse 3T3 cells) in both initiation and promotion stages (Asada et al., 2005).

2.3.2. Supporting Studies in Animals

Immunotoxicity

Humoral immunity in mice was not suppressed following subcutaneous (s.c.) injection of perylene for 1 or 14 days (see Table 4B), as measured by antibody responses to an antigen (sheep red blood cells [sRBCs]) in a plaque-forming cell (PFC) assay (White et al., 1985). The study also evaluated spleen weight, spleen cellularity, and thymus weight, and observed no statistically significant changes. A statistically significant increase in body weight was reported following a 14-day exposure to perylene. This study compared the response of perylene to the robust immunosuppressive response of BaP administered at the same dose level (40 mg/kg-day). It is unclear whether perylene would have elicited an immunosuppressive response if given at higher doses, for a longer duration, or via a different route of exposure. No additional in vivo studies evaluating immunotoxicity were identified. In an in vitro assay in human skin keratinocytes, perylene induced dose-dependent inflammatory cytokine secretion (interleukin-1α, interleukin-6) (Bahri et al., 2010).

Table 4B. Other Supporting Studies of Perylene				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Immunotoxicity in vivo studies				
T-cell-dependent antibody response study by s.c. injection	Female B6C3F1 mice (*n* = 8); daily s.c. injections containing 0 (corn oil vehicle) or 40 mg/kg-d (160 µmol/kg-d) for 1 or 14 d; spleen IgM response was evaluated 4 d after injection with sRBCs (body weight, spleen weight, thymus weight, cellularity, and number of PFCs).	No change in the spleen IgM response to sRBCs. No change in spleen or thymus weight or spleen cellularity. A statistically significant increase (~34%) in body weight was reported after the 14-d exposure.	Perylene did not impair humoral immunity in mice under the conditions of this study.	White et al. (1985)
Immunotoxicity in vitro studies				
Cytokine release and cytotoxicity in human keratinocytes	Keratinocytes (Clonetics) were dosed at various concentrations (1, 2, 5, 10, or 15 µM) with perylene, methylpyrene, or both dissolved in sodium dodecyl sulfate for 24 h−9 d (depending on endpoint). Cells were assessed for viability, colony forming efficiency, scrape-wound healing assay, apoptosis/necrosis, and cytokine secretion.	At the lowest tested concentration (1 µM), perylene decreased keratinocyte adhesion and viability in a concentration-dependent manner. Perylene reduced keratinocyte colony formation, and increased apoptosis. Interleukin-1α and interleukin-6 levels were significantly increased with increasing exposure to perylene (>2 µM). Toxicity was enhanced when perylene and methylpyrene were assessed as a mixture.	Perylene induced dose-dependent increases in inflammatory cytokine secretion and exerted a cytotoxic effect on human keratinocytes.	Bahri et al. (2010)
Carcinogenicity in vivo studies				
Dermal complete carcinogenicity study	Male C3H mice (*n* = 20); 60 µL of a 0.15% perylene solution in decalin per application; 2 times/wk for up to 82 wk. An appropriate negative control group was not included. BaP (0.14%) was used as a positive control.	Skin tumors Perylene: 0/16 (0%) Positive control (BaP): 15/21 (71%) (10 papillomas, 5 carcinomas) Note: Incidence is based on the number of mice alive at least 52 wk.	Perylene was not carcinogenic under the conditions of this study.	Horton and Christian (1974)

Table 4B. Other Supporting Studies of Perylene

Test	Materials and Methods	Results	Conclusions	References
Dermal complete carcinogenicity study	Male Swiss mice (*n* = 20); 0.3% perylene in benzene every 4 d for up to 24 wk; a benzene-only vehicle control group was not included. BaP (0.3%) was used as a positive control.	Skin tumors (unspecified) Perylene: 0/20 (0%) Positive control (BaP): 36/40 (90%)	Perylene was not carcinogenic under the conditions of this study.	Finzi et al. (1968)
Dermal complete carcinogenicity and initiation-promotion studies	Female CD-1 mice (number/group not specified); dermal application of 0 or 1% perylene 3 times/wk for 1 yr (vehicle not reported); a separate group of mice were initiated with a single 300 µg dermal dose of BaP followed by dermal application of 1% perylene 3 times/wk for 1 yr.	No increase in skin tumors in perylene or BaP + perylene treated mice, compared to vehicle control (incidence data not reported).	Perylene was not a complete carcinogen or tumor promotor under the conditions of this study. Data reporting is too limited for independent review (abstract only).	Anderson and Anderson (1987)
Dermal initiation-promotion study	Female Crl/CD-1(ICR)BR mice (*n* = 20); dermal application of 1 mg perylene in acetone applied in 10 doses (every other day), followed by 2.5 µg TPA in 0.1 mL acetone 3 times/wk for 25 wk; the vehicle control group was acetone with TPA promotion. BaP (0.05 mg) was used as a positive control.	Skin tumors ("predominantly" papillomas) Acetone + TPA: 1/20 (5%) Perylene + TPA: 1/20 (5%) Positive control (BaP + TPA): 18/20 (90%)	Perylene was not a tumor initiator under the conditions of this study.	El-Bayoumy et al. (1982)
Dermal initiation-promotion study	Female ICR/Ha Swiss mice (*n* = 20); single dermal application of 800 µg perylene in benzene followed by 2.5 µg TPA in 0.1 mL acetone 3 times/wk for 58–60 wk; four control groups were used: untreated, acetone, perylene initiating dose only, and TPA-only (with no initiator). A benzene vehicle control was not included. DMBA (20 µg in acetone) was used as a positive control.	Skin tumors Untreated control: 0/20 (0%) Acetone control: 0/20 (0%) Perylene only: 0/20 (0%) TPA only: 1/20 (5%) (1 papilloma) Perylene + TPA: 3/20 (15%) (3 papillomas) Positive control (DMBA + TPA): 19/20 (95%) (13 carcinomas, 6 papillomas)	Perylene was not a tumor initiator under the conditions of this study. Perylene may be a weak tumor initiator; papilloma incidence was slightly increased compared to controls but did not reach statistical significance.	Van Duuren et al. (1970)

Table 4B. Other Supporting Studies of Perylene

Test	Materials and Methods	Results	Conclusions	References
Dermal cocarcinogenicity study	Male C3H mice (*n* = 20); 60 µL of a 0 or 0.15% perylene solution in a 50:50 decalin:dodecane (De:Do) vehicle per application; 2 times/wk for up to 82 wk. BaP (0.14%) was used as a positive control using 100:0, 80:20, or 60:40 De:Do vehicle. Dodecane was selected as the cocarcinogen because it had previously been shown to be a skin cocarcinogen with benz[*a*]anthracene but is not a skin carcinogen when administered alone.	Skin tumors Vehicle control: 2/13 (15%) (2 papillomas) Perylene: 1/15 (7%) (1 papilloma) Positive control (BaP): 100% decalin: 15/21 (71%) (5 carcinomas, 10 papillomas) 80:20 De:Do: 13/15 (87%) (6 carcinomas; 7 papillomas) 60:40 De:Do: 15/15 (100%) (15 carcinomas) Note: Incidence is based on the number of mice alive at least 52 wk.	Perylene was not cocarcinogenic (with dodecane) under the conditions of this study.	Horton and Christian (1974)
Dermal tumor inhibition study	Male Swiss mice (*n* = 40); 0.3% BaP in benzene or 0.3% perylene and 0.3% BaP in benzene every 4 d for up to 24 wk.	Skin papillomas BaP: 36/40 (90%) BaP + perylene: 13/40 (30%)	Perylene inhibited the tumorigenic response of BaP under the conditions of this study. Statistical analysis of results was not performed by the study authors.	Finzi et al. (1968)
Lung tumor study by i.p. injection	Strain A mice (sensitive model for lung tumor induction); i.p. injection of 0, 200, 500, or 1,000 mg/kg perylene 3 times/wk for 8 wk followed by a 16-wk observation period.	No increase in lung adenomas compared to control (vehicle not reported; incidence data not reported).	Perylene did not induce lung tumors under the conditions of this study. Data reporting is too limited for independent review (abstract only).	Anderson and Anderson (1987)

BaP = benzo[*a*]pyrene; DMBA = 7,12-dimethylbenz[*a*]anthracene; IgM = immunoglobulin M; i.p. = intraperitoneal; *n* = number; s.c. = subcutaneous; sRBC = sheep red blood cell; PFC = plaque forming colony; TPA = 12-*O*-tetradecanoylphorbol acetate.

Cancer

Available skin painting studies (see Table 4B), while limited by design flaws (lack of negative controls, potentially inadequate dose levels, small group sizes) and/or limited reporting (abstract only), do not indicate that perylene is a complete dermal carcinogen or cocarcinogen. No skin tumors were observed in 16 mice following exposure to 0.15% perylene twice weekly in a decalin vehicle for up to 82 weeks; in contrast, the same protocol with 0.14% BaP induced skin tumors (Horton and Christian, 1974). Similarly, no skin tumors were observed in 20 mice exposed to 0.3% perylene in benzene every 4 days for up to 24 weeks, while exposure to 0.3% BaP induced skin tumors using the same protocol (Finzi et al., 1968). In a study only available as an abstract, dermal application of 1% perylene (vehicle not reported) 3 times weekly for 1 year did not increase the number of skin tumors, compared to vehicle control (incidence data not reported) (Anderson and Anderson, 1987).

Skin tumor initiation-promotion studies do not indicate that perylene is a strong tumor initiator or promotor. Perylene was not a mouse skin tumor initiator following single exposure (800 µg in benzene) or 10 repeated exposures (total dose 1 g in acetone) with 12-*O*-tetradecanoylphorbol-13 acetate (TPA) as a promotor (El-Bayoumy et al., 1982; Van Duuren et al., 1970). In both studies, the positive control group (BaP or 7,12-dimethylbenz[*a*]anthracene) showed expected tumor-initiating activity. In a study only available as an abstract, perylene was not a tumor promotor when applied as a 1% solution (vehicle not reported) 3 times weekly for 1 year following a single initiating dose of 300 µg BaP (Anderson and Anderson, 1987).

Two dermal studies also evaluated carcinogenic potential of perylene in the presence of other chemicals. Horton and Christian (1974) evaluated cocarcinogenic potential of 0.15% perylene twice weekly in a decalin/dodecane vehicle (50:50 ratio). Dodecane had previously been shown to be a skin cocarcinogen with benz[*a*]anthracene, but is not a skin carcinogen when administered alone (Horton and Christian, 1974). Animals coexposed to perylene did not have significantly increased skin papillomas (1/15) compared with animals exposed only to decalin/dodecane (2/13). In contrast, BaP and dodecane showed evidence of cocarcinogenicity following a similar protocol (Horton and Christian, 1974). In a study by Finzi et al. (1968), perylene coexposure decreased the number of skin tumors induced by BaP (13/40) compared to BaP alone (36/40); however, statistical analysis of the data was not performed. The study authors proposed that perylene prevented BaP-induced tumor formation via competitive binding to epidermal proteins.

In a study only available as an abstract, intraperitoneal (i.p.) injections of perylene at doses of 200–1,000 mg/kg 3 times/week for 8 weeks did not induce lung tumors in Strain A mice, a sensitive model for detecting lung tumor induction, following a 16-week postexposure observation period (Anderson and Anderson, 1987). Due to the limitations of these available injection and dermal cancer studies, it is not possible to thoroughly assess perylene's carcinogenic potential following oral and inhalation exposures.

2.3.3. Metabolism/Toxicokinetic Studies

There is limited information available on in vivo toxicokinetics or metabolism of perylene. A single study evaluated metabolism in rat subcutaneous tissue following s.c. injection of various PAHs (Flesher and Myers, 1990). In this study, perylene did not show any evidence of bioalkylation or metabolism within subcutaneous tissue. In contrast, a weakly carcinogenic PAH, benz[*a*]anthracene, showed evidence of bioalkylation substitution reactions in rat subcutaneous

tissue. Other tissues in the body were not evaluated for parent compound or metabolite levels in this study. No other studies were identified to evaluate in vivo toxicokinetics or metabolism of perylene. Because absorption and distribution of a chemical in the body are determined largely by physical and chemical properties related to chemical size and general structure (e.g., lipophilicity, vapor pressure, etc.), it is reasonable to assume that perylene will be absorbed and distributed similarly to other PAHs of similar size and structure with similar physical and chemical properties (e.g., BaP). PAHs, in general, are metabolized in multiple tissues in the body into more soluble metabolites, including dihydrodiols, phenols, quinones, and epoxides, that form conjugates with glucuronide, glutathione (GSH), or sulfate (U.S. EPA, 2017b; IARC, 2010; ATSDR, 1995).

Several studies have evaluated the potential for perylene to induce metabolic enzymes. Most studies have focused on aryl hydrocarbon hydroxylase (AHH), an enzyme induced by many PAHs (Neubert and Tapken, 1988; Asokan et al., 1986; Mukhtar et al., 1982; Neubert and Tapken, 1978). Findings for AHH induction by perylene are mixed. In dermal studies with neonatal rats, Asokan et al. (1986) reported a significant 1.6-fold induction of AHH in neonatal rat skin, but not neonatal liver, while Mukhtar et al. (1982) observed the opposite (a significant 1.6-fold increase in AHH in neonatal liver, but not the skin). In both studies, the induction by perylene was approximately an order of magnitude lower than known inducers (e.g., 3-methyl-cholanthrene, 7,12-demethylbenzanthracene). During gestational exposures, both AHH activity and overall "BaP hydrolase" activity were elevated in maternal livers, but not in fetal livers (Neubert and Tapken, 1988, 1978). "BaP hydrolase" activity was measured as total BaP breakdown, as opposed to activities of specific hydrolase enzymes. In these studies, the magnitude of perylene enzyme induction was ~25% lower than induction by BaP. In male rats, i.p. injections of perylene did not induce AHH in the liver (Harris et al., 1988). In vitro, perylene is a weak inducer of AHH and a weak binder of aryl hydrocarbon receptors (AhRs) in rat hepatocytes (Piskorska-Pliszczynska et al., 1986).

In general, exposure to perylene did not lead to induction of other metabolic enzymes measured in skin and/or liver, including 7-ethoxyresorufin *O*-deethylase (EROD), 7-ethoxycoumarin *O*-deethylase (ECOD), benzphetamine *n*-demethylase (BPD), nicotinamide adenine dinucleotide phosphate (NADPH)-cytochrome c, nicotinamide adenine dinucleotide hydrogen (NADH)-ferricyanide reductase, or cytochrome P450 (CYP450) (Harris et al., 1988; Asokan et al., 1986; Mukhtar et al., 1982). Following i.p. exposure to perylene, there was no evidence of induction of glycolytic enzymes, pyruvate kinase, or lactate dehydrogenase in the mouse lung (Rády et al., 1981; Rády et al., 1980).

3. DERIVATION OF PROVISIONAL VALUES

3.1. DERIVATION OF PROVISIONAL REFERENCE DOSES

No studies were located regarding toxicity of perylene to humans or animals via oral exposure. Due to the lack of oral toxicity data for perylene, subchronic and chronic provisional reference doses (p-RfDs) were not derived directly. Instead, screening subchronic and chronic p-RfDs are derived in Appendix A using an alternative analogue approach. Based on the overall analogue approach presented in Appendix A, BaP was selected as the most appropriate analogue for perylene for deriving screening subchronic and chronic p-RfDs (see Table 5).

3.2. DERIVATION OF PROVISIONAL REFERENCE CONCENTRATIONS

No studies were located regarding toxicity of perylene to humans or animals via inhalation exposure. Due to the lack of inhalation toxicity data for perylene, subchronic and chronic provisional reference concentrations (p-RfCs) were not derived directly. Instead, screening subchronic and chronic p-RfCs are derived in Appendix A using an alternative analogue approach. Based on the overall analogue approach presented in Appendix A, BaP was selected as the most appropriate analogue for perylene for deriving screening subchronic and chronic p-RfCs (see Table 5).

3.3. SUMMARY OF NONCANCER SCREENING PROVISIONAL REFERENCE VALUES

The noncancer screening provisional reference values for perylene are summarized in Table 5.

Table 5. Summary of Noncancer Reference Values for Perylene (CASRN 198-55-0)

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD (HED/HEC)	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-d)	Rat/ M, F	Neurobehavioral effects following early postnatal exposure	9×10^{-5}	$BMDL_{1SD}$	0.092[a] (based on analogue POD)	1,000	Chen et al. (2012); U.S. EPA (2017a)
Screening chronic p-RfD (mg/kg-d)	Rat/ M, F	Neurobehavioral effects following early postnatal exposure	9×10^{-5}	$BMDL_{1SD}$	0.092[a] (based on analogue POD)	1,000	Chen et al. (2012); U.S. EPA (2017a)
Screening subchronic p-RfC (mg/m^3)	Rat/F	Decreased embryo/fetal survival	2×10^{-6}	LOAEL	0.0046 (based on analogue POD)	3,000	Archibong et al. (2002); U.S. EPA (2017a)
Screening chronic p-RfC (mg/m^3)	Rat/F	Decreased embryo/fetal survival	2×10^{-6}	LOAEL	0.0046 (based on analogue POD)	3,000	Archibong et al. (2002); U.S. EPA (2017a)

[a]The POD was not converted into a HED using $BW^{3/4}$ because it is unknown whether allometric scaling is appropriate for exposure in early postnatal animals (see Appendix A for more details).

BMDL = benchmark dose lower confidence limit; BW = body weight; F = female(s); HEC = human equivalent concentration; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; M = male(s); POD = point of departure p-RfC = provisional inhalation reference concentration; p-RfD = provisional oral reference dose; SD = standard deviation; UF_C = composite uncertainty factor.

3.4. CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Although the scientific literature provides limited information on the mutagenicity and genotoxicity of perylene, no oral or inhalation studies have been conducted to assess its carcinogenicity. Available dermal studies and a single i.p. carcinogenicity study provide limited evidence of carcinogenic potential; the relevance of these findings to oral or inhalation exposure is unclear. Under the U.S. EPA Cancer Guidelines (U.S. EPA, 2005), there is "*Inadequate Information to Assess Carcinogenic Potential*" of perylene by oral or inhalation exposure (see Table 6).

Table 6. Cancer WOE Descriptor for Perylene (CASRN 198-55-0)

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	No human data are available.
"Likely to be Carcinogenic to Humans"	NS	NA	No adequate chronic animal cancer bioassays are available.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	No adequate chronic animal cancer bioassays are available.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**No adequate chronic animal cancer bioassays are available. Dermal and i.p. studies in animals provide limited evidence of carcinogenic potential.**
"Not Likely to be Carcinogenic to Humans"	NS	NA	No evidence of noncarcinogenicity following oral or inhalation exposure is available. No adequate chronic animal cancer bioassays are available.

i.p. = intraperitoneal; NA = not applicable; NS = not selected; WOE = weight of evidence.

3.5. DERIVATION OF PROVISIONAL CANCER RISK ESTIMATES

Due to inadequate information to assess carcinogenic potential, quantitative cancer risk estimates could not be derived for perylene (see Table 7).

Table 7. Summary of Cancer Risk Estimates for Perylene (CASRN 198-55-0)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	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.

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 perylene. However, some information is available for this chemical, which although insufficient to support derivation of provisional toxicity values under current guidelines, may be of use to risk assessors. In such cases, the Center for Public Health and Environmental Assessment (CPHEA) summarizes available information in an appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the provisional reference values to ensure their appropriateness within the limitations detailed in the assessment. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there could be more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the CPHEA.

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). 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 Wang et al. (2012) was developed to collect a more 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 (NLM, 2022a), the CompTox Chemicals Dashboard (U.S. EPA, 2022c), and the Organisation for Economic Co-operation and Development (OECD) Quantitative Structure-Activity Relationship (QSAR) Toolbox (OECD, 2022), 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 Beta version, 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 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], California Environmental Protection Agency [CalEPA], 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.

During the development of a systematic evidence map (SEM), toxicokinetic studies were identified and tagged as potentially relevant supplemental material. These studies were used to identify metabolic analogues (metabolites and metabolic precursors). Metabolites were also identified from the two OECD QSAR Toolbox 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, CalEPA, U.S. EPA IRIS, PPRTV assessments).

In vivo toxicity data for the target chemical (if available from the SEM) are evaluated to determine whether specific or characteristic toxicity was observed (e.g., cholinesterase inhibition, inhibition of oxidative phosphorylation). In addition, in vitro mechanistic data tagged as potentially relevant supplemental material from the SEM or obtained from tools including GenRA, ToxCast/Tox21, and Comparative Toxicogenomics Database (CTD) (CTD, 2022; Davis et al., 2021) were evaluated for this purpose. Data from CompTox Chemicals Dashboard ToxCast/Tox21 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, CalEPA, U.S. EPA IRIS, PPRTV assessments).

The tools used for the expanded analogue searches were selected because they are publicly available, which allows for transparency and reproducibility of the results, and because they are supported by U.S. and OECD agencies, updated regularly, and widely used. 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.

Analogue Search Results for Perylene

Candidate analogues for perylene were identified based on metabolic relationships, structural relationships, and toxicodynamic relationships. For candidates identified through these approaches, the U.S. EPA (IRIS and PPRTV assessments), ATSDR, and CalEPA sources were

searched for subchronic, intermediate, and chronic oral and inhalation toxicity values. Details are provided below (see "Identification of Structural Analogues with Established Toxicity Values").

Identification of Structural Analogues with Established Toxicity Values

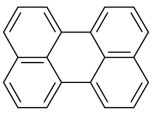
Perylene is not a member of an existing OECD or New Chemical category. Candidate structural analogues for perylene were identified using similarity searches in the OECD Toolbox, the U.S. EPA CompTox Chemicals Dashboard, and ChemIDplus tools (NLM, 2022a; OECD, 2022; U.S. EPA, 2022a). A total of 521 unique structural analogues were identified for perylene in the Dashboard, OECD QSAR Toolbox, and ChemIDplus (80% similarity threshold).

The list of potential analogues was reviewed by a chemist with expertise in read-across. Criteria for including/excluding candidates were as follows:

1. Exclude compounds with elements other than carbon and hydrogen.
2. Include compounds with four, five, or six fused six-carbon aromatic rings.
3. Exclude compounds with smaller or larger rings (greater than six or less than six carbon rings).
4. Include only compact, condensed compounds:
   a. compounds containing the pyrene fragment (17 compounds); or
   b. at least one ring shares bonds with three or more other rings (12 compounds).

Using these criteria, a total of 29 candidate structural analogues for perylene were identified, as shown in Table A-1. Two of the candidate structural analogues had relevant toxicity values: benzo[*a*]pyrene (BaP) and pyrene.

Table A-1. Candidate Structural Analogues Identified for Perylene based on Tools and Expert Judgment



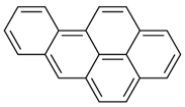
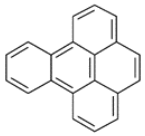
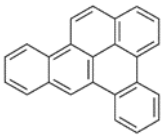
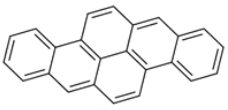
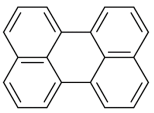
Tool (method)[a]	Analogue (CASRNs) Selected for Toxicity Value Searches[b]	Structure
Dashboard (Tanimoto method), OECD Toolbox (Dice method), and ChemIDplus (method not described)	**Benzo[*a*]pyrene (CASRN 50-32-8)**	
	Benzo[*e*]pyrene (CASRN 192-97-2)	
	Dibenzo(*a,e*)pyrene (CASRN 192-65-4)	
	Dibenzo[*a,h*]pyrene (CASRN 189-64-0)	

Table A-1. Candidate Structural Analogues Identified for Perylene based on Tools and Expert Judgment



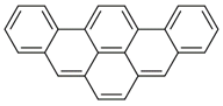
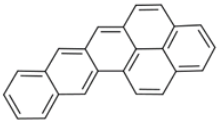
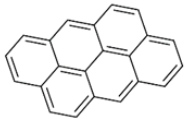
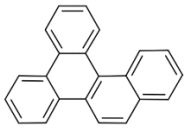
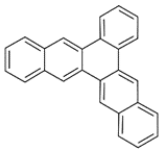
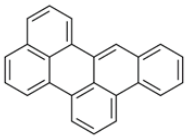
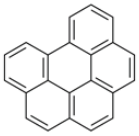
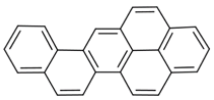
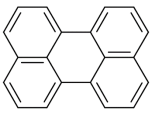
Tool (method)[a]	Analogue (CASRNs) Selected for Toxicity Value Searches[b]	Structure
	Dibenzo[*a,i*]pyrene (CASRN 189-55-9)	
	Dibenzo[*a,l*]pyrene (CASRN 191-30-0)	
	Naphtho(2,1,8-*qra*)naphthacene (CASRN 196-42-9)	
Dashboard (Tanimoto method) and ChemIDplus (method not described)	Anthanthrene (CASRN 191-26-4)	
	Benzo(*g*)chrysene (CASRN 196-78-1)	
	Benzo(*h*)pentaphene (CASRN 214-91-5)	
	Benzo(*a*)perylene (CASRN 191-85-5)	
	Benzo[*b*]perylene (CASRN 197-70-6)	
	Benzo(*g,h,i*)perylene (CASRN 191-24-2)	
	Benzo(*pqr*)picene (CASRN 189-96-8)	

Table A-1. Candidate Structural Analogues Identified for Perylene based on Tools and Expert Judgment



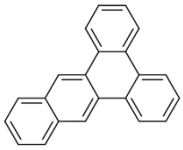
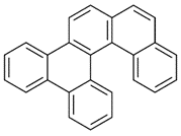
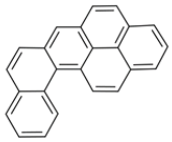
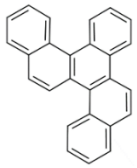
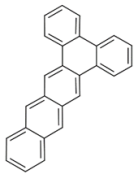
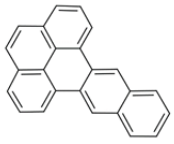
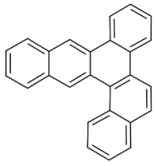
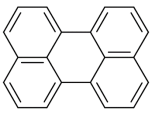
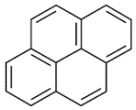
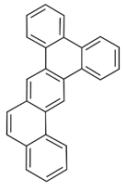
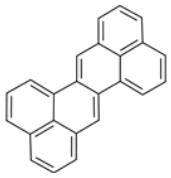
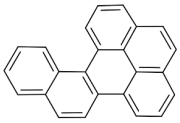
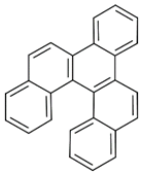
Tool (method)[a]	Analogue (CASRNs) Selected for Toxicity Value Searches[b]	Structure
	Dibenz[*a,c*]anthracene (CASRN 215-58-1)	
	Dibenzo[*c,g*]chrysene (CASRN 53156-66-4)	
	Dibenzo(*c,mno*)chrysene (CASRN 196-28-1)	
	Dibenzo(*c,p*)chrysene (CASRN 196-52-1)	
	Dibenzo(*g,p*)chrysene (CASRN 191-68-4)	
	Dibenzo(*a,c*)naphthacene (CASRN 216-00-2)	
	Dibenzo(*de,qr*)naphthacene (CASRN 193-09-9)	
	Dibenzo(*fg,op*)naphthacene (CASRN 192-51-8)	
	Naphtho(2,3-*g*)chrysene (CASRN 196-64-5)	

Table A-1. Candidate Structural Analogues Identified for Perylene based on Tools and Expert Judgment



Tool (method)[a]	Analogue (CASRNs) Selected for Toxicity Value Searches[b]	Structure
	Pyrene (CASRN 129-00-0)	
	Tribenz(*a,c,h*)anthracene (8CI)(9CI) (CASRN 215-26-9)	
	Triphenylene (CASRN 217-59-4)	
Dashboard (Tanimoto)	Dibenzo[*de,mn*]tetracene (CASRN 214-63-1)	
	Dibenzo[*ij,no*]tetraphene (CASRN 143214-92-0)	
	Naphtho[1,2-*g*]chrysene (CASRN 112772-15-3)	

[a]80% similarity threshold was applied.
[b]**Bold** shows compounds with oral or inhalation toxicity values.

Identification of Toxicokinetic Precursors or Metabolites with Established Toxicity Values

Experimental studies identifying metabolites of perylene were not identified in the scientific literature. Metabolism of other polycyclic aromatic hydrocarbons (PAHs) has been investigated extensively in both in vitro and in vivo studies (U.S. EPA, 2017a, b; ATSDR, 1995). Metabolites resulting from oxidation of PAHs include epoxides, dihydrodiols, phenols, and quinones (U.S. EPA, 2017a, b; ATSDR, 1995). Oxidized forms of perylene are candidate metabolites based on known metabolic pathways involving cytochrome P450 (CYP450) oxidation of other PAHs such as naphthalene, pyrene, and BaP (Shimada and Fujii-Kuriyama, 2004; ATSDR, 1995). Predicted metabolites of perylene were collected from the OECD QSAR

Toolbox (OECD, 2022). PubMed searches (searching "perylene" or "198-55-0" and "metabolite") were conducted to identify metabolic precursors to perylene. No metabolic precursors were identified. PubMed was also searched to identify other compounds that are metabolized to any of the observed or predicted metabolites of perylene (searching the metabolite name or [CASRN if available] and "metabolite"). No compounds that share at least one metabolite with perylene were identified in these searches.

Table A-2 summarizes the candidate metabolic analogues for perylene. The predicted metabolites of perylene are a result of CYP450 oxidation occurring at the 1- (bay) or 3- (peri) positions of the aromatic rings. Searches for relevant toxicity values for the candidate metabolic analogues of perylene did not identify oral or inhalation toxicity values for any of the observed or predicted metabolites.

Table A-2. Candidate Metabolic Analogues of Perylene

Relationship to Perylene	Compound
Metabolic precursor	None identified
Predicted metabolites[a]	3-Hydroxy-perylene[b]
	1-Hydroxy-perylene[b]
Shares common metabolite(s)	None identified

[a]Predicted metabolites of perylene were collected from the OECD QSAR Toolbox (OECD, 2022).
[b]CASRN not available for this metabolite.

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

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

The toxicological data for perylene, described in the main PPRTV assessment above, do not suggest any specific, characteristic toxicity (e.g., cholinesterase inhibition, inhibition of oxidative phosphorylation) that could be used to identify candidate analogues. One study examining immunosuppression after short-term subcutaneous administration of perylene in mice (White et al., 1985) showed no evidence of immunosuppression. No other relevant toxicity or mechanistic studies on perylene were identified.

Perylene was active in 11 PubChem bioactivity assays reported in the Dashboard (U.S. EPA, 2020b) but was not active in the three available ToxCast/Tox21 assays (U.S. EPA, 2020a). The GenRA option within the Dashboard offers an option to search for analogues based on similarities in activity in ToxCast/Tox21 in vitro assays; however, because perylene was not active in any ToxCast assays, there were no results (U.S. EPA, 2020c).

The CTD (2022) identified several compounds with gene interactions similar to interactions induced by perylene. In the CTD, similarity is measured by the Jaccard index, calculated as the size of the intersection of interacting genes for chemical A and chemical B divided by the size of the union of those genes (range from 0 [no similarity] to 1 [complete similarity]). Among the compounds with gene interactions similar to perylene, the numbers of

common gene interactions ranged from 1 to 2 and similarity indices ranged from 0.33 to 0.67. Although there was one compound with a similarity index over 0.5 (1-methylfluorene, CASRN 1730-37-6, similarity index of 0.67), the similarity was based on only two gene interactions and there were no relevant toxicity values available for this chemical, so it was not considered a candidate analogue.

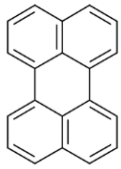
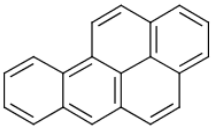
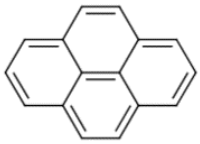
Summary

Searches for structural, metabolic, and toxicity/mechanistic analogues for perylene yielded a total of 31 unique candidate analogues: 2 metabolites and 29 structural analogues. Neither of the identified metabolic analogues had oral or inhalation noncancer toxicity values. Of the 29 structural candidates, 1 had relevant oral and inhalation noncancer toxicity values (BaP) and 1 had relevant oral noncancer toxicity values (pyrene).

Structural Analogues

BaP and pyrene were identified as candidate analogues of perylene based on structural similarity. Table A-3 illustrates the chemical structures and summarizes the physicochemical properties for perylene and the two candidate analogues. All three compounds are members of the PAH class of chemicals and are nonsubstituted PAHs. Perylene and BaP consist of five benzene rings, while pyrene contains only four benzene rings. Due to the aromatic ring number, perylene and BaP share the same molecular weight, while the molecular weight of pyrene is lower. Some physicochemical properties are similar for the target compound and both analogues. For example, melting points show that all the compounds are solids at room temperature. In addition, perylene and both candidate analogues have the potential for moderate volatilization from water to air based on their Henry's law constant values. Considering vapor pressure, water solubility and, octanol-water partition coefficient (log K_{ow}) values presented in Table A-3, BaP appears to be more similar to perylene than pyrene. Although all three compounds are expected to have low volatility from dry surfaces and will exist as particulates in the atmosphere, perylene and BaP, with vapor pressures of $> 5 \times 10^{-9}$ mm Hg, have lower potential for inhalation exposure as gases or vapors than does pyrene. Water solubility is considerably lower for perylene and BaP, compared to pyrene, and the log K_{ow} values for perylene and BaP are higher than that of pyrene. In general, compounds with log K_{ow} values >4 are considered hydrophobic chemicals, which are likely to partition to fat compartments in the body following absorption (Schwarzenbach et al., 2016). Consequently, partitioning to fat will be greater for perylene and BaP, compared to pyrene. Based on structural characteristics (i.e., five- vs. four-ring PAHs) and some physicochemical properties (vapor pressure, water solubility, log K_{ow}), BaP is a more similar candidate structural analogue to perylene than is pyrene.

Table A-3. Physical-Chemical Properties of Perylene and Candidate Structural Analogues

Chemical	Perylene[a]	BaP[b]	Pyrene[c]
Structure			
CASRN	198-55-0	50-32-8	129-00-0
Molecular weight (g/mol)	252.32	252.32	202.26
Melting point (°C)	274	177	150
Boiling point (°C)	>350 (estimated range 443−487)	495	399
Vapor pressure (mm Hg at 25°C)	5.25×10^{-9}	5.49×10^{-9}	4.5×10^{-6}
Henry's law constant (atm-m^3/mole)	1.06×10^{-6} (predicted average)	4.57×10^{-7}	1.19×10^{-5}
Water solubility (mg/L)	1.58×10^{-9}	8.40×10^{-9}	6.65×10^{-7}
Octanol-water partition coefficient (log K_{ow})	6.04	6.13	4.88

[a]The U.S. EPA CompTox Chemicals Dashboard (perylene CASRN 198-55-0) (U.S. EPA, 2022c). Accessed on January 18, 2023.
[b]The U.S. EPA CompTox Chemicals Dashboard (benzo[*a*]pyrene CASRN 50-32-8) (U.S. EPA, 2022b). Accessed on January 18, 2023.
[c]The U.S. EPA CompTox Chemicals Dashboard (pyrene CASRN 129-00-0) (U.S. EPA, 2022d). Accessed on January 18, 2023.
All values are experimental averages unless otherwise specified.

Structural alerts and predictions for genotoxicity and carcinogenicity were identified using computational tools as follows. Relevant structural alerts and toxicity predictions for noncancer health effects were identified using computational tools from the OECD (2022) QSAR Toolbox profilers, OCHEM (2022) ToxAlerts, and IDEAconsult (2018) Toxtree. The model results for perylene and its candidate analogue compounds are shown in Figure A-1. Concerns for protein binding, hepatotoxicity, renal toxicity, developmental/reproductive toxicity, metabolism/reactivity, and endocrine receptor binding are indicated for perylene and its candidate analogues. Based on structural alerts, BaP is a more similar candidate analogue to perylene than is pyrene.

Structural Category	Compounds (CASRN)			
	Perylene (198-55-0)	**Benzo[*a*]pyrene (50-32-8)**	**Pyrene (129-00-0)**	**Source**
Protein Binding				
Protein binding (based on a Michael Acceptor alert for a predicted hydroxylated metabolite)				Toxtree
Hepatotoxicity				
Hepatotoxicity (based on alerts for 3-methylcholanthrene)—Hazard Evaluation Support System (HESS)				OECD QSAR Toolbox
Hepatotoxicity (based on alerts for tamoxifen)—HESS				OECD QSAR Toolbox
Hepatotoxicity (based on alerts for α-naphthylisothiocyanate)—HESS				OECD QSAR Toolbox
Hepatotoxicity (based on alerts for carbamazepine)—HESS				OECD QSAR Toolbox
Hepatotoxicity (based on alerts for β-naphthylisothiocyanate)—HESS				OECD QSAR Toolbox
Hepatotoxicity (based on alerts for oxyphenisatin—HESS				OECD QSAR Toolbox
Hepatotoxicity (based on alerts for methylclofenapate)—HESS				OECD QSAR Toolbox
Renal Toxicity				
Renal toxicity (based on alerts for 2-amino-4,5-diphenyl thiazole) —HESS				OECD QSAR Toolbox
Renal toxicity (based on alerts for anthraquinone)—HESS				OECD QSAR Toolbox
Renal toxicity (based on alerts for carbamazepine)—HESS				OECD QSAR Toolbox
Developmental/Reproductive Toxicity				
Aryl hydrocarbon receptor (AhR) binders and prostaglandin receptor agonists (based on polycyclic aromatic hydrocarbons [PAHs]); potential for reproductive/ developmental toxicity (Developmental and Reproductive Toxicity [DART] scheme)—DART				OECD QSAR Toolbox
Metabolism/Reactivity				
Liver enzyme induction (based on aromatic hydrocarbons alert, Rank C)—HESS				OECD QSAR Toolbox
Endocrine Receptor Binding				
Estrogen receptor binding affinity potential (based on multicyclic hydrocarbons)—Estrogen Receptor Expert System (rtER Expert System)				OECD QSAR Toolbox

Model results or structural alerts indicating concern for toxicity.
Model results or structural alert indicating no concern for toxicity.
Models with results are presented in the heat map (models without results were omitted).

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

Figure A-1. Structural Alerts for Perylene and Candidate Analogues

Toxtree indicated the potential for protein binding based on predicted hydroxylated metabolites for perylene and both candidate analogues. PAHs, in general, are metabolized in multiple tissues in the body into more soluble metabolites, including dihydrodiols, phenols, quinones, and epoxides, that form conjugates with glucuronide, glutathione (GSH), or sulfate (U.S. EPA, 2017b; IARC, 2010; ATSDR, 1995). There is also limited experimental evidence of perylene metabolism (see Section 2.3.3)

The OECD QSAR Toolbox Hazard Evaluation Support System (HESS) model showed a concern for hepatotoxicity for perylene and both analogues based on structural similarity to 3-methylcholanthrene (inducer of hepatic enzymes) and tamoxifen (hepatic steatosis). There is supportive evidence for hepatic enzyme induction for both analogues and limited experimental evidence of perylene inducing various hepatic enzymes including AHH, "BaP hydrolase," 7-ethoxyresorufin *O*-deethylase (EROD), 7-ethoxycoumarin *O*-deethylase (ECOD), benzphetamine *n*-demethylase (BPD), and other CYP450 enzymes (see Section 2.3.3). The HESS model also showed a concern for hepatotoxicity for perylene and BaP based on structural similarity to α-naphthylisothiocyanate, which induces cholestasis, hyper-bilirubinemia, and necrotic injury in biliary epithelial cells. Concerns for perylene were also predicted based on a structural alert for carbamazepine, which is associated with vanishing bile duct syndrome; neither candidate analogue showed this alert. Other structural alerts showing concern for hepatotoxicity for BaP and/or pyrene (based on structural similarity to β-naphthylisothiocyanate, oxyphenisatin, or methylclofenapate) were not alerts for perylene.

The OECD QSAR Toolbox HESS model showed a concern for renal toxicity for perylene and both analogues based on structural similarity to 2-amino-4,5-diphenyl thiazole (renal polycystic disease). The HESS model also showed a concern for renal toxicity for perylene and BaP based on structural similarity to anthraquinone (renal degeneration). Concerns for perylene were also predicted based on a structural alert for carbamazepine, which is associated with acute renal failure, hyponatremia, and immunologically mediated acute interstitial nephritis without nephrotic syndrome; neither candidate analogue showed this alert.

The OECD QSAR Toolbox Developmental and Reproductive Toxicity (DART) model showed a concern for developmental and/or reproductive toxicity for perylene and BaP, but not pyrene, based on aryl hydrocarbon receptor (AhR) binders and prostaglandin receptor agonists. The structural alert applies to PAH compounds containing three to five fused aromatic rings aligned in line, such as BaP and benz[*a*]anthracene. Pyrene's aromatic rings are grouped together, which made it inactive for this particular model alert. There is also limited experimental evidence of perylene binding AhR (see Section 2.3.3 for additional context).

Other alerts from the OECD QSAR Toolbox include an alert from the HESS model for potential for liver enzyme induction for perylene and both candidate analogues based on the aromatic hydrocarbon structure and an alert from the Estrogen Receptor Expert System (rtER Expert System) for potential estrogen receptor binding affinity based on a multicyclic hydrocarbons structure. Although there are some inconsistencies that varied by model system, some predictive structure-activity relationship (SAR) tools support concern for mutagenicity/ carcinogenicity.

Metabolic Analogues

Table A-4 summarizes available toxicokinetic data for perylene and the structurally similar compounds identified as potential analogues.

Table A-4. Comparison of ADME Data for Perylene (CASRN 198-55-0) and Candidate Analogues

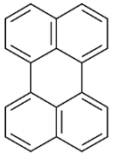
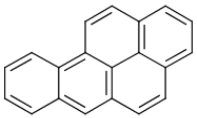
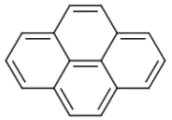
Chemical	Perylene	BaP	Pyrene
Structure			
CASRN	198-55-0	50-32-8	129-00-0
Absorption			
Rate and extent of absorption	• No experimental data.	**Laboratory animals (all routes):** • Absorbed by oral, inhalation, and dermal exposure. • Rate and extent of absorption is variable, depending on exposure medium (e.g., oral and dermal absorption enhanced in presence of oils and fats; dermal absorption decreased in presence of soils with high organic carbon content). • Significant mucociliary clearance of inhaled particulate to gut. • Absorption from gut depends on presence of bile in intestinal lumen.	**Laboratory animals (oral, i.t., dermal):** • Peak blood level achieved ~1 h after oral dosing. • Extensive oral absorption (68–92% in one study). • Absorbed through tracheal epithelium more rapidly than BaP following i.t. exposure. • Rapid and extensive dermal absorption in acetone (disappearance half-time of radiolabel from skin of 0.5–0.8 d; ~50% of applied radiolabel recovered in urine and feces within 6 d of application). • Dermal absorption of 94% in guinea pigs.
Distribution			
Extent of distribution	• No experimental data. • Based on log K_{ow} value >4, perylene is hydrophobic and is more likely to partition to fat compartments.	**Laboratory animals (all routes):** • Widely distributed throughout the body. • Initial rapid uptake into well-perfused tissues (e.g., lung, kidney, liver). • Subsequent accumulation, retention, and slow release from fat (consistent with log K_{ow} value >4). • High levels in gut (from any route) due to mucociliary clearance from respiratory tract and hepatobiliary excretion of metabolites. • Limited placental transfer.	**Laboratory animals (all routes):** • Widely distributed throughout the body. • Initial rapid uptake into well-perfused tissues (e.g., lung, kidney, liver). • Subsequent accumulation, retention, and slow release from fat (consistent with log K_{ow} value >4). • High levels in gut (from any route) due to mucociliary clearance from respiratory tract and hepatobiliary excretion of metabolites. • Limited placental transfer.

Table A-4. Comparison of ADME Data for Perylene (CASRN 198-55-0) and Candidate Analogues

Chemical	Perylene	BaP	Pyrene
Metabolism			
Rate; Primary reactive metabolites	• No experimental data. • By analogy to other PAHs, expected to be metabolized via CYP450 oxidation. • Metabolites predicted by both the in vivo rat metabolism simulator and rat liver S9 metabolism simulator (OECD QSAR Toolbox): 3-hydroxy-perylene, 1-hydroxy-perylene.	**Laboratory animals (all routes), in vitro:** • Metabolism is rapid and occurs in many tissues throughout the body. • Oxidized via CYP450; primary metabolites are 9-, 10-, 7,8-, 4,5-, and 2,3-dihydrodiols and epoxides, as well as various phenols, quinones, and derivatives. • Oxidative metabolism can be induced by CYP450 inducers. • Oxidative metabolites conjugated with GSH, glucuronic acid, and sulfate esters.	**Laboratory animals (i.p.)** • Oxidized to 1- and 4-hydroxypyrene, 1,6- and 1,8-dihydroxypyrene, 1,6- and 1,8-pyrenequinone, and *trans*-4,5-dihydro-4,5-dihydroxypyrene in rats and rabbits. • Oxidative metabolites conjugated with GSH, glucuronic acid, and sulfate esters. • By analogy to other PAHs, metabolism is expected to be mediated via CYP450 oxidation.
Enzyme induction	• Mixed evidence for weak induction of AHH in vivo; no evidence for induction of other monooxygenase enzymes. • Weak inducer of AHH in vitro; weak affinity for AhR binding.	• Induces monooxygenase enzymes in vivo and in vitro (AHH, EROD, etc.). • Strong affinity for AhR binding.	• Mixed evidence for weak induction of AHH and EROD in vivo; no evidence for induction of other monooxygenase enzymes. • Weak inducer of AHH in vitro; weak affinity for AhR binding.
Excretion			
Elimination half-time; route of excretion	• No experimental data.	**Laboratory animals (all routes):** • Elimination is rapid, with half-times of 22–30 h. • Primary route is biliary excretion to feces; urine is secondary route. • Excreted mainly as conjugated metabolites. • Small amounts excreted in breast milk.	**Laboratory animals (oral, dermal):** • Elimination is rapid (half-time not specified). • Eliminated in urine and feces in similar amounts.
References	OECD (2022); Harris et al. (1988); Asokan et al. (1986); Piskorska-Pliszczynska et al. (1986); Mukhtar et al. (1982); Neubert and Tapken (1978)	U.S. EPA (2017a); IARC (2010); ATSDR (1995); Harris et al. (1988); Piskorska-Pliszczynska et al. (1986); Mukhtar et al. (1982); Neubert and Tapken (1978)	OECD (2022); IARC (2010); ATSDR (1995); Lipniak and Brandys (1993); Asokan et al. (1986); Piskorska-Pliszczynska et al. (1986); Mukhtar et al. (1982); Boyland and Sims (1964)

ADME = absorption, distribution, metabolism, excretion; AhR = aryl hydrocarbon receptor; AHH = aryl hydrocarbon hydroxylase; BaP = benzo[*a*]pyrene; CYP450 = cytochrome P450; EROD = 7-ethoxyresorufin *O*-deethylase; GSH = glutathione; i.t. = intratracheal; K_{ow} = octanol-water partition coefficient; PAH = polycyclic aromatic hydrocarbon; OECD = Organisation for Economic Cooperation and Development; QSAR = quantitative structure-activity relationship.

No data on absorption or distribution are available for perylene. Both candidate analogues are absorbed via oral, inhalation, and dermal routes and show initial widespread distribution followed by accumulation and retention in fat (U.S. EPA, 2017a; IARC, 2010; ATSDR, 1995; Lipniak and Brandys, 1993). Rate and extent of absorption vary depending on exposure medium (i.e., enhanced in the presence of oils and fats), and oral absorption is dependent on presence of bile in the small intestines. Pyrene is absorbed more readily and completely than BaP. The candidate analogues are widely distributed in the body with preferential accumulation in fat as suggested by the log K_{ow} values >4. High levels are also observed in the gut (following exposure via any route) due to mucociliary clearance from the respiratory tract and hepatobiliary excretion of metabolites. Because absorption and distribution of a chemical in the body are determined largely by physical and chemical properties related to chemical size and general structure (e.g., lipophilicity [log K_{ow} values >4], vapor pressure, molecular weight, etc.) (Schwarzenbach et al., 2016), it is reasonable to assume that perylene will be absorbed and distributed similarly to the candidate analogues based on similar size, structure, and physicochemical properties.

No in vivo or in vitro metabolism data are available for perylene. In silico predictions from the OECD QSAR Toolbox predict metabolism of perylene via oxidation to 1- and 3-hydroxy-perylene. The metabolism of BaP has been extensively reviewed by the U.S. EPA (2017a), IARC (2010), and ATSDR (1995). BaP is oxidized by CYP450 in multiple tissues in the body to more soluble metabolites, including dihydrodiols, phenols, quinones, and epoxides, which then form conjugates with glucuronide, glutathione (GSH), or sulfate. Limited in vivo evidence also indicates that pyrene undergoes oxidative metabolism to 1- and 4-hydroxypyrene, 1,6- and 1,8-dihydroxypyrene, 1,6- and 1,8-pyrenequinone, and *trans*-4,5-dihydro-4,5-dihydroxypyrene (Boyland and Sims, 1964). Based on analogy to other PAHs (ATSDR, 1995), oxidative metabolism of pyrene is expected to be mediated by CYP450s.

As discussed in the main PPRTV assessment, some studies reported weak induction of the monooxygenase enzyme, aryl hydrocarbon hydroxylase (AHH), following in vivo exposure to perylene (Asokan et al., 1986; Mukhtar et al., 1982; Neubert and Tapken, 1978). Of the candidate analogues, BaP is a known inducer of monooxygenase enzymes, particularly AHH (ATSDR, 1995; Neubert and Tapken, 1978). Like perylene, evidence for AHH induction in vivo is mixed for pyrene (Asokan et al., 1986; Mukhtar et al., 1982; Neubert and Tapken, 1978). In vitro, perylene and pyrene are weak AhR binders and BaP is a strong AhR binder (Piskorska-Pliszczynska et al., 1986).

No elimination data are available for perylene. Elimination is rapid via all routes in laboratory animals (22−30 hours, see Table A-4) for BaP and via oral and dermal routes for pyrene (there are no data on elimination following inhalation exposure to pyrene) (U.S. EPA, 2017a, b; IARC, 2010; ATSDR, 1995; Lipniak and Brandys, 1993). For BaP, the primary route of elimination is via feces, with lesser amounts excreted via urine and small amounts excreted in breast milk. For all routes, BaP is excreted mainly as conjugated metabolites. Data for pyrene are less robust but indicate that similar amounts are eliminated via feces and urine.

In summary, there are no experimental toxicokinetic data for the target chemical, perylene. Absorption and distribution are similar for the candidate analogues. Similarities in log K_{ow} values suggest a similar potential accumulation in fat tissues for the target and analogue compounds. Experimental metabolism data are available for both candidate analogues, and metabolic pathways (CYP450 oxidation) are expected to be similar for the target compound based on in silico predictions from the OECD QSAR Toolbox. There is evidence of enzyme induction by perylene and both candidate analogues, although the magnitude of induction varies across compounds. Elimination rate is similar for both candidate analogues, with a higher portion of elimination occurring via feces for BaP. Based on the limited data available, both candidate analogues appear to be suitable metabolic analogues for perylene.

Toxicity-Like Analogues

Oral Exposure

No repeat-dose oral toxicity studies evaluating noncancer effects or acute oral lethality studies are available for perylene. The available oral toxicity values for candidate analogues are summarized in Table A-5. Critical effects for candidate analogues include neurodevelopmental effects (BaP) (U.S. EPA, 2017a) and kidney effects (pyrene) (U.S. EPA, 2007, 1990). Numerous additional toxicity targets have been identified for BaP at doses higher than the lowest lowest-observed-adverse-effect level (LOAEL) associated with neurodevelopmental effects (0.2 mg/kg-day), which corresponds to the $BMDL_{1SD}$ of 0.092 mg/kg-day presented in Table A-5. The lowest LOAELs for additional toxicity targets of BaP include: reproductive system (1 mg/kg-day), adult nervous system (2 mg/kg-day), cardiovascular system (12.5 mg/kg-day), immunological system (15 mg/kg-day), and the kidney and liver (30 mg/kg-day) (U.S. EPA, 2017a, b). Repeat-dose oral exposure data for pyrene are limited, and do not identify additional toxicity targets other than the kidney, for which effects were observed at ≥125 mg/kg-day (U.S. EPA, 2007). Reproductive and/or developmental toxicity have not been evaluated following oral exposure to pyrene.

Table A-5. Comparison of Available Oral Toxicity Values for Perylene (CASRN 198-55-0) and Candidate Structural Analogues

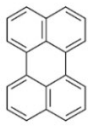
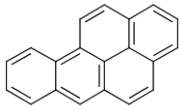
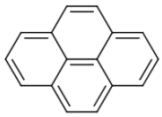
Chemical	Perylene	BaP	Pyrene
Structure			
CASRN	198-55-0	50-32-8	129-00-0
Subchronic oral toxicity values			
POD (mg/kg-d)	ND	The POD for the chronic RfD (0.092 mg/kg-d) is also applicable to subchronic exposure because it is based on a developmental study (see further details below)	75
POD type	ND	ND	NOAEL
Subchronic UF_c	ND	ND	300 (UF_H, UF_A, UF_D)
Subchronic p-RfD (mg/kg-d)	ND	ND	3×10^{-1}

Table A-5. Comparison of Available Oral Toxicity Values for Perylene (CASRN 198-55-0) and Candidate Structural Analogues

Chemical	Perylene	BaP	Pyrene
Critical effects	ND	ND	Kidney effects (renal tubular pathology, decreased kidney weights) at ≥125 mg/kg-d
Species	ND	ND	Mouse
Duration	ND	ND	13 wk
Route (method)	ND	ND	Oral (gavage)
Source	NA	NA	U.S. EPA (2007) (PPRTV)
Chronic oral toxicity values			
POD (mg/kg-d)	ND	0.092	75
POD type	ND	$BMDL_{1SD}$	NOAEL
Chronic UF_c	ND	300 (UF_H, UF_A, UF_D)	3,000 (UF_H, UF_A, UF_S, UF_D)
Chronic RfD/ p-RfD (mg/kg-d)	ND	3×10^{-4}	3×10^{-2}
Critical effects	ND	Neurodevelopmental effects (open field crossed squares at PND 69; elevated plus maze open arm entries at PND 70; Morris water maze hidden platform trial escape latency at PNDs 71–74)	Kidney effects (renal tubular pathology, decreased kidney weights) at ≥125 mg/kg-d
Species	ND	Rat	Mouse
Duration	ND	PNDs 5–11	13 wk
Route (method)	ND	Oral (gavage)	Oral (gavage)
Source	NA	U.S. EPA (2017a, 2017b) (IRIS)	U.S. EPA (1990) (IRIS)
Acute oral lethality data			
Oral LD_{50} (mg/kg)	ND	ND	ND
Toxicity at LD_{50}	ND	ND	ND
Source	NLM (2022c)	NLM (2022b); U.S. EPA (2017a)	NLM (2022d); U.S. EPA (2007)

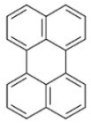
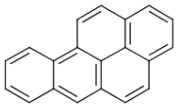
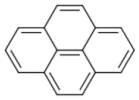
BaP = benzo[*a*]pyrene; BMDL = benchmark dose lower confidence limit; IRIS = Integrated Risk Information System; LD_{50} = median lethal dose; NA = not applicable; ND = no data; NOAEL = no-observed-adverse-effect level; PND = postnatal day; POD = point of departure; p-RfD = provisional reference dose; RfD = reference dose; SD = standard deviation; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Of the candidate analogues, BaP provides the lowest candidate point of departure (POD) based on neurodevelopment (0.092 mg/kg-day, which is nearly 3 orders of magnitude lower than the POD of 75 mg/kg-day for pyrene based on kidney effects). Additionally, the lowest LOAEL identified for kidney effects following repeat-dose oral exposure to BaP is 30 mg/kg-day (U.S. EPA, 2017a), which is lower than the POD for pyrene based on kidney effects. In the absence of repeated exposure oral toxicity data for perylene, there is no information with which to clearly identify the most suitable candidate analogue based on toxicity comparisons. From available toxicity data, BaP provides the most conservative candidate POD, which is based on neurodevelopmental effects. In development of the reference dose (RfD) for BaP, the U.S. EPA compared candidate values for developmental, reproductive, and immunological effects (U.S. EPA, 2017a, b). The overall RfD, based on neurobehavioral effects in rats exposed during the early postnatal period, was supported by numerous human and animal studies and was considered protective of all types of health effects. The MOA for neurodevelopmental effects of BaP is not fully understood; however, possible mechanisms may involve oxidative stress in the brain or disrupted gene and/or protein expression levels of neurotransmitters or receptors, resulting in altered neurotransmitter signaling in the brain (U.S. EPA, 2017a). Available data are inadequate to determine whether these possible mechanistic events might occur following exposure to perylene.

Inhalation Exposure

No repeat-exposure inhalation toxicity studies or acute inhalation lethality studies are available for perylene. Inhalation toxicity values for candidate analogues are presented in Table A-6. Of the candidate analogues, only BaP has an inhalation toxicity value, which is based on developmental effects (decreased embryo/fetal survival) (U.S. EPA, 2017a). No inhalation toxicity values were developed for pyrene due to lack of adequate data (U.S. EPA, 2007). Additional adverse toxicological effects have been identified for BaP at concentrations higher than the lowest LOAEL associated with developmental effects (0.025 mg/m^3), including reproductive toxicity at ≥0.075 mg/m^3 and neurodevelopmental effects at 0.1 mg/m^3 (only concentration evaluated for neurodevelopmental effects) (U.S. EPA, 2017a, b).

Table A-6. Comparison of Available Inhalation Toxicity Values for Perylene (CASRN 198-55-0) and Candidate Structural Analogues

Chemical	Perylene	BaP	Pyrene
Structure			
CASRN	198-55-0	50-32-8	129-00-0
Subchronic inhalation toxicity values			
POD (mg/m^3)	ND	The POD for the chronic RfC (0.0046 mg/m^3) is also applicable to subchronic exposure because it is based on a developmental study (see further details below)	ND
POD type	ND	ND	ND
Subchronic UF_c	ND	ND	ND
Subchronic p-RfC (mg/m^3)	ND	ND	ND
Critical effects	ND	ND	ND
Species	ND	ND	ND
Duration	ND	ND	ND
Route (method)	ND	ND	ND
Source	NA	NA	U.S. EPA (2007) (PPRTV)
Chronic inhalation toxicity values			
POD (mg/m^3)	ND	0.0046	ND
POD type	ND	LOAEL	ND
Chronic UF_c	ND	3,000 (UF_H, UF_A, UF_L, UF_D)	ND
Chronic p-RfC/RfC (mg/m^3)	ND	2×10^{-6}	ND
Critical effects	ND	Decreased embryo/fetal survival	ND
Species	ND	Rat	ND
Duration	ND	GDs 11–20	ND
Route (method)	ND	Inhalation (nose-only)	ND
Source	NA	U.S. EPA (2017a) (IRIS)	U.S. EPA (2007) (PPRTV)
Acute inhalation lethality data			
Oral LC_{50} (mg/m^3)	ND	ND	ND
Toxicity at LC_{50}	ND	ND	ND
Source	NLM (2022c)	NLM (2022b); U.S. EPA (2017a)	NLM (2022d); U.S. EPA (2007)

BaP = benzo[*a*]pyrene; GD = gestation day; IRIS = Integrated Risk Information System; LC_{50} = median lethal concentration; LOAEL = lowest-observed-adverse-effect level; NA = not applicable; ND = no data; POD = point of departure; NOAEL = no-observed-adverse-effect level; PPRTV = Provisional Peer-Revised Toxicity Value; p-RfC = provisional reference concentration; RfC = reference concentration; 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.

As described in U.S. EPA (2017a, 2017b), the U.S. EPA IRIS assessment derived candidate reference concentration (RfC) values for BaP for both reproductive and developmental effects. The overall RfC, based on decreased embryo/fetal survival following prenatal inhalation exposure, was considered protective of all types of health effects. The MOA for BaP-mediated developmental effects is unknown. Possible mechanisms may include covalent protein binding of oxidative metabolites, oxidative stress, and formation of reactive oxygen species; AhR-mediated effects on cell growth and differentiation; stimulation of apoptosis; disrupted development of fetal vascular system (resulting in impaired fetal nutrition); developmental immune dysfunction; and alterations in maternal hormones/hormone receptors following exposure during gestation (U.S. EPA, 2017a; IARC, 2010; Archibong et al., 2002; ATSDR, 1995). Based on structural alerts only, perylene would also be expected to show covalent protein binding of oxidative metabolites, AhR-mediated effects, and alterations in progesterone and estrogen binding. However, in vitro data suggest that perylene is a weak AhR inducer, whereas BaP is a strong AhR inducer (see Section 2.3). In the absence of repeated-exposure inhalation toxicity data for perylene, there is no information with which to clearly identify or rule out BaP as an appropriate analogue based on toxicity comparisons.

Weight-of-Evidence Approach

A tiered WOE approach as described in Wang et al. (2012) was used to select the overall best analogue chemical. The approach focuses on identifying a preferred candidate for three types of analogues: structural analogues, toxicokinetic or metabolic analogues, and toxicity-like analogues. Selection of the overall best analogue chemical is then based on all of the information from the three analogue types, and the following considerations used in a WOE approach: (1) lines of evidence from the U.S. EPA assessments are preferred; (2) biological and toxicokinetic data are preferred over the structural similarity comparisons; (3) lines of evidence that indicate pertinence to humans are preferred; (4) chronic studies are preferred over subchronic studies when selecting an analogue for a chronic value; (5) chemicals with more conservative/health-protective toxicity values may be favored; and (6) if there are no clear indications as to the best analogue chemical based on the other considerations, then the candidate analogue with the most structural similarity may be preferred.

BaP is the closest analogue based on structural characteristics and physicochemical properties. Perylene and BaP both contain five benzene rings, whereas pyrene contains only four benzene rings. Physicochemical properties (see Table A-3) suggest that pyrene is more volatile and water soluble than perylene or BaP. In addition, log K_{ow} values suggest that partitioning to fat is greater for perylene and BaP compared to pyrene. Perylene and BaP also share more common structural alerts from models than perylene and pyrene. There are no toxicokinetic data available for perylene, but in general, PAHs as a class show similar toxicokinetic profiles (e.g., CYP450 oxidation). Therefore, both BaP and pyrene are suitable toxicokinetic analogues. There are no oral or inhalation data available for perylene. Therefore, toxicity comparisons provide little basis for assessment of candidate analogues. For oral exposure, critical targets of toxicity were neurodevelopmental effects for BaP and kidney effects for pyrene. The neurodevelopmental effects of BaP provide the most sensitive measure of toxicity among the candidate analogue compounds, making BaP a health-protective analogue. For inhalation exposure, BaP is the only candidate analogue compound with an inhalation toxicity value, which is based on developmental effects.

In summary, both BaP and pyrene are considered suitable analogues. However, BaP is the closest analogue based on structural and physicochemical properties and provides the most health-protective oral toxicity value and the only inhalation toxicity value. Therefore, BaP is selected as the analogue compound for both oral and inhalation screening toxicity values.

ORAL NONCANCER TOXICITY VALUES

Derivation of a Screening Subchronic Provisional Reference Dose

Based on the overall analogue approach presented in this PPRTV assessment, BaP is selected as the analogue for perylene for derivation of screening subchronic and chronic provisional reference doses (p-RfDs). The study used for the U.S. EPA screening subchronic and chronic p-RfD values for perylene is an early postnatal gavage study of BaP in rats (U.S. EPA, 2017a; Chen et al., 2012). The *Toxicological Review of Benzo[a]pyrene (CASRN 50-32-8): Supplemental Information* (U.S. EPA, 2017b) provided the following summary:

> *Chen et al. (2012) treated male and female neonatal Sprague-Dawley rats (10/sex/group) with benzo[a]pyrene (unspecified purity) dissolved in peanut oil by gavage daily on PNDs 5−11, at doses of 0.02, 0.2, or 2 mg/kg in 3 mL vehicle/kg body weight, determined individually based upon daily measurements. This time period was described as representing the brain growth spurt in rodents, analogous to brain developmental occurring from the third trimester to 2 years of age in human infants. Breeding was performed by pairs of 9-week-old rats, with delivery designated as PND 0. Litters were culled to eight pups/dam (four males and four females, when possible) and randomly redistributed at PND 1 among the nursing dams; dams themselves were rotated every 2−3 days to control for caretaking differences, and cage-side observations of maternal behavior were made daily. One male and female from each litter were assigned per treatment group, and the following physical maturation landmarks were assessed daily in all treatment groups until weaning at PND 21: incisor eruption, eye opening, development of fur, testis decent, and vaginal opening.*
>
> *Neonatal sensory and motor developmental tests were administered to pups during the preweaning period at PNDs 12, 14, 16, and 18, and were behavioral tests administered to rats as adolescents (PNDs 35 and 36) or as adults (PNDs 70 and 71): each rat was only tested during one developmental period. All dosing was performed from 1,300 to 1,600 hours, and behavioral testing was during the "dark" period from 1,900 to 2,300 hours, although tests were performed in a lighted environment. Pups were observed individually and weighed daily, the order of testing litters was randomized each day, and all observations were recorded by investigators blinded to group treatment.*
>
> *Sensory and motor developmental tests, including the surface righting reflex test, negative geotaxis test, and cliff aversion test, were performed only once, while the forelimb grip strength test was assessed during three 60-second trials on PND 12. Rat movements during the open-field test were recorded by camera, and two blinded investigators scored movement and rearing separately during a 5-minute evaluation period. Blinded investigators directly observed video monitoring of rat movements during the elevated plus maze, and after a 5-minute free exploration period, recorded number of entries into the closed and open arms, time spent in the open arms, and latency to the first arm entry.*

Assessment of the Morris water maze was slightly different, in that the rats were habituated to the testing pool by a 60-second swim without a platform on the day prior to testing. The rats were then tested during a 60-second swim with a hidden platform present at a constant position each day for 4 days; on the 5th day, the rats were evaluated during a 60-second probe swim without a platform. The number of times each animal crossed the original platform location and the duration of time spent in the platform quadrant were recorded during this final evaluation. One pup/sex/litter were assigned for behavioral testing to each of four tracks: Track 1, surface righting reflex test, cliff aversion test, and open-field test (PNDs 12−18); Track 2, negative geotaxis test, forelimb grip strength test, and open-field test (PNDs 12−20); Track 3, elevated plus maze, Morris water maze, and open-field test (PNDs 34−36); and Track 4, elevated plus maze, Morris water maze, and open-field test (PNDs 69−71). All results were presented in graphic form only.

No significant effects on pup body weight were observed during the 7-day treatment period (PNDs 5−11). Three-way ANOVA (time × benzo[a]pyrene treatment × sex) indicated that effects of benzo[a]pyrene were not sex-dependent throughout the 71-day experiment, so both sexes were pooled together. From this pooled analysis, pups in the 2 mg/kg-day treatment group gained significantly less weight at both PND 36 and 71. There were no differences among treatment groups in incisor eruption, eye opening, development of fur, testis decent, or vaginal opening.

For all measurements of neonatal sensory and motor development, results from both sexes were analyzed together since benzo[a]pyrene was reported to have no significant interaction with sex by 3-way ANOVA. No significant differences were observed in either the cliff aversion or forelimb grip strength tests. In the surface righting reflex test, latency was increased in the 0.2 mg/kg-day group at PND 12, in the 0.02 and 2 mg/kg-day groups at PND 14, and in only the high-dose group at PND 16; latency was not significantly different in any group at PND 18. At PND 12, there was a dose-related increase in negative geotaxis latency associated with 0.02, 2, and 2 mg/kg-day benzo[a]pyrene, which was also present in the 2 mg/kg-day group at PND 14, but returned to control levels at PND 16 and 18. In the open field test, there were no significant differences in either locomotion or rearing activity at PND 18 or 20. At PND 34, the 2 mg/kg-day group exhibited significantly increased movement, but increases in rearing were not significant. At PND 69, increased locomotion was observed in both the 0.2 and 2 mg/kg-day groups, while rearing was significantly increased in only the 2 mg/kg-day treatment group.

The elevated plus maze performance was only evaluated in adolescent and adult rats. Unlike the previous tests, 3-way ANOVA revealed a statistically significant interaction between neonatal benzo[a]pyrene treatment and sex, so male and female performance was analyzed independently. No significant differences in PND 35 males were observed, and the only significant observation in PND 35 females was increased time spent in the open maze arms by the 2 mg/kg-day treatment group. Significantly decreased latency time to first open arm entry was observed in PND 70 males and females in both 0.2 and

2 mg/kg-day treatment groups; these groups also spent significantly more time in open maze arms, along with the 0.02 mg/kg-day female group. At PND 70, the 2 mg/kg-day males, along with the 0.2 and 2 mg/kg-day females, entered more frequently into open arms and less frequently into closed arms than the vehicle controls. In the Morris water maze, escape latency (time to reach the platform during each of the four testing days) was consistently increased in the 2 mg/kg-day treatment group of both sexes, in both adolescent and adult animals. These increases were statistically significant in both males and females treated with 2 mg/kg-day benzo[a]pyrene at both PNDs 39 and 74, and were also significantly elevated in 0.2 mg/kg-day animals of both sexes at PND 74. Likewise, performance during the 5th test day, in the absence of the escape platform, was significantly adversely affected by both metrics (decreased time spent in the target quadrant and decreased number of attempts to cross the platform location) in 2 mg/kg-day rats of both sexes at both PNDs 40 and 75. PND 75 females treated with 0.2 mg/kg-day benzo[a]pyrene also showed significant decreases in both performance metrics, while PND 75 0.2 mg/kg-day males only demonstrated significant differences in "time spent in target quadrant." Swim speed was also assessed, but there were no differences among any treatment group at either age evaluated.

The benchmark dose lower confidence limit with one standard deviation ($BMDL_{1SD}$) of 0.092 mg/kg-day was identified as the POD for BaP based on neurobehavioral effects during a susceptible life stage (U.S. EPA, 2017a). This POD is selected from among a suite of available endpoints because it represents multiple neurobehavioral endpoints from several behavioral tests (i.e., Morris water maze, elevated plus maze, and open field test). Similar effects were replicated among numerous additional studies. As described in U.S. EPA (2017a): "*modeling for each of the three endpoints resulted in $BMDL_{1SD}$ values that clustered in the range 0.092−0.16 mg/kg-day. The lower end of this range of BMDLs, 0.092 mg/kg-day, was selected to represent the point of departure (POD) from these three endpoints for RfD derivation."* Thus, the BMDLs representing different behavioral manifestations of neurotoxicity were considered together to define the POD for neurobehavioral changes. The U.S. EPA (2017a) did not convert the POD into a human equivalent dose (HED) using $BW^{3/4}$ because the critical study evaluated developmental toxicity in early postnatal animals directly exposed to BaP. $BW^{3/4}$ scaling was determined to be inappropriate because: (1) it is unknown if allometric scaling derived from adult animals is appropriate for extrapolating doses in neonates in the absence of quantitative toxicokinetic and toxicodynamic differences; and (2) differences in temporal patterns of development across species result in complications for interspecies dose extrapolation.

The RfD for BaP is derived using a composite uncertainty factor (UF_C) of 300, reflecting 10-fold uncertainty factors for interspecies extrapolation and intraspecies variability (UF_A and UF_H, respectively) and a 3-fold uncertainty factor for database uncertainties (UF_D) (U.S. EPA, 2017a). Wang et al. (2012) indicated that the uncertainty factors typically applied in deriving a toxicity value for the chemical of concern are the same as those applied to the analogue unless additional information is available. To derive the screening subchronic p-RfD for perylene from the BaP data, the UF_D of 3 is increased to 10 to account for the absence of repeat-dose oral toxicity data for perylene.

Screening Subchronic p-RfD = Analogue POD (HED) ÷ UF_C
= 0.092 mg/kg day ÷ 1,000
= **9×10^{-5} mg/kg day**

Table A-7 summarizes the uncertainty factors for the screening subchronic p-RfD for perylene.

Table A-7. Uncertainty Factors for the Screening Subchronic p-RfD for Perylene (CASRN 198-55-0)

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied to account for uncertainty associated with extrapolating from animals to humans when no cross-species dosimetric adjustment (HED calculation) is performed.
UF_D	10	A UF_D of 10 is applied to reflect database limitations for the BaP analogue and the absence of repeat-dose and reproductive/developmental toxicity data for perylene.
UF_H	10	A UF_H of 10 is applied for interindividual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of perylene in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a BMDL.
UF_S	1	A UF_S of 1 is applied because a developmental study was selected as the principal study. The developmental period is recognized as a susceptible life stage when exposure during a time window of development is more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991).
UF_C	1,000	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

BaP = benzo[*a*]pyrene; BMDL = benchmark dose lower confidence limit; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor; UF_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.

Derivation of a Screening Chronic Provisional Reference Dose

BaP is also selected as the analogue for perylene for derivation of a screening chronic p-RfD. The key study and calculation of the POD are described above for the subchronic p-RfD. In deriving the screening chronic p-RfD for perylene, the same uncertainty factors used for the screening subchronic p-RfD (UF_A of 10, UF_H of 10, and UF_D of 10) are applied. An additional uncertainty factor for study duration is not applied because a developmental study is used as the principal study.

Screening Chronic p-RfD = Analogue POD ÷ UF_C
= 0.092 mg/kg day ÷ 1,000
= **9×10^{-5} mg/kg day**

Table A-8 summarizes the uncertainty factors for the screening chronic p-RfD for perylene.

Table A-8. Uncertainty Factors for the Screening Chronic p-RfD for Perylene (CASRN 198-55-0)

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied to account for uncertainty associated with extrapolating from animals to humans when no cross-species dosimetric adjustment (HED calculation) is performed.
UF_D	10	A UF_D of 10 was applied to reflect database limitations for the BaP analogue and the absence of repeat-dose and reproductive/developmental toxicity data for perylene.
UF_H	10	A UF_H of 10 is applied for interindividual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of perylene in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a BMDL.
UF_S	1	A UF_S of 1 is applied because a developmental study was selected as the principal study. The developmental period is recognized as a susceptible life stage when exposure during a time window of development is more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991).
UF_C	1,000	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

BaP = benzo[*a*]pyrene; BMDL = benchmark dose lower confidence limit; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor; UF_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.

INHALATION NONCANCER TOXICITY VALUES

Derivation of a Screening Subchronic Provisional Reference Concentration

Based on the overall analogue approach presented in this PPRTV assessment, BaP is selected as the analogue for perylene for deriving the screening subchronic and chronic provisional reference concentrations (p-RfCs). The study used for the U.S. EPA screening subchronic and chronic p-RfC values for perylene is a prenatal inhalation study of BaP in rats (U.S. EPA, 2017a; Archibong et al., 2002). The *Toxicological Review of Benzo[a]pyrene (CASRN 50-32-8): Supplemental Information* (U.S. EPA, 2017b) provided the following summary:

> *Archibong et al. (2002) evaluated the effect of exposure to inhaled benzo[a]pyrene on fetal survival and luteal maintenance in timed-pregnant F344 rats. Prior to exposure on GD 8, laparotomy was performed to determine the number of implantation sites, and confirmed pregnant rats were divided into three groups, consisting of rats that had four to six, seven to nine, or more than nine conceptuses in utero. Rats in these groups were then assigned randomly to the treatment groups or control groups to ensure a similar distribution of litter sizes. Animals (10/group) were exposed to benzo[a]pyrene:carbon black aerosols at concentrations of 25, 75, or 100 μg/m^3 via nose-only inhalation, 4 hours/day on GDs 11−20. Control animals were either sham-exposed to carbon black or remained entirely unexposed. Results of particle size analysis of generated aerosols were reported by several other reports from this laboratory (Inyang et al., 2003; Ramesh et al., 2001a; Hood et al., 2000). Aerosols showed a trimodal distribution (average of cumulative mass, diameter) <95%, 15.85 μm; 89%, <10 μm; 55%, <2.5 μm; and 38%, <1 μm (Inyang et al., 2003). Ramesh et al.*

(2001a) reported that the MMAD (± geometric SD) for the 55% mass fraction with diameters <2.5 μm was 1.7 ± 0.085. Progesterone, estradiol-17β, and prolactin concentrations were determined in plasma collected on GDs 15 and 17. Fetal survival was calculated as the total number of pups divided by the number of all implantation sites determined on GD 8. Individual pup weights and crown-rump length per litter per treatment were determined on PND 4 (PND 0 = day of parturition).

Archibong et al. (2002) reported that exposure of rats to benzo[a]pyrene caused biologically and statistically significant ($p \leq 0.05$) reductions in fetal survival compared with the two control groups; fetal survival rates were 78.3, 38.0, and 33.8% per litter at 25, 75, and 100 μg/m^3, respectively, and 96.7% with carbon black or 98.8% per litter in untreated controls (see Table D-30). Consequently, the number of pups per litter was also decreased in a concentration-dependent manner. The decrease was ~50% at 75 μg/m^3 and ~65% at 100 μg/m^3, compared with sham-exposed and unexposed control groups. No effects on hormone levels were observed on GDs 15 or 17 at the low dose. Biologically significant decreases in mean pup weights (expressed as g per litter) of >5% relative to the untreated control group were observed at doses ≥75 μg/m^3 (14 and 16% decreases at 75 and 100 μg/m^3, respectively, $p < 0.05$). There were no statistically significant differences from the control groups in crown-rump length (see Table D-30).

Benzo[a]pyrene exposure at 75 μg/m^3 caused a statistically significant decrease in plasma progesterone, estradiol, and prolactin on GD 17; these levels were not determined in the rats exposed to 100 μg/m^3 (Archibong et al., 2002). Plasma prolactin is an indirect measure of the activity of decidual luteotropin, a prolactin-like hormone whose activity is necessary for luteal maintenance during pregnancy in rats. Control levels of prolactin increased from GD 15 to 17, but this increase did not occur in the rats exposed to 75 μg/m^3. Although the progesterone concentration at 75 μg/m^3 was significantly lower than in controls on GD 17, the authors thought that the circulating levels should have been sufficient to maintain pregnancy; thus, the increased loss of fetuses was thought to be caused by the lower prolactin levels rather than progesterone deficiency. The reduced circulating levels of progesterone and estradiol-17β among benzo[a]pyrene-treated rats were thought to be a result of limited decidual luteotropic support for the corpora lutea. The authors proposed the following mechanism for the effects of benzo[a]pyrene on fertility: benzo[a]pyrene or its metabolites decreased prolactin and decidual luteotropin levels, compromising the luteotropic support for the corpora lutea and thereby decreasing the plasma levels of progesterone and estradiol-17β. The low estradiol-17β may decrease uterine levels of progesterone receptors, thereby resulting in fetal mortality. Based on biologically and statistically significant decreases in pups/litter and percent fetal survival/per litter, the LOAEL was 25 μg/m^3; no NOAEL was identified.

The LOAEL of 25 μg/m^3 for decreased embryo/fetal survival was selected as the POD for BaP (U.S. EPA, 2017a). The POD was converted into a $LOAEL_{HEC}$ of 4.6 μg/m^3 (0.0046 mg/m^3) by the U.S. EPA (2017a):

By definition, the RfC is intended to apply to continuous lifetime exposures for humans (U.S. EPA, 1994a). EPA recommends that adjusted continuous exposures be used for developmental toxicity studies by the inhalation route as well as for inhalation studies of longer durations (U.S. EPA, 2002). The PODs were adjusted to account for the discontinuous daily exposure as follows:

$$\begin{aligned} POD_{ADJ} &= POD \times \text{hours exposed per day/24 hours} \\ &= LOAEL \times (\text{duration of exposure/24 hours}) \\ &= POD_{ADJ} \end{aligned}$$

Next, the human equivalent concentration (HEC) was calculated from the POD_{ADJ} by multiplying by a DAF, which, in this case, was the regional deposited dose ratio ($RDDR_{ER}$) for extrarespiratory (i.e., systemic) effects as described in Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (U.S. EPA, 1994a). The observed developmental effects are considered systemic in nature (i.e., extrarespiratory) and the normalizing factor for extrarespiratory effects of particles is body weight (i.e., the equivalent dose across species is mass deposited in the entire respiratory tract per unit body weight). The $RDDR_{ER}$ was calculated as follows:

$$RDDR_{ER} = (BW_H/BW_A) \times ((V_E)_A/(V_E)_H) \times ((F_{TOT})_A/(F_{TOT})_H)$$

where:

BW = body weight (kg);
VE = ventilation rate (L/minute); and
F_{TOT} = total fractional deposition.

The total fractional deposition includes particle deposition in the nasal-pharyngeal, tracheobronchial, and pulmonary regions. F_{TOT} for both animals and humans was calculated using the Multi-Path Particle Dosimetry (MPPD) model, a computational model used for estimating human and rat airway particle deposition (MPPD; Version 2.0 © 2006, as accessed through the former Hamner Institute; now publicly available through Applied Research Associates). F_{TOT} was based on the average particle size of 1.7 ± 0.085 µm (mass median aerodynamic diameter [MMAD] ± geometric SD) as reported in Wu et al. (2003a) for the exposure range 25−100 µm^3. For the model runs, the Yeh-Schum 5-lobe model was used for the human and the asymmetric multiple path model was used for the rat (see Appendix E for MPPD model output). Both models were run under nasal breathing scenarios after adjusting for inhalability. A geometric SD of 1 was used as the default by the model because the reported geometric SD of 0.085 was ≤1.05.

The human parameters used in the model for calculating F_{TOT} and in the subsequent calculation of the POD_{HEC} were as follows: human body weight, 70 kg; VE, 13.8 L/minute; breathing frequency, 16 per minute; tidal volume, 860 mL; functional residual capacity, 3,300 mL; and upper respiratory tract volume, 50 mL. Although the most sensitive population in Archibong et al. (2002) is the developing fetus, the adult rat dams were directly exposed. Thus, adult rat parameters were used in the calculation of the HEC. The parameters used for the

rat were body weight, 0.25 kg (a generic weight for male and female rats); VE, 0.18 L/minute; breathing frequency, 102 per minute; tidal volume, 1.8 mL; functional residual capacity, 4 mL; and upper respiratory tract volume, 0.42 mL. All other parameters were set to default values (see Appendix E).

Under these conditions, the MPPD model calculated F_{TOT} values of 0.621 for the human and 0.181 for the rat. Using the above equation, the $RDDR_{ER}$ was calculated to be 1.1.

From this, the POD_{HEC} was calculated as follows:

$$POD_{HEC} = POD_{ADJ} \times RDDR_{ER}$$

The RfC for BaP is derived from the $LOAEL_{HEC}$ of 0.0046 mg/m^3 using a UF_C of 3,000, reflecting a 10-fold LOAEL-to-no-observed-adverse-effect level (NOAEL) uncertainty factor (UF_L), UF_H, and UF_D and a 3-fold UF_A (U.S. EPA, 2017a). Wang et al. (2012) indicated that the uncertainty factors typically applied in deriving a toxicity value for the chemical of concern are the same as those applied to the analogue unless additional information is available. Given the limitations of the current database, the uncertainty factors for BaP were adopted for perylene.

Screening Subchronic p-RfC = Analogue POD ÷ UF_C
= 0.0046 mg/m^3 ÷ 3,000
= **2×10^{-6} mg/m^3**

Table A-9 summarizes the uncertainty factors for the screening subchronic p-RfC for perylene.

Table A-9. Uncertainty Factors for the Screening Subchronic p-RfC for Perylene (CASRN 198-55-0)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty associated with extrapolating from animals to humans, using toxicokinetic cross-species dosimetric adjustment (HEC calculation) as specified in the U.S. EPA (1994) guidelines.
UF_D	10	A UF_D of 10 is applied to reflect the database limitations for the BaP analogue and the absence of repeat-dose and reproductive/developmental toxicity data for perylene.
UF_H	10	A UF_H of 10 is applied for interindividual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of perylene in humans.
UF_L	10	A UF_L of 10 is applied for LOAEL-to-NOAEL extrapolation because the POD is a LOAEL.
UF_S	1	A UF_S of 1 is applied because a developmental study was selected as the principal study. The developmental period is recognized as a susceptible life stage when exposure during a time window of development is more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991).
UF_C	3,000	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

BaP = benzo[*a*]pyrene; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; UF = uncertainty factor; 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.

Derivation of a Screening Chronic Provisional Reference Concentration

BaP is also selected as the analogue for perylene for derivation of a screening chronic p-RfC. The key study and calculation of the POD are described above for the subchronic p-RfC. In deriving the screening chronic p-RfC for perylene, the same uncertainty factors used for the screening subchronic p-RfC (UF_A of 3, UF_H of 10, UF_D of 10, UF_L of 10) are applied. An additional uncertainty factor for study duration is not applied because a developmental study is used as the principal study.

$$\begin{aligned} \textbf{Screening Chronic p-RfC} &= \text{Analogue POD} \div UF_C \\ &= 0.0046\ \text{mg/m}^3 \div 3{,}000 \\ &= \mathbf{2 \times 10^{-6}\ mg/m^3} \end{aligned}$$

Table A-10 summarizes the uncertainty factors for the screening chronic p-RfC for perylene.

Table A-10. Uncertainty Factors for the Screening Chronic p-RfC for Perylene (CASRN 198-55-0)

UF	Value	Justification
UF_A	3	A UF_A of 3 is applied to account for uncertainty associated with extrapolating from animals to humans when a cross-species dosimetric adjustment (HEC calculation) as specified in the U.S. EPA (1994) guidelines.
UF_D	10	A UF_D of 10 is applied to reflect the database limitations for the BaP analogue and the absence of repeat-dose and reproductive/developmental toxicity data for perylene.
UF_H	10	A UF_H of 10 is applied for interindividual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of perylene in humans.
UF_L	10	A UF_L of 10 is applied for LOAEL-to-NOAEL extrapolation because the POD is a LOAEL.
UF_S	1	A UF_S of 1 is applied because a developmental study was selected as the principal study. The developmental period is recognized as a susceptible life stage when exposure during a time window of development is more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991).
UF_C	3,000	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

BaP = benzo[*a*]pyrene; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; UF = uncertainty factor; 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.

APPENDIX B. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). (2021). 2021 TLVs and BEIs: Based on the documentation of the threshold limit values for chemical substances and physical agents & biological exposure indices. Cincinnati, OH. https://portal.acgih.org/s/store#/store/browse/detail/a154W00000BOag7QAD

Anderson, D; Styles, JA. (1978). Appendix II. The bacterial mutation test: Six tests for carcinogenicity. Br J Cancer 37: 924-930. http://dx.doi.org/10.1038/bjc.1978.134

Anderson, JG; Mccalla, DR; Bryant, DW; Mccarry, BE; Bromke, AM. (1987). Metabolic activation of 3-nitroperylene in the Salmonella/S9 assay. Mutagenesis 279: 279-285. http://dx.doi.org/10.1093/mutage/2.4.279

Anderson, RS; Anderson, LM. (1987). Lack of effect of perylene as an initiator of lung tumors or as a promoter of skin tumors in mice [Abstract]. Fed Proc 46: 746.

Archibong, AE; Inyang, F; Ramesh, A; Greenwood, M; Nayyar, T; Kopsombut, P; Hood, DB; Nyanda, AM. (2002). Alteration of pregnancy related hormones and fetal survival in F-344 rats exposed by inhalation to benzo(a)pyrene. Reprod Toxicol 16: 801-808. http://dx.doi.org/10.1016/S0890-6238(02)00058-8

Asada, S; Sasaki, K; Tanaka, N; Takeda, K; Hayashi, M; Umeda, M. (2005). Detection of initiating as well as promoting activity of chemicals by a novel cell transformation assay using v-Ha-ras-transfected BALB/c 3T3 cells (Bhas 42 cells). Mutat Res Genet Toxicol Environ Mutagen 588: 7-21. http://dx.doi.org/10.1016/j.mrgentox.2005.07.011

Asokan, P; Das, M; Bik, DP; Howard, PC; Mccoy, GD; Rosenkranz, HS; Bickers, DR; Mukhtar, H. (1986). Comparative effects of topically applied nitrated arenes and their nonnitrated parent arenes on cutaneous and hepatic drug and carcinogen metabolism in neonatal rats. Toxicol Appl Pharmacol 86: 33-43. http://dx.doi.org/10.1016/0041-008X(86)90397-2

ATSDR (Agency for Toxic Substances and Disease Registry). (1995). Toxicological profile for polycyclic aromatic hydrocarbons - Update [ATSDR Tox Profile]. (CIS/97/00215). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. https://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=25

ATSDR (Agency for Toxic Substances and Disease Registry). (2021). Toxic substances portal: Toxicological profiles [Database]. Atlanta, GA. Retrieved from https://www.atsdr.cdc.gov/toxprofiledocs/index.html

Bahri, R; Saidane-Mosbahi, D; Rouabhia, M. (2010). Cytokine release and cytotoxicity in human keratinocytes induced by polycyclic aromatic hydrocarbons (1-methylpyrene and perylene). J Toxicol Environ Health A 73: 552-564. http://dx.doi.org/10.1080/15287390903566617

Boyland, E; Sims, P. (1964). Metabolism of polycyclic compounds. 23. The metabolism of pyrene in rats and rabbits. Biochem J 90: 391-398. http://dx.doi.org/10.1042/bj0900391

CalEPA (California Environmental Protection Agency). (2020). Consolidated table of OEHHA/CARB approved risk assessment health values. Sacramento, California. https://ww2.arb.ca.gov/resources/documents/consolidated-table-oehha-carb-approved-risk-assessment-health-values

CalEPA (California Environmental Protection Agency). (2022). OEHHA chemical database [Database]. Sacramento, CA: Office of Environmental Health Hazard Assessment. Retrieved from https://oehha.ca.gov/chemicals

Carver, JH; Machado, ML; MacGregor, JA. (1985). Petroleum distillates suppress in vitro metabolic activation: Higher [S-9] required in the Salmonella/microsome mutagenicity assay. Environ Mutagen 7: 369-379. http://dx.doi.org/10.1002/em.2860070311

Carver, JH; Machado, ML; Macgregor, JA. (1986). Application of modified Salmonella/microsome prescreen to petroleum-derived complex mixtures and polynuclear aromatic hydrocarbons (PAH). Mutat Res 247: 247-253. http://dx.doi.org/10.1016/0165-7992(86)90042-4

Casto, BC; Pieczynski, WJ; DiPaolo, JA. (1973). Enhancement of adenovirus transformation by pretreatment of hamster cells with carcinogenic polycyclic hydrocarbons. Cancer Res 33: 819-824.

Casto, BC; Pieczynski, WJ; Janosko, N; DiPaolo, JA. (1976). Significance of treatment interval and DNA repair in the enhancement of viral transformation by chemical carcinogens and mutagens. Chem Biol Interact 13: 105-125.

Chen, C; Tang, Y; Jiang, X; Qi, Y; Cheng, S; Qiu, C; Peng, B; Tu, B. (2012). Early postnatal benzo(a)pyrene exposure in Sprague-Dawley rats causes persistent neurobehavioral impairments that emerge postnatally and continue into adolescence and adulthood. Toxicol Sci 125: 248-261. http://dx.doi.org/10.1093/toxsci/kfr265

Crespi, CL; Thilly, WG. (1984). Assay for gene mutation in a human lymphoblast line, AHH-1, competent for xenobiotic metabolism. Mutat Res 128: 221-230. http://dx.doi.org/10.1016/0027-5107(84)90110-6

CTD (Comparative Toxicogenomics Database). (2022). Perylene: Comparative toxicogenomics database [Database]: MDI Biological Laboratory. Retrieved from http://ctdbase.org/detail.go?type=chem&acc=D010569

Davis, AP; Grondin, CJ; Johnson, RJ; Sciaky, D; Wiegers, J; Wiegers, TC; Mattingly, CJ. (2021). The comparative toxicogenomics database (CTD): update 2021 [Database]: MDI Biological Laboratory. NC State University. Retrieved from http://ctdbase.org/

De Flora, S. (1981). Study of 106 organic and inorganic compounds in the Salmonella/microsome test. Carcinogenesis 2: 283-298. http://dx.doi.org/10.1093/carcin/2.4.283

De Flora, S; Zanacchi, P; Camoirano, A; Bennicelli, C; Badolati, GS. (1984). Genotoxic activity and potency of 135 compounds in the Ames reversion test and in a bacterial DNA-repair test [Review]. Mutat Res 133: 161-198. http://dx.doi.org/10.1016/0165-1110(84)90016-2

DiPaolo, JA; Popescu, NC. (1974). Chromosome bands induced in human and syrian hamster cells by chemical carcinogens. Br J Cancer 30: 103-108. http://dx.doi.org/10.1038/bjc.1974.120

Durant, JL; Busby, WF, Jr; Lafleur, AL; Penman, BW; Crespi, CL. (1996). Human cell mutagenicity of oxygenated, nitrated and unsubstituted polycyclic aromatic hydrocarbons associated with urban aerosols. Mutat Res DNA Repair 371: 123-157. http://dx.doi.org/10.1016/S0165-1218(96)90103-2

ECHA (European Chemicals Agency). (2022). Substance infocard: Perylene. Available online at https://www.echa.europa.eu/web/guest/substance-information/-/substanceinfo/100.005.365 (accessed April 5, 2022).

El-Bayoumy, K; Hecht, SS; Hoffmann, D. (1982). Comparative tumor initiating activity on mouse skin of 6-nitrobenzo[a]pyrene, 6-nitrochrysene, 3-nitroperylene, 1-nitropyrene and their parent hydrocarbons. Cancer Lett 16: 333-337. http://dx.doi.org/10.1016/0304-3835(82)90015-5

Finzi, C; Daudel, P; Prodi, G. (1968). Interference among polycyclic hydrocarbons in experimental skin carcinogenesis. Eur J Cancer 3: 497-501. http://dx.doi.org/10.1016/0014-2964(68)90087-X

Flesher, JW; Myers, SR. (1990). Bioalkylation of benz(a)anthracene as a biochemical probe for carcinogenic activity: Lack of bioalkylation in a series of six noncarcinogenic polynuclear aromatic hydrocarbons. Drug Metab Dispos 18: 163-167.

Florin, I; Rutberg, L; Curvall, M; Enzell, CR. (1980). Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology 15: 219-232. http://dx.doi.org/10.1016/0300-483X(80)90055-4

Goldfarb, JL; Suuberg, EM. (2008). Vapor pressures and enthalpies of sublimation of ten polycyclic aromatic hydrocarbons determined via the Knudsen effusion method. Journal of Chemical and Engineering Data 53: 670-676. http://dx.doi.org/10.1021/je7005133

Gupta, RC; Earley, K; Sharma, S. (1988). Use of human peripheral blood lymphocytes to measure DNA binding capacity of chemical carcinogens. PNAS 85: 3513-3517. http://dx.doi.org/10.1073/pnas.85.10.3513

Harris, M; Kamps, C; Safe, S. (1988). Role of the 4-5S binding protein in the induction of aryl hydrocarbon hydroxylase in the rat. Carcinogenesis 9: 1475-1480. http://dx.doi.org/10.1093/carcin/9.8.1475

Hera, C; Pueyo, C. (1988). Response of the L-arabinose forward mutation assay of Salmonella typhimurium to frameshift-type mutagens. Mutat Res 203: 39-45. http://dx.doi.org/10.1016/0165-1161(88)90006-4

Ho, CH; Clark, BR; Guerin, MR; Barkenbus, BD; Rao, TK; Epler, JL. (1981). Analytical and biological analyses of test materials from the synthetic fuel technologies: IV. Studies of chemical structure-mutagenic activity relationships of aromatic nitrogen compounds relevant to synfuels. Mutat Res 85: 335-345. http://dx.doi.org/10.1016/0165-1161(81)90224-7

Horton, AW; Christian, GM. (1974). Cocarcinogenic versus incomplete carcinogenic activity among aromatic hydrocarbons: Contrast between chrysene and benzo(b)triphenylene. J Natl Cancer Inst 53: 1017-1020. http://dx.doi.org/10.1093/jnci/53.4.1017

IARC (International Agency for Research on Cancer). (1983). Evaluation of the carcinogenic risk of chemicals to humans. International Agency for Research on Cancer. World Health Organization.

IARC (International Agency for Research on Cancer). (1998). Perylene. In Polynuclear aromatic compounds, part 1: Chemical, environmental and experimental data Summary of data reported and evaluation (pp. 51). Lyon, France: World Health Organization. https://monographs.iarc.fr/wp-content/uploads/2018/06/mono32.pdf

IARC (International Agency for Research on Cancer). (2010). Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures [IARC Monograph]. Lyon, France. http://monographs.iarc.fr/ENG/Monographs/vol92/mono92.pdf

IDEAconsult (IDEAconsult Ltd). (2018). Toxtree: Toxic hazard estimation by decision tree approach (Version 3.1.0) [Database]. Retrieved from https://apps.ideaconsult.net/data/ui/toxtree

IPCS. (2020). INCHEM: Chemical safety information from intergovernmental organizations [Database]. Geneva, Switzerland: World Health Organization, Canadian Centre for Occupational Health and Safety. Inter-Organization Programme for the Sound Management of Chemicals. Retrieved from http://www.inchem.org/

Kaden, DA; Hites, RA; Thilly, WG. (1979). Mutagenicity of soot and associated polycyclic aromatic hydrocarbons to Salmonella typhimurium. Cancer Res 39: 4152-4159.

Lavoie, EJ; Bedenko, EV; Hirota, N; Hecht, SS; Hoffmann, D. (1979). A comparison of the mutagenicity, tumor-initiating activity and complete carcinogenicity of polynuclear aromatic hydrocarbons. In PW Jones; P Leber (Eds.), Polynuclear aromatic hydrocarbons (pp. 705-721). Ann Arbor, MI: Ann Arbor Science Publishers, Inc.

Lipniak, M; Brandys, J. (1993). Toxicokinetics of fluoranthene, pyrene and benz(a)anthracene in the rat. Polycycl Aromat Compd 3: 111-119. http://dx.doi.org/10.1080/10406639308047863

Lofroth, G; Toftgard, R; Nilsson, L; Agurell, E; J-A, G. (1984). Short-term bioassays of nitro derivatives of benzo(a)pyrene and perylene. Carcinogenesis 5: 925-930. http://dx.doi.org/10.1093/carcin/5.7.925

Mersch-Sundermann, V; Mochayedi, S; Kevekordes, S. (1992). Genotoxicity of polycyclic aromatic hydrocarbons in Escherichia coli PQ37. Mutat Res 278: 1-9. http://dx.doi.org/10.1016/0165-1218(92)90279-9

Mukhtar, H; Link, CM; Cherniack, E; Kushner, DM; Bickers, DR. (1982). Effect of topical application of defined constituents of coal tar on skin and liver aryl hydrocarbon hydroxylase and 7-ethoxycoumarin deethylase activities. Toxicol Appl Pharmacol 64: 541-549. http://dx.doi.org/10.1016/0041-008X(82)90251-4

Neubert, D; Tapken, S. (1978). Some data on the induction of monooxygenases in fetal and neonatal mouse tissues. In Role of pharmacokinetics in prenatal and perinatal toxicology: Third Symposium on Prenatal Development, Berlin, 1978. Stuttgart, Germany: Thieme.

Neubert, D; Tapken, S. (1988). Prenatal induction of benzo-a-pyrene hydroxylases in mice. Arch Toxicol 62: 192-199. http://dx.doi.org/10.1007/bf00570139

NIOSH (National Institute for Occupational Safety and Health). (2018). NIOSH pocket guide to chemical hazards. Index of chemical abstracts service registry numbers (CAS No.). Atlanta, GA. http://www.cdc.gov/niosh/npg/npgdcas.html

NIST (National Institute of Standards and Technology). (2022). NIST Chemistry WebBook, SRD 69. Perylene (CAS 198-55-0). Available online at https://webbook.nist.gov/cgi/cbook.cgi?ID=C198550&Mask=4#ref-18

NLM (National Library of Medicine). (2022a). ChemIDplus advanced [Database]. Bethesda, MD: National Institutes of Health, National Library of Medicine. Retrieved from https://chem.nlm.nih.gov/chemidplus/

NLM (National Library of Medicine). (2022b). PubChem compounds summary: Benzo[a]pyrene, 50-32-8. Available online at https://pubchem.ncbi.nlm.nih.gov/compound/2336

NLM (National Library of Medicine). (2022c). PubChem compounds summary: Perylene, 198-55-0. Available online at https://pubchem.ncbi.nlm.nih.gov/compound/9142

NLM (National Library of Medicine). (2022d). PubChem compounds summary: Pyrene, 129-00-0. Available online at https://pubchem.ncbi.nlm.nih.gov/compound/31423

NTP (National Toxicology Program). (2021). Report on carcinogens, fifteenth edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service. http://dx.doi.org/10.22427/NTP-OTHER-1003

OCHEM (Online Chemical Database). (2022). ToxAlerts (Version 4.2.151) [Database]: Online Chemical Database with Modeling Environment. Helmholtz Zentrum Muenchen - Deutsches Forschungszentrum fuer Gesundheit und Umwelt. Retrieved from https://ochem.eu/alerts/home.do

OECD (Organisation for Economic Co-operation and Development). (2022). The OECD QSAR toolbox [version 4.5] [Database]. Retrieved from http://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm

OSHA (Occupational Safety & Health Administration). (2021a). Air contaminants: Occupational safety and health standards for shipyard employment, subpart Z, toxic and hazardous substances. (OSHA Standard 1915.1000). Washington, DC. https://www.osha.gov/laws-regs/regulations/standardnumber/1915/1915.1000

OSHA (Occupational Safety & Health Administration). (2021b). Safety and health regulations for construction: Occupational health and environmental controls: Gases, vapors, fumes, dusts, and mists. Washington, DC. https://www.osha.gov/laws-regs/regulations/standardnumber/1926/1926.55

OSHA (Occupational Safety & Health Administration). (2021c). Table Z-1: Limits for air contaminants. Occupational safety and health standards, subpart Z, toxic and hazardous substances. Washington, DC. https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.1000TABLEZ1

Penman, BW; Kaden, DA; Liber, HL; Skopek, TR; Thilly, WG; Hites, RA. (1980). Perylene is a more potent mutagen than benzo(a)pyrene for S. typhimurium. Mutat Res 271: 271-277. http://dx.doi.org/10.1016/0165-1218(80)90060-9

Piskorska-Pliszczynska, J; Keys, B; Safe, S; Newman, MS. (1986). The cytosolic receptor binding affinities and AHH induction potencies of 29 polynuclear aromatic hydrocarbons. Toxicol Lett 34: 67-74. http://dx.doi.org/10.1016/0378-4274(86)90146-3

Popescu, NC; Amsbaugh, SC; DiPaolo, JA. (1980). Enhancement of N-methyl-N'-nitro-N-nitrosoguanidine transformation of Syrian hamster cells by a phorbol diester is independent of sister chromatid exchanges and chromosome aberrations. Proc Natl Acad Sci USA 7282: 7282-7286. http://dx.doi.org/10.1073/pnas.77.12.7282

Popescu, NC; Turnbull, D; Dipaolo, JA. (1977). Sister chromatid exchange and chromosome aberration analysis with the use of several carcinogens and noncarcinogens. J Natl Cancer Inst 59: 289-293. http://dx.doi.org/10.1093/jnci/59.1.289

Rády, P; Arany, I; Boján, F; Kertai, P. (1980). Effect of carcinogenic and non-carcinogenic chemicals on the activities of four glycolytic enzymes in mouse lung. Chem Biol Interact 31: 209-213. http://dx.doi.org/10.1016/0009-2797(80)90007-1

Rády, P; Arany, I; Uzvolgyi, E; Bojan, F. (1981). Activity of pyruvate kinase and lactic acid dehydrogenase in mouse lung after transplacental exposure to carcinogenic and noncarcinogenic chemicals. Toxicol Lett 8: 223-228. http://dx.doi.org/10.1016/0378-4274(81)90105-3

Reddy, MV; Gupta, RC; Randerath, E; Randerath, K. (1984). 32 P-postlabeling test for covalent DNA binding of chemicals in vivo: Application to a variety of aromatic carcinogens and methylating agents. Carcinogenesis 5: 231-244. http://dx.doi.org/10.1093/carcin/5.2.231

Sakai, M; Yoshida, D; Mizusaki, S. (1985). Mutagenicity of polycyclic aromatic hydrocarbons and quinones on salmonella typhimurium TA97. Mutat Res 156: 61-67. http://dx.doi.org/10.1016/0165-1218(85)90007-2

Salamone, MF; Heddle, JA; Katz, M. (1979). The mutagenic activity of thirty polycyclic aromatic hydrocarbons (PAH) and oxides in urban airborne particulates. Environ Int 2: 37-43. http://dx.doi.org/10.1016/0160-4120(79)90092-8

Schwarzenbach, RP; Gschwend, PM; Imboden, DM. (2016). Environmental organic chemistry (3rd ed.). Hoboken, NJ: Wiley.

Shimada, T; Fujii-Kuriyama, Y. (2004). Metabolic activation of polycyclic aromatic hydrocarbons to carcinogens by cytochromes P450 1A1 and 1B1 [Review]. Cancer Sci 95: 1-6. http://dx.doi.org/10.1111/j.1349-7006.2004.tb03162.x

Sirianni, SR; Huang, CC. (1978). Sister chromatid exchange induced by promutagens/carcinogens in Chinese hamster cells cultured in diffusion chambers in mice. Proc Soc Exp Biol Med 158: 269-274. http://dx.doi.org/10.3181/00379727-158-40186

TCEQ (Texas Commission on Environmental Quality). (2015). TCEQ guidelines to develop toxicity factors: revised September 2015. (RG-442). Austin, TX. https://web.archive.org/web/20170305201245/http://www.tceq.texas.gov/publications/rg/rg-442.html/

TCEQ (Texas Commission on Environmental Quality). (2022). TRRP protective concentration levels. Retrieved from https://www.tceq.texas.gov/remediation/trrp/trrppcls.html

Thayer, KA; Angrish, M; Arzuaga, X; Carlson, LM; Davis, A; Dishaw, L; Druwe, I; Gibbons, C; Glenn, B; Jones, R; Kaiser, JP; Keshava, C; Keshava, N; Kraft, A; Lizarraga, L; Persad, A; Radke, EG; Rice, G; Schulz, B; ... Vetter, N. (2022). Systematic evidence map (SEM) template: Report format and methods used for the US EPA Integrated Risk Information System (IRIS) program, Provisional Peer Reviewed Toxicity Value (PPRTV) program, and other "fit for purpose" literature-based human health analyses. Environ Int 169: 107468. http://dx.doi.org/10.1016/j.envint.2022.107468

Thilly, WG; Longwell, J; Andon, BM. (1983). General approach to the biological analysis of complex mixtures. Environ Health Perspect 48: 129-136. http://dx.doi.org/10.2307/3429464

U.S. EPA (U.S. Environmental Protection Agency). (1990). Integrated Risk Information System (IRIS) chemical assessment summary for pyrene (CASRN 129-00-0). Washington, DC: National Center for Environmental Assessment, Integrated Risk Information System. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0445_summary.pdf

U.S. EPA (U.S. Environmental Protection Agency). (1991). Guidelines for developmental toxicity risk assessment. Fed Reg 56: 63798-63826.

U.S. EPA (U.S. Environmental Protection Agency). (1994). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry [EPA Report]. (EPA600890066F). Research Triangle Park, NC. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=71993&CFID=51174829&CFTOKEN=25006317

U.S. EPA (U.S. Environmental Protection Agency). (2005). Guidelines for carcinogen risk assessment [EPA Report]. (EPA630P03001F). Washington, DC. https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2007). Provisional peer-reviewed toxicity values for pyrene (CASRN 129-00-0) [EPA Report]. Cincinnati, OH. https://cfpub.epa.gov/ncea/pprtv/documents/Pyrene.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2011a). Chemical assessment clustering engine (ChemACE). Retrieved from https://www.epa.gov/tsca-screening-tools/chemical-assessment-clustering-engine-chemace

U.S. EPA (U.S. Environmental Protection Agency). (2011b). Health effects assessment summary tables (HEAST) for superfund [EPA Report]. Washington, DC. https://epa-heast.ornl.gov/heast.php

U.S. EPA (U.S. Environmental Protection Agency). (2012). Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.11 [Computer Program]. Washington, DC. Retrieved from https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface

U.S. EPA (U.S. Environmental Protection Agency). (2017a). Toxicological review of benzo[a]pyrene (CASRN 50-32-8) [EPA Report]. (EPA635R17003Fa). Washington, DC: U.S. Environmental Protection Agency, Integrated Risk Information System. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0136tr.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2017b). Toxicological review of benzo[a]pyrene (CASRN 50-32-8): Supplemental information [EPA Report]. (EPA635R17003Fb). Washington, DC: U.S. Environmental Protection Agency, Integrated Risk Information System. https://cfpub.epa.gov/si/si_public_file_download.cfm?p_download_id=535926&Lab=NCEA

U.S. EPA (U.S. Environmental Protection Agency). (2018). 2018 Edition of the drinking water standards and health advisories tables [EPA Report]. (EPA 822-F-18-001). Washington, DC: U.S. Environmental Protection Agency, Office of Water. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100U7U8.txt

U.S. EPA. (2020a). CompTox Chemicals Dashboard: Perylene [Bioactivity, invitrodb version 3.3] [Database]. Retrieved from https://comptox.epa.gov/dashboard/chemical/details/DTXSID4047753

U.S. EPA. (2020b). CompTox Chemicals Dashboard: Perylene [Bioactivity, PubChem] [Database]. Retrieved from https://comptox.epa.gov/dashboard/chemical/details/DTXSID4047753

U.S. EPA. (2020c). CompTox Chemicals Dashboard: Perylene [GenRA] [Database]. Retrieved from https://comptox.epa.gov/dashboard/chemical/details/DTXSID4047753

U.S. EPA (U.S. Environmental Protection Agency). (2021). TSCA chemical substance inventory. Download the non-confidential TSCA inventory. Available online at https://www.epa.gov/tsca-inventory/how-access-tsca-inventory

U.S. EPA (U.S. Environmental Protection Agency). (2022a). CompTox chemicals dashboard. Washington, DC. Retrieved from https://comptox.epa.gov/dashboard

U.S. EPA (U.S. Environmental Protection Agency). (2022b). CompTox chemicals dashboard: Benzo(a)pyrene. Available online at https://comptox.epa.gov/dashboard/chemical/details/DTXSID2020139 (accessed August 2, 2022).

U.S. EPA (U.S. Environmental Protection Agency). (2022c). CompTox chemicals dashboard: Perylene [Database]. Retrieved from https://comptox.epa.gov/dashboard/chemical/details/DTXSID4047753

U.S. EPA (U.S. Environmental Protection Agency). (2022d). CompTox chemicals dashboard: Pyrene. Available online at https://comptox.epa.gov/dashboard/chemical/details/DTXSID3024289 (accessed August 2, 2022).

U.S. EPA (U.S. Environmental Protection Agency). (2022e). Integrated risk information system (IRIS) database [Database]. Washington, DC. Retrieved from http://www.epa.gov/iris/

Van Duuren, BL; Sivak, A; Goldschmidt, BM; Katz, C; Melchionne, S. (1970). Initiating activity of aromatic hydrocarbons in two-stage carcinogenesis. J Natl Cancer Inst 44: 1167-1173.

von der Hude, W; Behm, C; Gürtler, R; Basler, A. (1988). Evaluation of the SOS chromotest. Mutat Res 203: 81-94. http://dx.doi.org/10.1016/0165-1161(88)90023-4

Wang, NC; Zhao, QJ; Wesselkamper, SC; Lambert, JC; Petersen, D; Hess-Wilson, JK. (2012). Application of computational toxicological approaches in human health risk assessment. I. A tiered surrogate approach. Regul Toxicol Pharmacol 63: 10-19. http://dx.doi.org/10.1016/j.yrtph.2012.02.006

White, KL; Lysy, HH; Holsapple, MP. (1985). Immunosuppression by polycyclic aromatic hydrocarbons: A structure-activity relationship in B6C3F1 and DBA/2 mice. Immunopharmacology 9: 155-164. http://dx.doi.org/10.1016/0162-3109(85)90011-6

Zhao, W; Ramos, KS. (1995). Inhibition of DNA synthesis in primary cultures of adult rat hepatocytes by benzo[a]pyrene and related aromatic hydrocarbons: Role of Ah receptor-dependent events. Toxicology 99: 179-189. http://dx.doi.org/10.1016/0300-483X(94)03028-Z