EPA/690/R-22/006F | September 2022 | FINAL

United States
Environmental Protection
Agency

Provisional Peer-Reviewed Toxicity Values for

The Aromatic High Carbon Range Total Petroleum Hydrocarbon (TPH) Fraction (Cancer) (various CASRNs)

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

United States Environmental Protection Agency

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https://www.epa.gov/pprtv

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Center for Public Health and Environmental Assessment
Office of Research and Development
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TABLE OF CONTENTS

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
C#	carbon number
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
EC	equivalent carbon
EPA	Environmental Protection Agency
ER	estrogen receptor
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-*S*-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	*N*-acetyl-β-D-glucosaminidase
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure-activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_C	composite uncertainty factor
UF_D	database uncertainty factor
UF_H	intraspecies uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
U.S.	United States of America
WBC	white blood cell

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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR THE AROMATIC HIGH CARBON RANGE TOTAL PETROLEUM HYDROCARBON (TPH) FRACTION (CANCER)

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's eComments Chemical Safety web page (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 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

This Provisional Peer-Reviewed Toxicity Value (PPRTV) assessment supports a fraction-based approach to risk assessment for mixtures of petroleum hydrocarbons U.S. EPA (2022a, 2009). In this approach, total petroleum hydrocarbon (TPH) fractions are defined based on expected transport in the environment and analytical methods used to quantify environmental contamination by TPH mixtures. TPH components were first classified into aromatics and aliphatics, and each of these two major fractions were further separated into low, medium, and high carbon range fractions. This PPRTV assessment describes the cancer assessment approach for the aromatic high carbon range fraction of TPH. The toxicity values described herein are used in the assessment of Complex Mixtures of Petroleum Hydrocarbons that is intended to replace current approaches used at TPH-contaminated sites U.S. EPA (2022a, 2009).

In general, fraction-based approaches involve: (1) dividing a complex mixture into groups based on similarities in their chemical structures or chemical properties; (2) measuring the concentrations of these groups (or the components within the group) in environmental media or estimating the rates of human exposure in mg/kg-day to these groups; (3) selecting an approach to characterize a dose-response relationship for the group; (4) combining the dose-response approach and the exposure estimates for all members of the group to estimate health risks from the group; and (5) estimating risks or hazards posed by exposure to the complex mixture using the risk characterization information from the individual groups [adapted from Atsdr (2018)].

1.1. DEFINITION OF THE AROMATIC HIGH CARBON RANGE FRACTION

The aromatic high carbon range fraction includes aromatic hydrocarbons with a carbon (C) range of C10−C32 (contains between 10 and 32 carbons, inclusive) and an equivalent carbon (EC)[1] number index range of EC11−EC35 that occur in, or co-occur with, petroleum contamination. It should be noted that the aromatic medium carbon range fraction of the TPH mixture assessment also includes C10 compounds but, unlike the aromatic high carbon range fraction, is restricted to those with EC9−EC < 11.[2] The EC index is equivalent to the retention time of the compound on a boiling point gas chromatography (GC) column (nonpolar capillary column), normalized to *n*-alkanes NJ DEP (2010); Sternberg et al. (1962). As such, EC numbers are the physical characteristic that underpin analytical separation of petroleum components. EC numbers are useful because they are more closely related to environmental mobility than carbon number. Grouping based on EC numbers provides a consistent basis for logically placing petroleum hydrocarbon compounds into fractions, because EC measures correlate with physicochemical properties such as water solubility, vapor pressure, Henry's law constant, and soil adsorption coefficient (log K_{oc}). Individual compounds in this fraction have a backbone consisting of one or more aromatic rings, which can be substituted with alkane, alkene, and other nonaromatic ring structures. Example compounds include 1,2,4-triethylbenzene, 1-methylnaphthalene, 1,1-biphenyl, fluorene, and benzo[*a*]pyrene (BaP).

[1]Based on an empirical relationship, the EC value can be estimated from a compound's boiling point (BP; °C) using the following equation: $EC = 4.12 + 0.02\ (BP) + 6.5 \times 10^{-5}\ (BP)^2$; see Gustafson et al. (1997a).
[2]The "EC criterion" avoids placing the generally less toxic substituted benzenes (C9−C10) with PAHs, naphthalenes, and 1,1-biphenyl in the same fraction.

The aromatic high carbon range fraction as described above is further subdivided for the purposes of this document as follows. Unsubstituted polycyclic aromatic hydrocarbons (PAHs) consist of aromatic hydrocarbons comprised of two to six fused aromatic hydrocarbon rings and exclude all compounds with alkyl or other substituents on the ring as well as compounds with anything other than carbon and hydrogen in their composition (i.e., exclude heterocyclic compounds). Substituted PAHs (subPAHs) include alkyl-substituted PAH derivatives such as 1,4-dimethylphenanthrene, 1-methylnaphthalene, and 5-methylchrysene. Carcinogenic fraction members that cannot be classified as either PAH or subPAH include all other aromatic hydrocarbons within the C10–C32 and EC11–EC35 ranges that occur in petroleum contamination, such as 1,1-biphenyl.

1.2. OVERVIEW OF PHYSICOCHEMICAL PROPERTIES AND ENVIRONMENTAL FATE

The systematic chemical names, synonyms [following guidance in Nist (2020b)], CASRNs, chemical abbreviations, and chemical structures for 1,1-biphenyl, 1-methylnaphthalene, and the seven PAHs in this document are listed in Table 1 and in Appendix B of U.S. EPA (2022a). The physicochemical properties for these chemicals, compiled from the CompTox Chemicals Dashboard U.S. EPA (2021), are provided in Table 2. As indicated by the octanol-water partition coefficient (log K_{ow}) and octanol-air partition coefficient (log K_{oa}) values, PAHs are generally solids at room temperature; they have moderate to low water solubility and vapor pressure. Members of this fraction generally are expected to have little to no mobility in soil, based on measured log K_{oc} data.

Table 1. Synonyms and Abbreviations for Chemicals in this PPRTV Assessment[a]

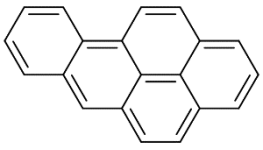
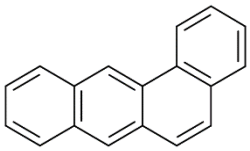
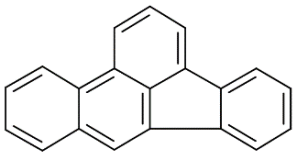
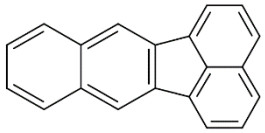
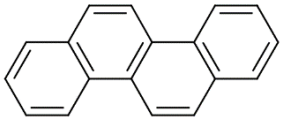
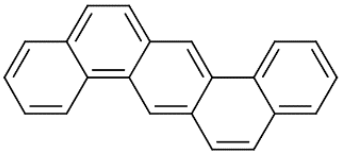
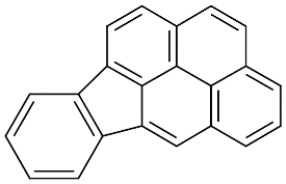
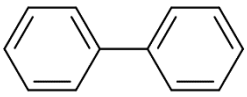
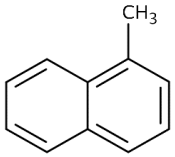
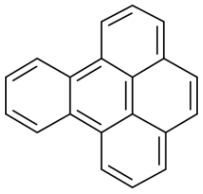
Chemical (common synonyms[b])	CASRN	Abbreviation	Structure
Benzo[*a*]pyrene (benzo[*pqr*]tetraphene; benzo[*def*]chrysene; 1,2-benzpyrene; 3,4-benzopyren; 4,5-benzpyrene; 6,7-benzopyrene)	50-32-8	BaP	
Benz[*a*]anthracene (tetraphene; benzo[*b*]phenanthrene; 1,2-benzanthracene; 2,3-benzophenanthrene; 1,2-benzanthrene; naphthanthracene)	56-55-3	BaAC	
Benz[*e*]acephenanthrylene (benzo[*b*]fluoranthene; benzo[*e*]fluoranthene; benzo[*e*]acephenanthrylene; 3,4-benz[*e*]acephenanthrylene; 2,3-benzofluoranthene; 3,4-benzofluoranthene)	205-99-2	BeAPE	

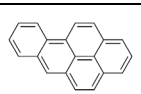
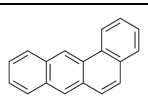
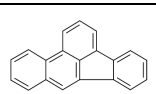
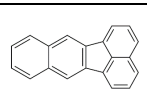
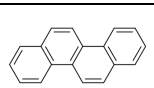
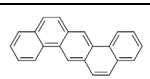
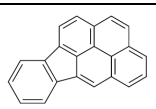
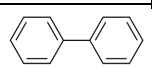
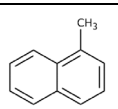
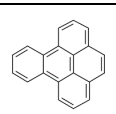
Table 1. Synonyms and Abbreviations for Chemicals in this PPRTV Assessment[a]

Chemical (common synonyms[b])	CASRN	Abbreviation	Structure
Benzo[*k*]fluoranthene (bibenzo[*b,jk*]fluorene; 8,9-benzofluoranthene; 11,12-benzofluoranthene; 2,3:1′,8′-biaphthylene)	207-08-9	BkFA	
Chrysene (benzo[*a*]phenanthrene; 1,2-benzophenanthrene)	218-01-9	CH	
Dibenz[*a,h*]anthracene (benzo[*k*]tetraphene; 1,2:5,6-dibenzoanthracene; 1,2:5,6-benzanthracene; 1,2:5,6-benz[*a*]anthracene)	53-70-3	DBahAC	
Indeno[1,2,3-*c,d*]pyrene (*o*-phenylenepyrene; 1,10-(*o*-phenylene)pyrene; 1,10-(1,2-phenylene)pyrene; 2,3-(*o*-phenylene)pyrene; 2,3-phenylenepyrene)	193-39-5	I123cdP	
1,1-Biphenyl (biphenyl; 1,1′-biphenyl)	92-52-4	BH	
1-Methylnaphthalene (naphthalene, 1-methyl-)	90-12-0	1MeNPT	
Benzo[*e*]pyrene	192-97-2	BeP	

[a]Only chemicals with toxicity values are listed.
[b]Synonyms are listed according to Nist (2020b) and include valid synonyms from U.S. EPA CompTox Chemicals Dashboard; https://comptox.epa.gov/dashboard; accessed 03-30-2020 U.S. EPA (2021).

PPRTV = Provisional Peer-Reviewed Toxicity Value; U.S. EPA = U.S. Environmental Protection Agency.

Table 2. Physicochemical Properties of Selected Aromatic High Carbon Range Compounds[a]

Chemical	BaP	BaAC	BeAPE	BkFA	CH	DBahAC	I123cdP	BH	1MeNPT	BeP
Structure										
CASRN	50-32-8	56-55-3	205-99-2	207-08-9	218-01-9	53-70-3	193-39-5	92-52-4	90-12-0	192-97-2
Molecular formula	$C_{20}H_{12}$	$C_{18}H_{12}$	$C_{20}H_{12}$	$C_{20}H_{12}$	$C_{18}H_{12}$	$C_{22}H_{14}$	$C_{22}H_{12}$	$C_{12}H_{10}$	$C_{11}H_{10}$	$C_{20}H_{12}$
EC number[b]	30.0	25.3	25.0	28.7	26.1	32.5	32.6	13.5	12.7	27.80
Molecular weight (g/mol)	252.316	228.294	252.316	252.316	228.294	278.354	276.338	154.212	142.201	252.316
Melting point (°C)	177	159	166	217	255	268	164	69.8	−3.10	178
Boiling point (°C)	495	437	434*	480	448	524	536	255	242	469*
Vapor pressure (mm Hg at 25°C)	5.48×10^{-9}	2.10×10^{-7}	5.00×10^{-7}	9.65×10^{-10}	6.23×10^{-9}	9.55×10^{-10}	7.05×10^{-10}*	8.93×10^{-3}	6.70×10^{-2}	5.70×10^{-9}
Henry's law constant (atm-m^3/mol at 25°C)	4.57×10^{-7}	1.20×10^{-5}	6.57×10^{-7}	5.84×10^{-7}	5.23×10^{-6}	9.24×10^{-7}*	3.48×10^{-7}	3.08×10^{-4}	5.14×10^{-4}	1.07×10^{-6}*
Water solubility (mg/L at 25°C)	8.4×10^{-9}	5.23×10^{-8}	9.4×10^{-9}	3.2×10^{-9}	1.22×10^{-8}	4.31×10^{-9}	6.9×10^{-10}	4.60×10^{-5}	1.95×10^{-4}	1.89×10^{-8}
Log K_{ow}	6.13	5.6	5.78	6.11	5.81	6.63	6.74*	4.01	3.87	6.44
Log K_{oa}	9.61*	9.37*	8.64*	9.38*	9.37*	11.7*	11.7*	6.15	5.01*	10.3*
Log K_{oc}	5.95	5.30	5.42*	4.34	5.20*	6.22	6.20	3.27	3.36	5.67*

[a]Data are presented as experimental averages from the U.S. EPA CompTox Chemicals Dashboard unless otherwise stated; https://comptox.epa.gov/dashboard; updated 02-03-2021 U.S. EPA (2021).
[b]EC number was developed by the TPHCWG and is proportional to the BP of a chemical. EC number is analogous to an *n*-paraffin retention time index and can be estimated using the following equation: EC = 4.12 + 0.02 (BP) + 6.5×10^{-5} $(BP)^2$ NIST (2020a; Edwards et al. (1997; Gustafson et al. (1997b).
*Predicted value.

BaAC = benz[*a*]anthracene; BaP = benzo[*a*]pyrene; BeAPE = benz[*e*]acephenanthrylene; BeP = benzo[*e*]pyrene; BH = 1,1-biphenyl; BP = boiling point; BkFA = benzo[*k*]fluoranthene; CH = chrysene; DBahAC = dibenz[*a,h*]anthracene; EC = equivalent carbon; I123cdP = indeno[1,2,3-*c,d*]pyrene; K_{oa} = octanol-air partition coefficient; K_{oc} = soil adsorption coefficient; K_{ow} = octanol-water partition coefficient; 1MeNPT = 1-methylnaphthalene; TPHCWG = Total Petroleum Hydrocarbon Criteria Working Group; U.S. EPA = U.S. Environmental Protection Agency.

Volatilization of members of this fraction from water and moist soil will be moderate based upon the measured Henry's law constant values. Volatilization from dry soil surfaces is expected to be low to moderate based upon the measured vapor pressure values. Measured aerobic and anaerobic biodegradation data are available for the representative compounds. Under aerobic conditions, some PAHs are expected to have slow removal by biodegradation in unacclimated systems and more rapid biodegradation in acclimated systems. Acclimation periods (days to months) have been observed prior to the onset of microbial degradation in tests using soil not previously exposed to PAHs. It is thought that this occurs because small population(s) of organisms capable of PAH degradation must attain sufficient densities before detectable PAH reduction is observed Mihelcic and Luthy (1988). 1,1-Biphenyl undergoes biodegradation more readily than many PAHs, as demonstrated in a modified test where 1,1-biphenyl achieved 66% of its theoretical biochemical oxygen demand (BOD) after 14 days ECHA (2019; Oecd (2009). Under anaerobic conditions, biodegradation reactions are believed to occur slowly for all fraction members. Members of the aromatic high carbon range fraction do not contain hydrolysable functional groups; therefore, the rate of hydrolysis is expected to be negligible for all fraction members. In the atmosphere, the rate of photooxidation is expected to be moderate for fraction members. Many of the fraction members, except, for example, 1,1-biphenyl, contain chromophores that absorb at wavelengths >290 nm, and are therefore expected to be susceptible to direct photolysis by sunlight NLM (2017a, b, c, d, e, f, g, 2015a, b, 2014, 2005). When the fraction members occur in the atmosphere in the particulate phase, they will be physically removed by wet and dry deposition.

1.3. OVERVIEW OF MIXTURE ASSESSMENT METHODS

A number of different approaches have been developed and used to estimate risks and hazards posed by exposures to chemical mixtures encountered in the environment. The three utilized in this PPRTV assessment are the indicator chemical approach, the relative potency factor approach, and integrated addition. The choice of approaches is based on the available analytical chemistry.

The simplest of these approaches to implement is the indicator chemical approach Atsdr (2018). The indicator chemical approach estimates the risk or hazard of a mixture by evaluating the dose-response assessment developed for a component of the mixture to the exposure rate of the entire mixture. The indicator chemical approach is used when there are only measures of the concentrations of this fraction (i.e., no information is available on the concentrations of individual chemicals in this fraction).

In addition to the indicator approach, the U.S. Environmental Protection Agency (EPA) *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (U.S. EPA (2000, 1986) describes the following two broad categories of approaches for assessing human health risks and health hazards associated with environmental exposures to chemical mixtures: component methods and whole mixture methods. Component-based approaches, which involve analyzing the toxicity of a mixture's individual components, have more inherent uncertainty and are recommended when appropriate toxicity data on a mixture of concern, or on a sufficiently similar mixture (discussed below), are unavailable U.S. EPA (2000, 1986). In this PPRTV assessment, two component approaches are described for assessing cancer risks posed by exposures to the aromatic high carbon range fraction, when there are sufficient component exposure and toxicity data: (1) the relative potency factor (RPF) approach is used to evaluate cancer risks posed by selected PAHs and (2) a general integrated addition approach is used to

assess cancer risks posed by the aromatic high carbon range fraction. This includes a group of PAHs that mediate carcinogenicity through a mutagenic mode of action (MOA), as well as two other non-PAH carcinogens (i.e., 1,1-biphenyl and 1-methylnaphthalene) placed in separate groups because their carcinogenicity does not appear to be mediated through a mutagenic MOA. These component-based approaches are pursued and described in subsequent sections of this assessment.

Chemical mixture assessments are conducted most appropriately with quantitative dose-response information resulting from comparable exposures to the mixture of concern. If the dose-response data are insufficient to develop a health reference value for the specific mixture of concern in the environment, the second option that the U.S. EPA *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* U.S. EPA (2000) recommends is a "sufficient similarity" approach that uses a health reference value from a characterized surrogate mixture to estimate the hazard or risk associated with exposures to the mixture of concern. This method requires chemistry and toxicity data on both the potential surrogate mixture and the mixture of concern (e.g., an in vitro endpoint that is related to the apical endpoint observed in an epidemiological study or whole animal study), and a health reference value (e.g., from an in vivo study) on the surrogate mixture. If the chemistry and toxicity data indicate that the mixtures are "sufficiently similar" to one another, then the health reference value for the surrogate mixture can be used as a proxy for the mixture of concern. No data were identified that were suitable to implement a whole mixture approach.

The choice of a chemical mixtures risk assessment method is driven by the available data. Starting with the method requiring the least information and then discussing methods requiring more information, the following subsections summarize the indicator chemical approach, the RPF approach, and the integrated addition approach.

1.3.1. Indicator Chemical Approach

When the chemical composition of a mixture or a mixture fraction is not known, or toxicity measures are only available for a few individual chemicals in a mixture, the toxicity of an individual chemical can be used as an indicator for the toxicity of a mixture or a mixture fraction Atsdr (2018). Atsdr (2018) describes an indicator chemical as "a chemical . . . selected to represent the toxicity of a mixture because it is characteristic of other components in the mixture and has adequate dose-response data." Indicator chemical approaches are typically implemented to assess risks in a health-protective manner; the chemical chosen as an indicator is among the best characterized toxicologically and likely among the most toxic components of the mixture. The indicator chemical needs to have adequate dose-response data to indicate hazard potential or dose-response relationship for cancer, depending on the purpose of the assessment. The health risk value of the indicator chemical is integrated with exposure estimates for the mixture or mixture fraction to estimate health risk from the group (i.e., calculate fraction-specific hazard index or a fraction-specific cancer risk estimate for a specific exposure pathway). This approach does not scale for the potency of individual constituents; instead, it assumes that toxicity of all measured members of the fraction can be adequately estimated, given the purpose of the risk assessment, by the indicator chemical.

1.3.2. Relative Potency Factor Approach

The RPF approach is a component-based approach that assumes components in a mixture act in a toxicologically similar manner. Such an assumption can be made when toxicologic data on all components of a mixture are not available, and when the class of chemicals comprising the mixture shares a known or suspected common MOA. Implementing an RPF approach requires a quantitative dose-response assessment for an index chemical (IC) and pertinent scientific data that allow the toxic potency of the mixture components to be meaningfully compared to that of the IC.

Under the assumption of dose addition, the health risk associated with exposure to a mixture can be estimated as follows: initially, the chemical component doses are scaled relative to the potency of an IC, and then these scaled doses are summed and expressed as an index chemical equivalent dose (ICED) for the mixture. For any given mixture, the general equation below highlights the steps involved in estimating the ICED.

$$\mathrm{ICED} = \sum \mathrm{RPF_i} D_i + D_{\mathrm{IC}}$$

where

$IC =$ index chemical
$ICED =$ index chemical equivalent dose of the mixture (e.g., mg/kg-day)
$RPF_i =$ relative potency factor of the *i*th PAH detected in the mixture (unitless)
$D_i =$ dose of the *i*th chemical detected in the mixture (mg/kg-day)
$D_{IC} =$ dose of index chemical in the mixture (mg/kg-day), given that the value of the RPF for the IC is 1

RPFs for individual components can be estimated using the slope factors of the *i*th components.

$$\begin{aligned} RPF_j &= slope_j \div slope_{IC} \\ &= R/BMD_{R-i} \div R/BMD_{R-IC} \\ &= BMD_{R-IC} \div BMD_{R-i} \end{aligned}$$

where

$BMD =$ benchmark dose
$R =$ response

Next, a plausible upper bound on cancer risk can be estimated by multiplying the ICED by the cancer risk estimate for the IC (e.g., oral slope factor [OSF] in $[\text{mg/kg-day}]^{-1}$, oral unit risk in $[\text{mg/L}]^{-1}$, or inhalation unit risk (IUR) in $[\text{mg/m}^3]^{-1}$).

1.3.3. Integrated Addition Approach

Many mixture exposures, including the aromatic high carbon range fraction, contain component chemicals that cause cancer in toxicologically dissimilar ways. This recognition of the different bioactivities associated with complex mixtures led the U.S. EPA to develop a hybrid general additivity approach that incorporated both dose addition and response addition, yielding the probabilistic risk of the toxicologically relevant endpoint of concern—in this case, carcinogenic risk of the mixture. While an RPF approach may be most applicable to an assessment of cancer risk posed by PAHs comprised of the aromatic high carbon TPH fraction, other TPH members of this fraction (e.g., 1-methylnaphthalene and 1,1-biphenyl) may cause cancer through different MOAs. For exposures to mixtures composed of such components and when needed data are available, the U.S. EPA recommends the use of an integrated addition approach.

For chemicals eliciting a common endpoint, the integrated addition approach begins with separation of the mixture components into dose-additive groups U.S. EPA (2003) based on similar MOAs (i.e., "similarity groups"). Next, the assumptions of similarity within groups, and then of toxicological independence across groups, are evaluated. If there are interactions [defined by the U.S. EPA as a deviation from results predicted using an additivity model with individual component exposure and dose-response data U.S. EPA (2000); e.g., synergism or antagonism], other mixture assessment methods would be preferred. Otherwise, within each similarity group, the RPF approach is used to estimate the health risk associated with exposures to the group of chemicals. The similarity group risks are then combined across all groups using response addition to estimate the risk posed by the entire mixture U.S. EPA (2000). In this assessment, the MOAs of chemicals such as 1,1-biphenyl are assumed to be independent from the MOAs of the PAHs. The specific steps of the integrated addition approach include:

- Forming toxicological similarity groups based on available information on MOA (e.g., two similarity groups could cause the same effect through different MOAs); similarity groups can vary in size from a single member to many members.
- Selecting an IC for each similarity group.
- Developing RPFs for each similarity group, reflecting intragroup potency differences, and exposure estimates.
- Calculating an ICED for each similarity group, based on the RPFs and component exposure estimates.
- Calculating each similarity group mixture risk (as probability) for the common effect(s) using the IC dose-response function.
- Estimating the total mixture risk using response addition across the similarity group risk estimates using the following equation:

$$R_{MIX} = \sum R_J$$

where

R_{MIX} = risk posed by the mixture
R_J = risk posed by the *j*th subgroup (unitless)

1.3.4. Limitations and Uncertainties Associated with Component Methods

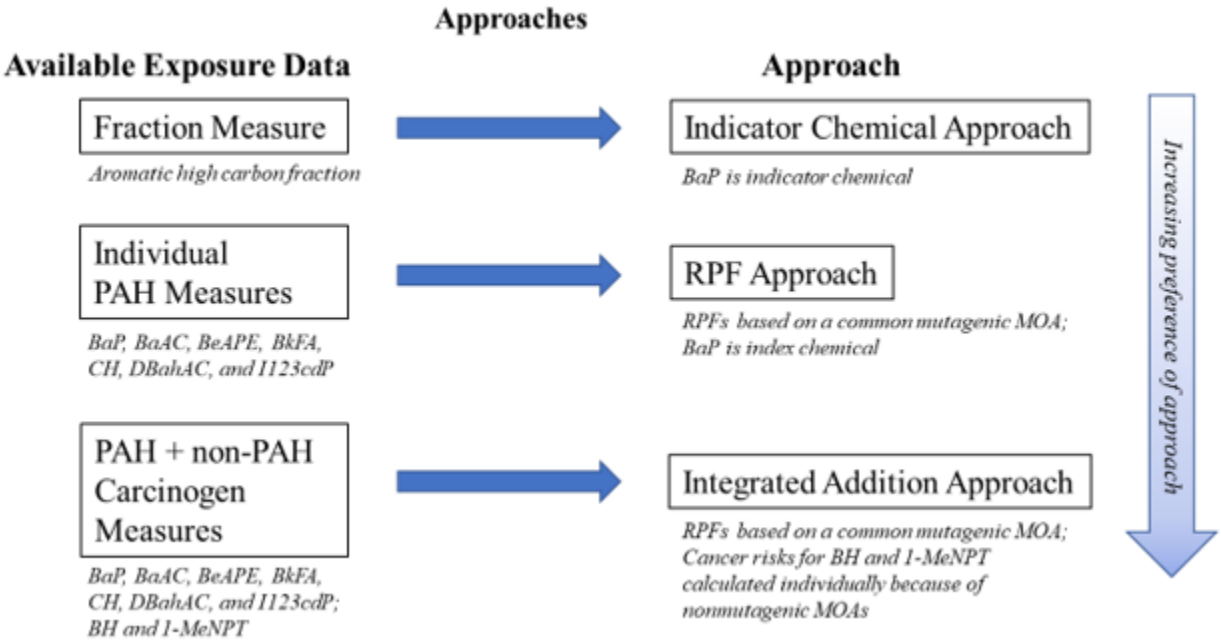
Component methods involve substantial uncertainties that should be considered prior to their application. In particular, component methods can be misinterpreted to reflect well-characterized risk, due to knowledge of chemical component concentrations. In fact, a poor understanding of the magnitude and nature of toxicological interactions can limit the confidence of calculated risk. In addition, information is often lacking on the identity of some mixture components, and mixture composition is often affected by fate and transport processes. As a result, real-world mixture exposures may not always be reflective of unweathered mixtures tested in laboratory settings. The IC and/or indicator chemical is selected based on the best available data, even though all components of the fraction have not been structurally well-characterized or tested for carcinogenic potential.

1.4. REVIEW OF AVAILABLE ASSESSMENTS

The U.S. EPA relied on the literature search described in a separate PPRTV assessment that evaluates noncancer hazards associated with exposures to the aromatic high carbon range fraction of TPH mixtures U.S. EPA (2022b); in addition, in June of 2020 and August of 2021, U.S. EPA searched the literature to identify constituents of the fraction having existing cancer risk values or relative potency estimates in the Integrated Risk Information System [IRIS], PPRTV assessments, and U.S. EPA documents. These cancer risk values and relative potency estimates are used in the approaches described below.

1.5. DOCUMENT OVERVIEW

The remainder of the document is divided into three sections. Each section describes, in detail, the application of the approach to the assessment of cancer risk posed by exposure to the aromatic high carbon fraction, including the information needed to implement each approach. Section 2 addresses the indicator chemical approach and the selection of BaP as an indicator chemical for the assessment of cancer risks posed by inhalation and oral route exposures to the aromatic high carbon range fraction. Section 3 describes the U.S. EPA's RPFs for some PAHs, a group of chemicals assumed to be toxicologically similar within the aromatic high carbon range fraction. It also describes the selection of BaP as the IC. Section 4 details the integrated addition approach as implemented for carcinogens in the aromatic high carbon range fraction including those that are and are not PAHs. Figure 1 summarizes the three approaches and indicates preference order for each approach.



Three approaches are available to estimate the cancer risk associated with exposure to chemicals in the aromatic high carbon range fraction. Approach selection should be driven by the available exposure data. Increased analytical characterization of fraction components allows for more refined risk estimates with less inherent uncertainty. Approach preference is inversely correlated with approach uncertainty.

BaAC = benz[*a*]anthracene; BaP = benzo[*a*]pyrene; BeAPE = benz[*e*]acephenanthrylene; BH = 1,1-biphenyl; BkFA = benzo[*k*]fluoranthene; CH = chrysene; DBahAC = dibenzo[*a,h*]anthracene; I123cdP = indeno[1,2,3-*c,d*]pyrene; 1-MeNPT = 1-methylnaphthalene; MOA = mode of action; PAH = polycyclic aromatic hydrocarbon; RPF = relative potency factor; TPH = total petroleum hydrocarbon.

Figure 1. Provisional Peer-Reviewed Toxicity Approaches for the Aromatic High Carbon Range TPH Fraction Cancer Assessment

2. INDICATOR CHEMICAL METHOD

For some sites that are contaminated with TPH mixtures, only the mass of the aromatic high carbon range fraction is measured; the concentrations of the individual components within the fraction are not known. In this case, an indicator chemical can be selected to represent the toxicity of the fraction. The cancer dose-response estimate for the indicator chemical can be integrated with the exposure data for the entire mass of the fraction to estimate cancer risk posed by exposure to the fraction. This approach can be considered a health-protective default approach used to evaluate potential cancer risks from exposures to the aromatic high carbon hydrocarbon fraction. The primary assumption is that the cancer OSF and IUR of the indicator chemical provide a reasonable or health-protective estimate of those for the entire fraction. Sections 2.1 and 2.1.1 describe the criteria for selecting an indicator chemical.

2.1. CONSIDERATIONS FOR INDICATOR CHEMICAL SELECTION FOR THE AROMATIC HIGH CARBON HYDROCARBON FRACTION CANCER ASSESSMENT

The criteria suggested for selecting chemicals for potential use as indicator chemicals for the aromatic high carbon range fraction cancer assessment are as follows:

- The indicator chemical should occur in the aromatic high carbon range (i.e., within the C and EC number range of the hydrocarbon fraction).
- The health effect(s) of the indicator chemical must be similar to what is observed from exposures to the fraction or what is anticipated based on available studies of the identified components of the fraction. For this cancer assessment, the carcinogenicity associated with potential indicator chemicals needed to be characterized (i.e., for a cancer assessment, it should be characterized as a carcinogen).
- The indicator chemical should have available cancer risk estimates (e.g., OSF or provisional oral slope factors [p-OSFs]) from the U.S. EPA or another appropriate source, or adequate data for the direct derivation of cancer risk estimates.
- The carcinogenic potency of the indicator chemical should be similar to, or greater than, those of the other likely fraction components.

2.1.1. Indicator Chemical Selection

BaP was selected as the indicator chemical for the fraction following consideration of other chemicals in the fraction. Initially, the U.S. EPA considered 17 chemicals that occur in this fraction that the Agency for Toxic Substances and Disease Registry (ATSDR) evaluated in their PAH profile Atsdr (1995); see Table 3. ATSDR's rationale for choosing these 17 chemicals included: (1) more information was available on these than on the others; (2) they were suspected to be more harmful than some of the others; and (3) there was documentation of effects that were known to be characteristic of PAHs. Of these 17 PAHs, BaP was the only PAH with an existing U.S. EPA OSF or IUR. Additional information that explains how BaP met the considerations articulated in Section 2.1 is summarized below.

Table 3. Chemicals Considered in the ATSDR PAH Toxicological Profile[a]			
Acenaphthene	Benzo[*a*]pyrene	Benzo[*k*]fluoranthene	Fluorene
Acenaphthylene	Benzo[*e*]pyrene	Chrysene	Indeno[1,2,3-*c,d*]pyrene
Anthracene	Benzo[*g,h,i*]perylene	Dibenz[*a,h*]anthracene	Phenanthrene
Benz[*a*]anthracene	Benzo[*j*]fluoranthene	Fluoranthene	Pyrene
Benz[*e*]acephenanthrylene			

[a]Atsdr (1995).

ATSDR = Agency for Toxic Substances and Disease Registry; PAH = polycyclic aromatic hydrocarbon.

BaP has 20 carbons, within the carbon range (C10−C32) for this fraction. The EC for BaP is 30.0, also within the range of EC11−EC35 for the fraction ATSDR (1999).

BaP has been characterized as carcinogenic to humans by international health organizations including U.S. EPA (2017) and IARC (2010); see also Straif et al. (2005). BaP has been shown to induce tumors in animal studies both at the site of administration Culp et al. (1998; Gaylor et al. (1998; Weyand et al. (1995) and at distal sites Weyand et al. (2004; Kroese et al. (2001). Table 4 lists other PAHs that have been characterized by the International Agency for Research on Cancer (IARC) as Group 1 (carcinogenic to humans), Group 2A (probably carcinogenic to humans), or Group 2B (possibly carcinogenic to humans) IARC (2010).

Table 4. PAHs Classified by the IARC as Group 2B or Greater Human Carcinogens[a]

Common Name	Group
Benz[*j*]aceanthrylene	2B
Benz[*a*]anthracene[b]	2B
Benzo[*b*]fluoranthene[b] (benz[*e*]acephenanthrylene in this assessment)	2B
Benzo[*j*]fluoranthene	2B
Benzo[*k*]fluoranthene[b]	2B
Benzo[*c*]phenanthrene	2B
Benzo[*a*]pyrene[b]	1
Chrysene[b]	2B
Cyclopenta[*cd*]pyrene	2A
Dibenz[*a,h*]anthracene[b]	2A
Dibenzo[*a,h*]pyrene	2B
Dibenzo[*a,i*]pyrene	2B
Dibenzo[*a,l*]pyrene	2A
Indeno[1,2,3-*c,d*]pyrene[b]	2B

[a]IARC (2010).
[b]Also classified by the U.S. EPA as "*Carcinogenic to Humans*" or as *probable human carcinogens* U.S. EPA (2017, 1991).

Group 1 = *carcinogenic to humans*; Group 2A = *probably carcinogenic to humans*; Group 2B = *possibly carcinogenic to humans*; IARC = International Agency for Research on Cancer; PAH = unsubstituted polycyclic aromatic hydrocarbon; U.S. EPA = U.S. Environmental Protection Agency.

PAHs are observed and measured in mixtures that are known to be carcinogenic to humans, and treatments with various PAH mixtures and individual PAHs promote tumor development in laboratory animals Atsdr (1995). There is strong evidence of carcinogenicity among human occupational exposure studies involving PAH mixtures containing BaP, such as aluminum production, chimney sweeping, coal gasification, coal-tar distillation, coke production, iron and steel founding, and paving and roofing with coal tar pitch. Of these studies, several demonstrate a positive exposure-response relationship with cumulative BaP exposure and lung cancer U.S. EPA (2017). Individual PAHs also have been associated with increased tumorigenesis primarily in laboratory animal bioassays. U.S. EPA (1991) previously categorized seven PAHs as Group B2, *probable human carcinogens* (see Section 3.2), under the 1986 U.S. EPA Cancer Guidelines U.S. EPA (1986).

Laboratory animal evidence supporting the carcinogenic potential of BaP via oral and dermal routes of administration is robust, including dose-response data in multiple species U.S. EPA (2017). Two well-conducted, chronic oral cancer bioassays provided dose-response data Kroese et al. (2001; Culp et al. (1998) and supported development of an OSF. Kroese et al. (2001) conducted a gavage study of BaP carcinogenicity in rats of both sexes and found that BaP induced tumors at multiple sites, specifically in the liver, forestomach, auditory canal, and oral

cavity. In a study using B6C3F1 female mice exposed to BaP in the diet Beland and Culp (1998; Culp et al. (1998), the study authors reported portal-of-entry tumors, including papillomas and/or carcinomas of the forestomach, esophagus, tongue, and larynx. Dermal exposure studies using BaP with several strains of mice demonstrated dose-response trends for skin tumors across a range of doses and study durations Sivak et al. (1997; Grimmer et al. (1984; Habs et al. (1984; Grimmer et al. (1983; Habs et al. (1980; Schmähl et al. (1977; Schmidt et al. (1973; Roe et al. (1970; Poel (1963, 1959).

In comparison to the data available for oral and dermal routes of exposure, BaP dose-response data are more limited for the inhalation route. The only inhalation carcinogenicity study of BaP Thyssen et al. (1981) was limited by an atypical delivery method (adsorption onto salt crystals), but clearly demonstrated upper respiratory tract tumors following BaP exposure in hamsters and supported estimation of an IUR U.S. EPA (2017). Positive responses were also reported in several studies employing intratracheal instillation of BaP Feron and Kruysse (1978; Feron et al. (1973; Henry et al. (1973; Saffiotti et al. (1972).

Although the exact composition of complex PAH mixtures varies, BaP is routinely detected in many occupational and urban settings IPCS (1998; Petry et al. (1996; Atsdr (1995; Hecht et al. (1974) and in environmental media contaminated with PAH mixtures Shen (2016; Delgado et al. (2005). Given the frequency of detection and its relative carcinogenic potency among PAHs routinely detected in the environment, BaP has therefore been proposed to contribute significantly to the overall carcinogenicity of a PAH mixture, even when present in low concentrations Petry et al. (1996; U.S. EPA (1993).

Finally, in 2017, the U.S. EPA concluded that under U.S. EPA's *Guidelines for Carcinogen Risk Assessment* U.S. EPA (2005), BaP is "*Carcinogenic to Humans*" based on strong and consistent evidence in animals and humans U.S. EPA (2017). The U.S. EPA also published a cancer OSF and an IUR for BaP on IRIS. The OSF was 1 per mg/kg-day based on forestomach, esophagus, tongue, and larynx tumors observed in Wistar rats and in female B6C3F1 mice in the Kroese et al. (2001) and Beland and Culp (1998) studies, respectively. The IUR was 6×10^{-1} per mg/m^3 based on elevated incidences of squamous cell neoplasia in the larynx, pharynx, trachea, nasal cavity, esophagus, and forestomach in Wistar rats observed by Thyssen et al. (1981). BaP is a known carcinogen in test animals following exposures through the oral, inhalation, and dermal routes of exposure. Studies in multiple animal species demonstrate that BaP is carcinogenic at multiple tumor sites (alimentary tract, liver, kidney, respiratory tract, pharynx, and skin) by all routes of exposure. Exposure to other PAH members of the aromatic high carbon fraction has been reported to promote tumorigenesis in similar target tissues. For example, increased incidences of hepatomas and pulmonary adenomas were observed in mice orally exposed to benz[*a*]anthracene Klein (1963). Forestomach papillomas were found in mice orally exposed to dibenz[*a,h*]anthracene and croton oil Berenblum and Haran (1955). Much like BaP, chrysene induces melanocytes in dermally exposed mice Iwata et al. (1981). In addition, benz[*a*]anthracene, benz[*e*]acephenanthrylene, benzo[*j*]fluoranthene, dibenz[*a,h*]anthracene, and indeno[1,2,3-*c,d*]pyrene have been shown to induce skin tumors in studies with laboratory animals Atsdr (1995). Although tumorigenesis has been observed in similar target tissues for aromatic high carbon range PAH members, BaP is among the most potent characterized carcinogens in this fraction. Thus, it is assumed that this approach will be health-protective because the carcinogenic potency of BaP is assigned to the entire fraction. In

summary, BaP meets the considerations for selection as an indicator chemical for carcinogenicity associated with this fraction U.S. EPA (2017, 1993).

2.1.2. Estimating Cancer Risk Using Indicator Chemical

Based on increased incidences of alimentary tract tumors observed in both the Kroese et al. (2001) rat bioassay and the Beland and Culp (1998) mouse bioassay, U.S. EPA (2017) estimated that the OSF for BaP was 1 per mg/kg-day. Based on increased incidences of gastrointestinal (GI) tract and respiratory tract tumors observed in the Thyssen et al. (1981) hamster bioassay, U.S. EPA (2017) estimated an IUR of 6×10^{-1} per mg/m^3. If an indicator chemical approach is used, these health reference values can be integrated with estimates of the exposure rates for the aromatic high carbon range fraction to estimate the oral or inhalation cancer risk.

$$R_{MIX} = OSF_{BaP} \times IR_F$$

where

R_{MIX} = risk posed by the mixture
OSF_{BaP} = oral slope factor for benzo[a]pyrene (per mg/kg-day)
IR_F = oral intake rate of aromatic high carbon fraction (mg/kg-day)

$$R_{MIX} = IUR_{BaP} \times C_F$$

where

R_{MIX} = risk posed by the mixture
IUR_{BaP} = inhalation unit risk for benzo[a]pyrene (per µg/m^3)
C_F = concentration of aromatic high carbon fraction in air (µg/m^3)

Of the three approaches described in this assessment, the indicator chemical method requires the least analytical characterization of the aromatic high carbon fraction, but has the most inherent uncertainty; as such, this approach is preferred only when exposure data on fraction components are unavailable. Uncertainty arises in this method because the indicator chemical is used to represent the toxicity of an untested portion of the mixture.

3. RELATIVE POTENCY FACTORS APPROACH FOR POLYCYCLIC AROMATIC HYDROCARBONS IN THE AROMATIC HIGH CARBON RANGE FRACTION

For some sites that are contaminated with TPH mixtures, the mass of the aromatic high carbon fraction and the concentrations of some individual PAHs[3] are measured. This section discusses the selection of BaP as the IC (see Section 3.1) and the use of Estimated Order of Potential Potency (EOPP) factors for seven PAHs developed in the U.S. EPA's 1993 *Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons* U.S. EPA (1993) to estimate cancer risk associated with PAHs in the aromatic high carbon TPH fraction (see Section 3.2). EOPPs are conceptually and quantitatively consistent with RPFs. RPFs are based on an assumption of dose addition. The RPF method assumes that component chemicals are toxicologically similar. It also assumes that component doses can be added when toxic potency is scaled relative to the potency of an IC. Component exposure data are required for this approach.

3.1. SELECTION OF BENZO[A]PYRENE AS AN INDEX CHEMICAL

The U.S. EPA's Mixtures Guidance U.S. EPA (2000) characterizes an appropriate IC as typically the best-studied member of the chemical class, having the largest body of high-quality data describing exposure and health effects. Further, an appropriate IC is expected to have toxic effects similar to the rest of the members of the class (i.e., effects progress to the apical endpoint via a similar MOA), and to have quantitative dose-response assessments of acceptable scientific quality, including those that allow meaningful comparison of the toxic potencies of the component chemicals and the IC. This section reviews these characteristics as they apply to BaP within the aromatic high carbon fraction.

BaP is the most suitable PAH to use as an IC for carcinogenic PAHs identified in the aromatic high carbon range TPH fraction. As described in Section 2, in addition to its structural similarity to the PAHs in this chemical class, BaP is well-studied, and has a robust evidence base of both bioassay data and MOA information.

Evidence suggests that the PAHs of the aromatic high carbon fraction (including BaP) exhibit similar structures. The carcinogenic activity of PAH compounds is influenced by specific structural features, and the relationship between these structural features and mechanistic events related to PAH carcinogenesis has been evaluated Bruce et al. (2008); Vijayalakshmi and Suresh (2008). Boström et al. (2002) reported that PAHs having four or more benzene rings generally exhibit greater carcinogenic potency than PAHs with two or three benzene rings. In addition, there is evidence that the carcinogenic activity of PAHs is also related to the specific arrangement of the benzene rings; PAHs with at least four rings and a classic bay or fjord region (see Figure 2) display a greater tendency towards bioactivation, particularly to diol epoxide metabolites, relative to other PAHs lacking these features IARC (2010). Some PAHs with these structural features have been thoroughly studied, and there is extensive documentation describing their tumorigenic potency Harvey (1991). The more highly reactive diol epoxide stereoisomers readily bind to cellular macromolecules to form protein and deoxyribonucleic acid (DNA) adducts, the latter being associated with genotoxicity. As discussed in IARC (2010) and

[3]As noted earlier in this document, the U.S. EPA defined PAHs as unsubstituted compounds with two to six fused aromatic rings made up only of carbon and hydrogen atoms. The definition of the PAHs excludes their alkyl-substituted derivatives.

elsewhere, there is a body of epidemiology literature documenting the detection of PAH-derived diol epoxide-DNA adducts in human populations exposed to complex PAH mixtures.

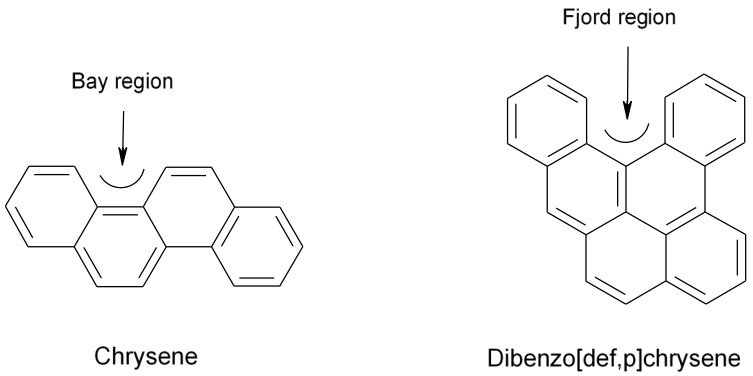


Figure 2. Bay and Fjord Regions of Polycyclic Aromatic Hydrocarbons

Those PAHs classified by the U.S. EPA as *probable human carcinogens* (see Table 4), are known to form PAH DNA adducts and are considered mutagenic IARC (2010). Given the mutagenic MOA for these PAHs, the dose-additive approach described in this section assumes that carcinogenic PAHs within this TPH fraction act in a toxicologically similar manner; that is, it is assumed that these PAHs promote carcinogenesis by a mutagenic MOA. Such an assumption is consistent with implementation of the RPF approach, which assumes toxicologic similarity when toxicity data are missing on some components of a mixture.

The various mutagenic mechanisms, as well as the existence of numerous pathways through which tumor initiation and progression may proceed, are briefly summarized below and discussed in much more detail in assessments conducted by IARC (2010), the World Health Organization IPCS (1998), Atsdr (1995), and Boström et al. (2002). Biological perturbations that have been observed to occur in response to PAH exposure and can be plausibly linked to carcinogenesis include:

- Oxidative metabolism to reactive intermediates that covalently bind to DNA, ribonucleic acid (RNA), and proteins (diol epoxide, radical cation, and *o*-quinone pathways).
- Formation of PAH DNA adducts (stable and/or depurinating adducts).
- Mutations in cancer-related genes (e.g., TP53 tumor suppressor genes or RAS oncogenes) resulting in carcinogenesis.
- Enhancement of tumor promotion and progression via alteration of gene expression and cell signaling pathways; some of these alterations are mediated through aryl hydrocarbon receptor (AhR) activation and others are elicited in response to cytotoxicity and cell signaling perturbations in the presence of BaP derived metabolic products.

At least three distinct mutagenic mechanisms have been identified by which carcinogenic PAHs are believed to act: (1) formation of diol epoxides (via cytochrome P450 [CYP450] and epoxide hydrolase metabolism) leading to stable and unstable DNA adducts, mainly at guanine and adenine sites, which can lead to mutations in protooncogenes and tumor suppressor genes; (2) radical cation (via CYP450 peroxidase metabolism) formation, leading to generation of

unstable adducts at guanine and adenine sites, and ultimately to apurinic sites and mutation in the RAS oncogenes; and (3) *o*-quinones with generation of reactive oxygen species (ROS) (via metabolism by aldo-keto reductase enzymes), leading to stable and unstable DNA adducts, and induction of mutations, including in tumor suppressor gene, *TP53* Atsdr (2018; Xu et al. (2009; Jiang et al. (2007; Jiang et al. (2005; Xue and Warshawsky (2005; Bolton et al. (2000; Penning et al. (1999; Harvey (1996; Cavalieri and Rogan (1995).

Oncogene and/or tumor suppressor gene mutations, including mutations in TP53 and the KRAS oncogene, have been observed in human lung tumors following exposure to smoky coal emissions known to contain complex mixtures of PAHs DeMarini et al. (2001). The mutation spectrum from these lung tumors appears to be unique and consistent with exposure to PAHs in the absence of cigarette smoke. In experimental animal models, KRAS and HRAS oncogenes and/or TP53 tumor suppressor gene mutations in forestomach, lung, and skin tumors have also been observed following PAH exposure Chakravarti et al. (2008; Conney et al. (2001; Culp et al. (2000; Smith et al. (2000; Nesnow et al. (1998; Nesnow et al. (1996, 1995; Mass et al. (1993).

Cellular proliferation following PAH exposure has been associated with several distinct key events including AhR activation, cytotoxicity, and inflammation. Some, but not all, PAHs bind to the AhR, which leads to upregulation of genes related to growth and differentiation Boström et al. (2002). AhR-null mice were found to be completely resistant to BaP-induced complete skin carcinogenesis Shimizu et al. (2000). Some PAHs are metabolized to *o*-quinones, which can generate cytotoxic ROS Bolton et al. (2000; Penning et al. (1999; Flowers-Geary et al. (1996; Flowers-Geary et al. (1993), with the resulting inflammation potentially contributing to the tumor promotion process. Other mechanisms by which PAHs affect cell survival, growth, and differentiation, thus contributing to tumor promotion and progression, include sustained alterations of cell cycle processes (e.g., activation of epidermal growth factor receptor, *ras*/*raf*/mitogen-activated protein kinase, and cyclooxygenase-2-generated prostaglandin E2 signaling), elevated polyamine synthesis through ornithine decarboxylase induction, resistance to apoptosis, inhibition of gap junctional intracellular communication, and suppression of the immune system IARC (2010; Rundhaug and Fischer (2010).

3.2. U.S. EPA'S RELATIVE POTENCY FACTOR APPROACH FOR POLYCYCLIC AROMATIC HYDROCARBONS

In 1993, the U.S. EPA published the *Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons*, a component-based approach to assessing cancer risks posed by PAH mixtures in the environment, that recommended RPFs termed "estimated order of potential potency" (EOPP) factors for seven PAHs [see Table 5; U.S. EPA (1993)]. The seven unsubstituted PAHs included: BaP, benz[*a*]anthracene, benz[*e*]acephenanthrylene (synonym, benzo[*b*]fluoranthene), benzo[*k*]fluoranthene, chrysene, dibenz[*a,h*]anthracene, and indeno[1,2,3-*c,d*]pyrene. U.S. EPA (1991) previously categorized these seven PAHs as Group B2, *probable human carcinogens* under the 1986 U.S. EPA Cancer Guidelines U.S. EPA (1986). This RPF approach focused on unsubstituted PAHs that had three or more fused aromatic rings containing only carbon and hydrogen atoms. In addition to structural similarity, these well-studied PAHs demonstrate the formation of DNA-reactive metabolites that are associated with the induction of DNA damage and tumorigenesis, which appears to be mediated through a mutagenic MOA. The underpinning of the RPF approach is the concept of dose additivity, which follows from an assumption of toxicological similarity. Specifically, the toxicodynamic response pathways of dose-additive chemicals share at least one

common key event (i.e., biochemical process) that links a molecular initiating event to an apical outcome (or multiple related apical health outcomes). The doses or their resulting products "add" at this key event. Given that all PAHs in this approach are assumed to be carcinogenic via a mutagenic MOA, the estimation of cancer risks posed by PAH mixtures in the aromatic high carbon range fraction relies on an assumption of dose addition among component chemicals.

Table 5. RPFs for PAH Carcinogenicity in the U.S. EPA 1993 Provisional Guidance[a]

PAH (abbreviation)	RPF	Data Source(s)
Benzo[*a*]pyrene (BaP)	1	NA
Benz[*a*]anthracene (BaAC)	0.1	Bingham and Falk (1969)
Benz[*e*]acephenanthrylene (BeAPE)[b]	0.1	Habs et al. (1980)
Benzo[*k*]fluoranthene (BkFA)	0.01	Habs et al. (1980)
Chrysene (CH)	0.001	Wynder and Hoffmann (1959)
Dibenz[*a,h*]anthracene (DbahAC)	1	Wynder and Hoffmann (1959)
Indeno[1,2,3-*c,d*]pyrene (I123cdP)	0.1	Habs et al. (1980); Hoffmann and Wynder (1966)

[a]U.S. EPA (1993).
[b]Formerly benzo[*b*]fluoranthene.

NA = not applicable; PAH = polycyclic aromatic hydrocarbon; RPF = relative potency factor; U.S. EPA = U.S. Environmental Protection Agency.

The assessment in U.S. EPA (1993) focused on the structurally similar PAHs that have tumor incidence data from in vivo animal skin painting bioassays. This RPF approach acknowledges the complexity of the tumor development process and the likely differences in other key events among different PAHs. Most importantly, it avoids the excessive uncertainty of basing PAH relative potency on specific precursor events having uncertain quantitative relationships with actual tumor formation. The EOPP values were all calculated from lifetime "skin painting" bioassays and were rounded to the closest order of magnitude.

3.2.1. Estimating Cancer Risk Using the Relative Potency Factor Approach

If an RPF approach is used, the BaP OSF and IUR estimates can be integrated with estimates of the individual PAH exposure rates (or concentrations) to estimate the oral or inhalation cancer risk associated with exposure to the fraction.

$$R_{MIX} = OSF_{BaP} \times ICED$$

where

R_{MIX} = risk posed by the mixture
OSF_{BaP} = oral slope factor for benzo[a]pyrene (per mg/kg-day)
$ICED$ = index chemical equivalent dose (mg/kg-day)

The doses of the individual components are scaled by the RPFs found in Table 5, and then summed to yield the ICED of the entire mixture ($ICED_{MIX}$).

$$ICED_{MIX} = \sum_{j=1}^{n} d_j \times RPF_j$$

where

d = dose of the individual mixture component (mg/kg-day)
RPF = relative potency factor associated with the individual mixture component (unitless)

An identical approach can be applied to inhalation concentrations as applied to exposure via oral exposure.

$$R_{MIX} = IUR_{BaP} \times ICEC$$

where

R_{MIX} = risk posed by the mixture
IUR_{BaP} = inhalation unit risk for benzo[a]pyrene (per µg/m^3)
$ICEC$ = index chemical equivalent concentration (µg/m^3)

$$ICEC_{MIX} = \sum c_j \times RPF_j$$

where

c = concentration of the individual mixture component (µg/m^3)
RPF = relative potency factor associated with individual mixture component (unitless)

Of the three approaches described in this assessment, the RPF approach requires analytical characterization of some carcinogenic PAH components of the aromatic high carbon fraction; as such, this approach is preferred when component exposure data for carcinogenic PAHs, but not non-PAH carcinogens, are available. Uncertainty exists in the RPF approach because it does not use direct toxicity and dose-response data for every member of its chemical class.

4. USING INTEGRATED ADDITION TO ESTIMATE CANCER RISKS POSED BY POLYCYCLIC AROMATIC HYDROCARBONS AND OTHER CARCINOGENS IN THE AROMATIC HIGH CARBON FRACTION

For some sites that are contaminated with TPH mixtures, the mass of the aromatic high carbon range fraction and the concentrations (or exposure rates) of some individual PAHs and other carcinogens that are not PAHs and occur in this fraction are measured. This section describes the use of an integrated addition model to estimate cancer risks posed by PAHs, subPAHs, and other carcinogenic fraction members measured in the aromatic high carbon fraction. For chemicals eliciting a common endpoint, the integrated addition approach begins with identification of different dose-additive groups based on suspected or known MOAs for chemicals identified in the fraction, and then the mixture components are assigned into these dose-additive groups based on toxicological similarity U.S. EPA (2003). Next, the assumptions of similarity within groups and then of toxicological independence across groups are evaluated. If there are interactions [e.g., U.S. EPA (2000) explains that interactions are departures from what would be expected under some form of additivity, such as synergism)], other mixture assessment methods would be preferred. Otherwise, within each similarity group, the RPF approach is used to estimate the group risk. The similarity group risks are then combined across all groups using response addition to estimate mixture risk U.S. EPA (2000).

This assessment assumes that the carcinogenic MOAs of the PAHs are independent of the subPAH, 1-methylnaphthalene, and the other carcinogenic fraction member, 1,1-biphenyl. As explained in Section 3.1, the PAHs, distinct from the subPAH and the other carcinogenic fraction members, appear to mediate their carcinogenic activity through a mutagenic MOA. The carcinogenicity of 1,1-biphenyl does not appear to be related to mutagenicity; metabolites of this compound may induce genetic damage through oxidative damage and cytotoxicity, leading to carcinogenic responses (see Section 4.1). For 1-methylnaphthalene, the MOA data from a small number of genotoxicity tests suggest equivocal evidence of a mutagenic MOA (see Section 4.2).

4.1. 1,1-BIPHENYL ORAL CANCER ASSESSMENT

Published in 2013, the IRIS assessment for 1,1-biphenyl (CASRN 92-52-4) concluded that, under U.S. EPA's *Guidelines for Carcinogen Risk Assessment* U.S. EPA (2005), the database for 1,1-biphenyl provides "*Suggestive Evidence of Carcinogenic Potential*" U.S. EPA (2013). This was based on an increased incidence of urinary bladder tumors in male F344 rats Umeda et al. (2002) and liver tumors in female BDF1 mice Umeda et al. (2005) exposed to 1,1-biphenyl in the diet for 104 weeks, as well as information on mode of carcinogenic action. U.S. EPA (2013) concluded that the in vitro evidence did not indicate that 1,1-biphenyl was mutagenic; however, biphenyl metabolites may induce genetic damage through oxidative damage and cytotoxicity.

The U.S. EPA derived a screening OSF of 8×10^{-3} per mg/kg-day U.S. EPA (2013). This is based on an analysis of liver adenomas or carcinomas that occurred in female BDF1 mice following oral exposures to 1,1-biphenyl Umeda et al. (2005). U.S. EPA (2013) did not derive an IUR for 1,1-biphenyl.

4.2. 1-METHYLNAPHTHALENE CANCER ASSESSMENT

The 2005 PPRTV assessment for 1-methylnaphthalene (CASRN 90-12-0) concluded that, under the U.S. EPA's *Guidelines for Carcinogen Risk Assessment* U.S. EPA (2005), the database for 1-methylnaphthalene provides "*Suggestive Evidence of Carcinogenic Potential*" U.S. EPA (2008). U.S. EPA (2008) reported that the database of information regarding the carcinogenicity of 1-methylnaphthalene in laboratory animals was limited to a single carcinogenicity study. In this study, male and female B6C3F1 mice (50/sex/group) were administered 1-methylnaphthalene in the diet for 81 weeks Murata et al. (1993). Under the conditions of the study, statistically significant increased incidences of lung adenomas and combined lung adenomas and adenocarcinomas were observed in exposed male mice, but not female mice. MOA data for 1-methylnaphthalene-induced lung tumors in the male mice are limited to results of a few genotoxicity tests that provide equivocal evidence of a mutagenic MOA.

U.S. EPA (2008) derived a p-OSF of 2.9×10^{-2} per mg/kg-day. This is based on lung adenoma or carcinoma (combined) observed in male mice from the Murata et al. (1993) 81-week oral study. U.S. EPA (2008) concluded that there were no appropriate human or animal data from which to derive an IUR for 1-methylnaphthalene and the updated literature search conducted in August of 2021 by U.S. EPA found no other inhalation studies of this compound that evaluated cancer outcomes.

4.3. APPLYING THE INTEGRATED ADDITION METHOD TO ESTIMATE CANCER RISK FROM THE AROMATIC HIGH CARBON FRACTION

The U.S. EPA assumes that the MOAs for carcinogenicity associated with the PAHs, 1,1-biphenyl, and 1-methylnaphthalene exposures are toxicologically independent. In Section 1.3.2, the U.S. EPA summarized evidence that PAHs cause cancer through a mutagenic MOA. U.S. EPA (2013) concluded that 1,1-biphenyl does not appear to be mutagenic and U.S. EPA (2008) concluded that the evidence for a mutagenic MOA for 1-methylnaphthalene was equivocal. It seems reasonable to conclude that the PAHs (as defined in this assessment), 1,1-biphenyl, and 1-methylnaphthalene are toxicologically independent. At this time, 1,1-biphenyl and 1-methylnaphthalene are the only chemicals identified as having carcinogenic activity within the aromatic high carbon fraction that are not defined as PAHs in this document. The U.S. EPA assumes that the PAHs form one subgroup exhibiting a common mutagenic MOA within this fraction and that 1,1-biphenyl, with a likely nonmutagenic MOA, and 1-methylnaphthalene, with an uncertain MOA, are the only chemicals in a second group and a third group, respectively.

Given these data, the U.S. EPA suggests using an integrated addition model to evaluate carcinogenic risks. To implement such a model, the cancer risks from 1-methylnaphthalene, 1,1-biphenyl, and the PAHs need to be estimated separately.

Initially, multiplying the 1-methylnaphthalene p-OSF by its intake rate results in an estimate of the cancer risk associated with 1-methylnaphthalene. Similarly, multiplying the 1,1-biphenyl OSF by its intake rate generates an estimate of the 1,1-biphenyl cancer risk. Then, multiplying the ICED of the PAHs by the BaP OSF results in an estimate of the cancer risk associated with the PAHs. The aromatic high carbon fraction cancer risk (R_{MIX}) can be estimated by summing the calculated cancer risks from 1-methylnaphthalene, 1,1-biphenyl, and the seven PAHs.

$$R_J = OSF_J \times ICED_J$$

where

$R_J =$ risk posed by the *j*th chemical group (unitless)
$OSF_J =$ oral slope factor of the index compound of the *j*th chemical group (per mg/kg-day)
$ICED_J =$ index chemical equivalent dose of the *j*th chemical group (mg/kg-day)

$$R_{MIX} = \sum R_J$$

where

$R_{MIX} =$ risk posed by the fraction
$R_J =$ risk posed by the *j*th subgroup (unitless)

The inhalation risk equation for the PAH described in Section 3.2.1 can be used to estimate the cancer risk associated with the inhalation of this fraction.

Of the three approaches described in this assessment, the integrated addition approach requires the most analytical characterization of the aromatic high carbon fraction, but has the least inherent uncertainty; as such, this is the preferred approach for estimating the risk posed by this fraction when data are available. However, response addition of known carcinogens may yield incorrect risk estimates when there are toxicologic interactions that can enhance or inhibit the cancer potency.

5. CONCLUSION

This PPRTV assessment provides three approaches for evaluating the cancer risk associated with exposures to the aromatic high carbon range fraction. The selection of a specific approach depends on the available data. The application of the indicator chemical method requires concentration or exposure rate data for the fraction. This is the least preferred of the three approaches because of the assumption that the entire fraction is as carcinogenic as BaP. The application of the RPF method requires concentration or exposure rate data for up to seven individual PAHs. The application of the integrated addition method requires exposure rate or concentration data on individual PAHs that mediate their carcinogenicity through a mutagenic MOA and other compounds that are unlikely to mediate their carcinogenicity through a mutagenic MOA of the fraction. This is the preferred method of the three approaches presented in this PPRTV assessment.

APPENDIX A. REFERENCES

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