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Provisional Peer-Reviewed Toxicity Values for

Complex Mixtures of Aliphatic and Aromatic Hydrocarbons (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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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 COMPLEX MIXTURES OF ALIPHATIC AND AROMATIC HYDROCARBONS (VARIOUS CASRNS)

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 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 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.

EXECUTIVE SUMMARY

This Provisional Peer-Reviewed Toxicity Value (PPRTV) assessment document describes a fraction-based approach to risk assessment for complex mixtures of aliphatic and aromatic hydrocarbons. This approach is implemented following a chemical analysis of the total petroleum hydrocarbon (TPH) mixture that is present. The components of TPHs are generally classified into aliphatics and aromatics, and each of these major fractions are then further separated into low, medium, and high carbon range fractions based on the number of carbon (C) atoms in the compounds and/or the compounds' equivalent carbon (EC) number index. In all, the following six fractions of TPH mixtures are addressed:

- Aliphatic low carbon range TPH fraction
- Aliphatic medium carbon range TPH fraction
- Aliphatic high carbon range TPH fraction
- Aromatic low carbon range TPH fraction
- Aromatic medium carbon range TPH fraction
- Aromatic high carbon range TPH fraction

In this effort, the U.S. EPA is updating the PPRTV assessments for the aliphatic low carbon range TPH fraction (U.S. EPA, 2022a), the aromatic medium carbon range TPH fraction (U.S. EPA, 2022d), the aromatic high carbon range TPH fraction cancer assessment (U.S. EPA, 2022b), the aromatic high carbon range TPH fraction noncancer assessment (U.S. EPA, 2022c), and the TPH mixture assessment (i.e., this document). The U.S. Environmental Protection Agency (U.S. EPA) published its PPRTV assessments for TPHs in 2009. The primary motivation for updating this PPRTV assessment was the release of updated toxicity values from the U.S. EPA's Integrated Risk Information System (IRIS) program and/or PPRTV assessments for several key constituents of the aliphatic low carbon range fraction and aromatic medium and high carbon range fractions since 2009. U.S. EPA also revised the fraction boundaries for the aromatic medium and high carbon range fractions both to align the fraction definitions with the fractions resulting from current analytical methods and to avoid grouping the generally less toxic substituted benzenes (now in the aromatic medium carbon fraction) with the polycyclic aromatic hydrocarbons (PAHs), naphthalenes, and 1,1-biphenyl (in aromatic high carbon range fraction).

The fraction-based approach examines the noncancer hazards or cancer risks associated with exposure to each of six fractions defined by chemical properties, and then describes the integration of these fraction hazards and risks to evaluate hazards or risks posed by exposures to the mixture. This PPRTV assessment presents toxicity values for the aliphatic and aromatic hydrocarbon fractions, including subchronic and chronic provisional reference doses (p-RfDs) and provisional reference concentrations (p-RfCs), cancer weight-of-evidence (WOE) assessments, provisional oral slope factors (p-OSFs), and provisional inhalation unit risks (p-IURs). This document also presents risk assessment methods for these fractions and chemical mixtures that are intended to replace current approaches used at TPH-contaminated sites.

The assessment follows a data-driven approach and describes methodological options according to the available analytical chemistry data. Tables ES-1 and ES-2 summarize the selected noncancer provisional toxicity values for each fraction under two exposure options (Options 1 and 2, respectively). Option 1 is utilized when exposure data are available for the

fraction, rather than individual chemicals in the fraction; Option 2 is utilized when exposure data include measures of individual chemicals in a fraction. For cancer risk assessment, an indicator chemical or surrogate mixture approach is generally employed for each fraction; only a single option generally is utilized, because fewer cancer risk estimates are available for individual chemicals (see Table ES-3). The exception is the cancer risk assessment for the aromatic high carbon range fraction that has three options, depending on the available analytic data. For the cancer assessment for this fraction, Option 1 relies on an indicator chemical approach. Option 2 uses a component approach for selected PAHs (see Table ES-4). Option 3 relies on an integrated additivity approach that accounts for the contributions to carcinogenic risk from the selected PAH, but also the contributions of two other carcinogens that can occur in this fraction (i.e., 1,1-biphenyl and 1-methylnaphthalene).

Depending on the available information about the chemicals present, the toxicity of each of the six aliphatic or aromatic hydrocarbon fractions is estimated in one or more of the following ways.

- Indicator Chemical Approach: The toxicity value for an individual compound is selected to represent the entire fraction.
- Hazard Index (HI) Approach: A hazard quotient (HQ) is calculated as the ratio of human exposure to a health hazard reference value (RfV) for each mixture component chemical, and HQs are summed generate an HI. This approach is based on dose addition.
- Relative Potency Factor (RPF) Approach: Using RPFs, chemical component doses are scaled relative to the potency of an index chemical (IC) and these scaled doses are summed and expressed as an index chemical equivalent dose (ICED) for the mixture. This approach is based on dose addition.
- Response-Addition Approach: The response-addition approach assumes simple independent action for mixture chemicals that cause the same effect, assuming that each impact is an independent response. The response to the mixture is predicted by summing the risk estimates for the mixture components under the law of statistical independence.
- Integrated Addition Approach: Mixture components are separated into dose-additive groups based on similar mode of action (MOA); risks are calculated separately for each similarity group and summed using response addition. This approach integrates dose and response addition.
- Surrogate Mixture Approach: Chemical mixtures can be generated in a manner considered similar to a mixture (or mixture fraction) that might be encountered in the environment. Health risk values derived from toxicological tests conducted on these mixtures can be used as surrogates for a mixture that was generated by a similar process and encountered in the environment. For fractions with multiple methods available, methodology selection should be driven by the available exposure data.

Section 1 of this document defines the fractions, and provides overviews of the fraction approach and the various mixtures methods used to evaluate risks and hazards associated with the fraction. Section 2 details the literature searched and data reviewed as well as the selection of various mixture approaches. Section 3 reviews the toxicity values defined for the TPH fractions. An overview of how the presented approaches are applied in this PPRTV assessment is described in Section 4.

Table ES-1. Fraction-Specific Noncancer Toxicity Values for Option 1: Exposure Media Analyzed for BTEX and Fractions

Secondary Fraction	Assessment Method	Subchronic RfD or p-RfD (mg/kg-d)[a]	Chronic RfD or p-RfD (mg/kg-d)[a]	Subchronic RfC or p-RfC (mg/m^3)	Chronic RfC or p-RfC (mg/m^3)
Aliphatic					
Low carbon range (C5−C8 [EC5−EC8])[b]	Indicator chemical	0.05 (cyclohexene)	0.005 (cyclohexene)	2 (*n*-hexane)	0.4 (*n*-heptane)
Medium carbon range (C9−C18 [EC > 8−EC16])	Surrogate mixture	*0.1 (mid-range aliphatic hydrocarbon streams)*	*0.01 (mid-range aliphatic hydrocarbon streams)*	0.1 (mid-range aliphatic hydrocarbon streams)	0.1 (mid-range aliphatic hydrocarbon streams)
High carbon range (C19−C32 [EC > 16−EC35])	Surrogate mixture	30 (white mineral oil)	3 (white mineral oil)	NA	NA
Aromatic					
Low carbon range (C6−C8 [EC6−EC < 9])	Hazard Index	Benzene: 0.01 Toluene: 0.8 Ethylbenzene: 0.05[c] Xylenes: 0.4	Benzene: 0.004 Toluene: 0.08 Ethylbenzene: 0.1[c] Xylenes: 0.2	Benzene: 0.08 Toluene: 5 Ethylbenzene: 9 Xylenes: 0.4	Benzene: 0.03 Toluene: 5 Ethylbenzene: 1 Xylenes: 0.1
Medium carbon range (C9−C10 [EC9−EC < 11])[b]	Indicator chemical	0.04 (trimethylbenzenes)	0.01 (trimethylbenzenes)	0.2 (trimethylbenzenes)	0.06 (trimethylbenzenes)
High carbon range (C10−C32 [EC11−EC35])[b]	Indicator chemical	0.0003 (benzo[*a*]pyrene)	0.0003 (benzo[*a*]pyrene)	0.000002 (benzo[*a*]pyrene)	0.000002 (benzo[*a*]pyrene)

[a]Risk estimates in *italics* are PPRTV screening values. Screening values are not assigned confidence statements; however, confidence in these values is presumed to be low. Screening values are derived when the data do not meet all requirements for deriving a provisional toxicity value. Screening values are derived using the same methodologies and undergo the same development and review processes (i.e., internal and external peer review, etc.) as provisional values; however, there is generally more uncertainty associated with these values.
[b]Risk estimates(s) updated in 2022 as part of this TPH approach (U.S. EPA, 2022a, c, d).
[c]The subchronic p-RfD for ethylbenzene is lower than the chronic value because it was derived using data that were not available when the IRIS RfD was derived.

BTEX = benzene, toluene, ethylbenzene, and xylenes; C = carbon; EC = equivalent carbon; IRIS = Integrated Risk Information System; NA = not applicable; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; RfC = reference concentration; RfD = reference dose.

Table ES-2. Fraction-Specific Noncancer Toxicity Values for Option 2: Analytical Data Available for Individual Components and Fractions

Fraction and Carbon Range	Assessment Method	Subchronic RfD or p-RfD (mg/kg-d)[a]	Chronic RfD or p-RfD (mg/kg-d)[a]	Subchronic RfC or p-RfC (mg/m^3)[a]	Chronic RfC or p-RfC (mg/m^3)[a]
Aliphatic					
Low (C5−C8 [EC5−EC8])[b]	Hybrid	Components: Cyclohexene: 0.05 *n-Heptane: 0.003* *n*-Hexane: 0.3 Methylcyclopentane: 0.4 *2,4,4-Trimethylpentene: 0.1* Surrogate for balance of fraction:[c] 0.05 (cyclohexene)	Components: Cyclohexene: 0.005 *n-Heptane: 0.0003* *2,4,4-Trimethylpentene: 0.01* Surrogate for balance of fraction:[c] 0.05 (cyclohexene)	Components: Cyclohexane: 18 *n*-Heptane: 4 *n*-Hexane: 2 *n*-Pentane: 10 Surrogate for balance of fraction:[c] 2 (*n*-hexane)	Components: Cyclohexane: 6 *Cyclohexene: 1* *n*-Heptane: 0.4 *n*-Hexane: 0.7 *n*-Pentane: 1 Surrogate for balance of fraction:[c] 0.4 (*n*-heptane)
Medium (C9−C18 [EC > 8−EC16])	Surrogate mixture	*0.1* *(mid-range aliphatic hydrocarbon streams)*	*0.01* *(mid-range aliphatic hydrocarbon streams)*	0.1 (mid-range aliphatic hydrocarbon streams)	0.1 (mid-range aliphatic hydrocarbon streams)
High (C19−C32 [EC > 16−EC35])	Surrogate mixture	30 (white mineral oil)	3 (white mineral oil)	NA	NA
Aromatic					
Low (C6−C8 [EC6−EC < 9])	Hazard Index	Benzene: 0.01 Toluene: 0.8 Ethylbenzene: 0.05 Xylenes: 0.4	Benzene: 0.004 Toluene: 0.08 Ethylbenzene: 0.1 Xylenes: 0.2	Benzene: 0.08 Toluene: 5 Ethylbenzene: 9 Xylenes: 0.4	Benzene: 0.03 Toluene: 5 Ethylbenzene: 1 Xylenes: 0.1
Medium (C9−C10 [EC9−EC < 11])[b]	Hybrid	Components *n-Propylbenzene: 0.1* *tert-Butylbenzene: 0.1* *sec-Butylbenzene: 0.1* *n*-Butylbenzene: 0.1 Trimethylbenzenes: 0.04 Surrogate for balance of fraction:[c] 0.04 (trimethylbenzenes)	Components Isopropylbenzene: 0.1 *n-Propylbenzene: 0.1* *tert-Butylbenzene: 0.1* *sec-Butylbenzene: 0.1* *n*-Butylbenzene: 0.05 Trimethylbenzenes: 0.01 Surrogate for balance of fraction:[c] 0.01 (trimethylbenzenes)	Components: *n-Propylbenzene: 1* Trimethylbenzenes: 0.2 Surrogate for balance of fraction:[c] 0.2 (trimethylbenzenes)	Components: Isopropylbenzene: 0.4 *n-Propylbenzene: 1* Trimethylbenzenes: 0.06 Surrogate for balance of fraction:[c] 0.06 (trimethylbenzenes)

Table ES-2. Fraction-Specific Noncancer Toxicity Values for Option 2: Analytical Data Available for Individual Components and Fractions

Fraction and Carbon Range	Assessment Method	Subchronic RfD or p-RfD (mg/kg-d)[a]	Chronic RfD or p-RfD (mg/kg-d)[a]	Subchronic RfC or p-RfC (mg/m^3)[a]	Chronic RfC or p-RfC (mg/m^3)[a]
High (C10−C32 [EC11−EC35])[b]	Hybrid	Components: Acenaphthene: 0.2 Anthracene: 1 Benzo[*a*]pyrene: 0.0003 1,1-Biphenyl: 0.1 Fluoranthene: 0.1 Fluorene: 0.4 2-Methylnaphthalene: 0.004 Naphthalene: 0.6 Pyrene: 0.3 Surrogate for balance of fraction:[c] 0.0003 (benzo[*a*]pyrene)	Components: Acenaphthene: 0.06 Anthracene: 0.3 Benzo[*a*]pyrene: 0.0003 1,1-Biphenyl: 0.5 Fluoranthene: 0.04 Fluorene: 0.04 *1-Methylnaphthalene: 0.007* 2-Methylnaphthalene: 0.004 Naphthalene: 0.02 Pyrene: 0.03 Surrogate for balance of fraction:[c] 0.0003 (benzo[*a*]pyrene)	Components: *1,1-Biphenyl: 0.004* Benzo[*a*]pyrene: 0.000002; Benzo[*e*]pyrene: 0.000002 Surrogate for balance of fraction:[c] 0.000002 (benzo[*a*]pyrene)	Components: *1,1-Biphenyl: 0.0004* Benzo[*a*]pyrene: 0.000002; Benzo[*e*]pyrene: 0.000002; Naphthalene: 0.003 Surrogate for balance of fraction:[c] 0.000002 (benzo[*a*]pyrene)

[a]Toxicity values in *italics* are PPRTV screening values. Screening values are not assigned confidence statements; however, confidence in these values is presumed to be low. Screening values are derived when the data do not meet all requirements for deriving a provisional toxicity value. Screening values are derived using the same methodologies and undergo the same development and review processes (i.e., internal and external peer review, etc.) as provisional values; however, there is generally more uncertainty associated with these values.
[b]Fraction toxicity value(s) updated in 2022 (U.S. EPA, 2022c).
[c]Balance of fraction in any given exposure medium equals the total fraction mass concentration minus the sum of the mass concentrations of the individual components listed.

C = carbon; EC = equivalent carbon; NA = not applicable; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; RfC = reference concentration; RfD = reference dose.

Table ES-3. Fraction-Specific Cancer Toxicity Values

Fraction and Carbon Range	Assessment Method	OSF (mg/kg-d)$^{-1}$ [a]	IUR (mg/m^3)$^{-1}$ [a]
Aliphatic			
Low (C5−C8 [EC5−EC8])[b]	Surrogate mixture	NA; data do not support cancer risk assessment	*2.0 × 10^{-4}* (*commercial hexane*)
Medium (C9−C18 [EC > 8−EC16])	Surrogate mixture	NA; data do not support cancer risk assessment	*4.5 × 10^{-3}* (*mid-range aliphatic hydrocarbon streams*)
High (C19−C32 [EC > 16−EC35])	NA; data do not support cancer risk assessment		
Aromatic			
Low (C6−C8 [EC6−EC < 9])	Indicator chemical	Benzene: 1.5 × 10^{-2}–5.5 × 10^{-2}	Benzene: 2.2 × 10^{-3}–7.8 × 10^{-3}
Medium (C9−C10 [EC9−EC < 11])[b]	NA; data do not support cancer risk assessment		
High (C10−C32 [EC11−EC35])[b]	Indicator Chemical (Option 1); Relative Potency Factor (Option 2); Integrated Addition (Option 3)	1,1-Biphenyl: 8 ×10^{-3} *1-Methylnaphthalene: 2.9 × 10^{-2}* Benzo[*a*]pyrene: 1 See relative potency values in Table 20	Benzo[*a*]pyrene: 6 × 10^{-1}

[a]Toxicity values in *italics* PPRTV are screening values. Screening values are not assigned confidence statements; however, confidence in these values is presumed to be low. Screening values are derived when the data do not meet all requirements for deriving a provisional toxicity value. Screening values are derived using the same methodologies and undergo the same development and review processes (i.e., internal and external peer review, etc.) as provisional values; however, there is generally more uncertainty associated with these values.
[b]Toxicity value(s) updated in 2022 (U.S. EPA, 2022a, b, d).

C = carbon; EC = equivalent carbon; IUR = inhalation unit risk; NA = not applicable; OSF = oral slope factor; PAH = polycyclic aromatic hydrocarbon; RPF = relative potency factor.

Table ES-4. RPFs for PAH Carcinogenicity[a]

PAH (abbreviation)	RPF	Data Source(s) for RPF Values
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.

1. INTRODUCTION

This Provisional Peer-Reviewed Toxicity Value (PPRTV) assessment document is the principal document outlining the methodology for assessing noncancer health hazards and cancer risks associated with exposures to petroleum hydrocarbons. The methodology uses a fraction-based approach that examines the noncancer hazards or cancer risks associated with exposure to each of six fractions defined by chemical properties, and then describes the integration of these fraction hazards and risks to evaluate hazard or risk posed by exposures to the mixture. For each petroleum hydrocarbon fraction, the methodology includes the chemical mixture hazard assessment and risk assessment methods, definition of fractions, selection of indicator chemicals or specific components for the mixture risk assessment methods, and selection of toxicity values for the indicator chemicals or the specific components. This PPRTV assessment is intended to be used in conjunction with fraction-specific PPRTV assessments (U.S. EPA, 2022a, b, c, d, 2009p, q, r) and to replace current approaches used at total petroleum hydrocarbon (TPH)-contaminated sites. The fraction-specific PPRTV assessments assess hazard and risk using applicable, but different, methods based on available data. Methods used include the indicator chemical approach, hazard index (HI) approach, relative potency factor (RPF) approach, response-addition approach, integrated addition approach, and surrogate mixture approach; these methods are summarized in Section 1.2 and described in the specific fraction documents. In this data-driven approach, the choice of method depends on the chemical analyses conducted at a site.

Contamination of the environment by petroleum hydrocarbons is widespread. The initial contaminating materials range from crude oils to a wide variety of refined fuels and lubricating oils (IPCS, 1982). These hydrocarbon products are complex mixtures containing perhaps hundreds of hydrocarbon compounds, including aliphatic compounds (straight-chain, branched-chain, and cyclic alkanes and alkenes) and aromatic compounds (benzene and alkylbenzenes, polycyclic aromatic hydrocarbons [PAHs][1]) (Potter and Simmons, 1998). In addition, some of these products contain nonhydrocarbon additives or contaminants [see discussion in Chapter 5 of ATSDR (1999) and references therein].

Once released into the environment, the composition of a hydrocarbon product will change due to differential fate and transport of its components (i.e., some of these processes are sometimes referred to as "weathering") (Kuppusamy et al., 2020). In general, the more soluble and/or volatile mixture components will migrate to other locations and environmental media, while other components may be degraded (e.g., by microorganisms in soils and bodies of water) (Das and Chandran, 2011), leaving the relatively nonmobile and less readily degraded compounds (i.e., a weathered product) at the original location of release (Kuppusamy et al., 2019; Truskewycz et al., 2019; Balseiro-Romero et al., 2018; Stelljes and Watkin, 1993; Dragun, 1988; Bossert and Bartha, 1986; Coleman et al., 1984). Thus, the actual aliphatic and aromatic hydrocarbon mixture at a contaminated site, to which a population could be exposed, will vary with the quantity of petroleum hydrocarbon initially released, composition of the initial

[1]In this document, the U.S. Environmental Protection Agency (U.S. EPA) defines PAHs as unsubstituted compounds with two to six fused aromatic rings made up only of carbon and hydrogen atoms. The definition of the PAH excludes their alkyl substituted derivatives.

hydrocarbon mixture, location, time, and environmental medium, among other factors [see discussion in Chapter 5 of ATSDR (1999)].

The assessment of human health risks posed by petroleum hydrocarbon-contaminated sites involves measurement for all chemicals that originated in crude oils or petroleum products, known as TPHs. TPH is a loosely defined aggregate that depends on the method of analysis as well as the contaminating material. By definition, TPH is the measurable amount of petroleum-based hydrocarbon in an environmental medium and represents the total mass of hydrocarbons present without identifying individual compounds (ATSDR, 1999). As TPH is not a consistently defined entity, the assessment of health effects and development of toxicity criteria for the complex mixture as a whole is problematic, although this would be the preferred approach.

Some toxicity data are available for whole, unweathered hydrocarbon products (Cooper and Mattie, 1996; Bruner et al., 1993; Kinkead et al., 1992; Kanerva et al., 1987; Gaworski et al., 1985); however, there are limitations to using the whole-product data due to composition variability caused by differences in the crude oils from which hydrocarbon products are refined, differences in the refining processes, and differences in formulations of the final products. In addition, the identity of the released material may not be known, or multiple products may have been released, potentially at different times. Toxicity data for whole hydrocarbon products that are relatively heterogeneous are not necessarily applicable to the weathered materials or petroleum hydrocarbon mixtures in the environment to which exposures occur. These environmental petroleum hydrocarbon mixtures have been transported through individual compartments in the environment and subjected to partitioning (i.e., transfer between environmental compartments) and transformation, mediated by biological, chemical, or physical agents.

The Total Petroleum Hydrocarbon Criteria Working Group (TPHCWG) estimated there to be approximately 250 individually identified hydrocarbon components of various petroleum-derived fuels and crude oil (Potter and Simmons, 1998; Weisman, 1998; Gustafson et al., 1997). Toxicity data are available for only a relatively small number of these components. Thus, any attempt to assess the health effects of TPHs from the individual hydrocarbon components is inherently uncertain because many of the known components lack appropriate toxicity data. In addition, the resources needed to analyze for all known TPH constituents are likely to be prohibitive.

In recognition of the inapplicability of whole-product toxicity data to many contamination scenarios, the impact of differential fate and transport associated with individual contaminants, the impracticality of chemically analyzing each constituent separately, and the need for risk-based assessment of petroleum hydrocarbons, an approach has been developed to assess aliphatic and aromatic petroleum hydrocarbons on the basis of fractions with similar physical and chemical properties (MassDEP, 2003; ATSDR, 1999; MassDEP, 1994).

1.1. DEFINITION OF THE FRACTIONS

Specific petroleum hydrocarbon fractions for risk assessment were initially defined by a consortium of governmental agencies, professional organizations, academia, and industry more than 20 years ago on the basis of physicochemical properties, environmental fate, toxicity, and analytical chemistry considerations (MassDEP, 2003; Gustafson et al., 1997; MassDEP, 1994).

More recent examples of TPH risk assessment using a fraction-based approach include CCME (2021), BCMoE (2018), ARBCA (2012), and Redman et al. (2014). In brief, the components of TPHs are generally classified into aliphatics and aromatics, and each of these major fractions are then further separated into low, medium, and high carbon range fractions based on the number of carbon (C) atoms in the compounds and/or the compounds' equivalent carbon (EC) number index.[2] The EC index is related to the compounds' potential transport in the environment and is equivalent to the retention time of the compounds on a boiling-point gas chromatography (GC) column (nonpolar capillary column), normalized to *n*-alkanes. For example, benzene, a C6 aromatic compound, has an EC of 6.5 because its boiling point and GC retention time are approximately halfway between those of *n*-hexane (C6 [EC6]) and *n*-heptane (C7 [EC7]). Further details regarding the initial fraction definitions are available in previous reports (MassDEP, 2003; Gustafson et al., 1997; MassDEP, 1994). In addition, Wang et al. (2012) used comparative molecular field analysis to assess whether chemical members of the fractions exhibit similar chemistry and found that this analysis supported the current fraction definitions.

Since the origination of the fraction method, additional toxicity information has become available for constituents of some fractions, and there have been advances in analytical characterization of petroleum hydrocarbons. U.S. EPA has reviewed and revised the analytical methods applicable to petroleum hydrocarbons; the analytical methods match the fractions developed in this PPRTV assessment.

This document is an update of the PPRTV assessments for TPHs that U.S. EPA published in 2009 (U.S. EPA, 2009a, b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, s, t). The primary motivation for this update was the release of updated toxicity values from the U.S. EPA's Integrated Risk Information System (IRIS) program and/or PPRTV assessments for several key constituents of the aliphatic low carbon range fraction and aromatic medium and high carbon range fractions. These included toxicity values for benzo[*a*]pyrene (BaP) (IRIS, U.S. EPA, 2017); trimethylbenzenes (TMBs) (IRIS, U.S. EPA, 2016b); *n*-heptane (PPRTV, U.S. EPA, 2016a); 1,1-biphenyl (IRIS, U.S. EPA, 2013b); methylcyclohexane (PPRTV, U.S. EPA, 2013a); *sec*-butylbenzene (PPRTV, U.S. EPA, 2012c); *tert*-butylbenzene (PPRTV, U.S. EPA, 2012d); fluoranthene (PPRTV, U.S. EPA, 2012b); acenaphthene (PPRTV, U.S. EPA, 2011b); *n*-butylbenzene (PPRTV, U.S. EPA, 2010b); cyclohexane (PPRTV, U.S. EPA, 2010a); 1-methylnaphthalene (PPRTV, U.S. EPA, 2008); and benzo[*e*]pyrene (BeP) (PPRTV, U.S. EPA, 2021b).

In this update, the fraction boundaries for the aliphatic low, medium, and high carbon range fractions and the aromatic low carbon range fraction remain unchanged (see Figures 1 and 2 in Section 1.2). Fraction boundaries for the aromatic medium and high carbon range fractions were revised to accomplish the following goals:

1) Align the fraction definitions with the fractions resulting from current analytical methods as a practical approach to facilitate application.
2) Avoid grouping the generally less toxic substituted benzenes (C9−C10) with PAHs, naphthalenes, and 1,1-biphenyl.

[2]Based on an empirical relationship, the EC index can be calculated 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. (1997).

The redefined aromatic fractions are C9−C10 (EC9−EC < 11) (medium carbon range) and C10−C32 (EC11−EC35) (high carbon range). Naphthalene, which is C10 (EC11.57), is grouped with the high carbon range. Here, the U.S. EPA specifically is updating the PPRTV assessments for the aliphatic low carbon range TPH fraction (U.S. EPA, 2022a), the aromatic medium carbon range TPH fraction (U.S. EPA, 2022d), the aromatic high carbon range TPH fraction cancer assessment (U.S. EPA, 2022b), the aromatic high carbon range TPH fraction noncancer assessment (U.S. EPA, 2022c), and the TPH mixture assessment (i.e., this document).

1.2. OVERVIEW OF THE APPROACH

The framework for the fractionation approach to risk assessment for complex mixtures of aliphatic and aromatic petroleum hydrocarbons is derived from, and consistent with, U.S. EPA mixtures guidelines and supplemental guidance (U.S. EPA, 2000, 1986) and risk assessment guidance for the U.S. EPA Superfund program (U.S. EPA, 1989). The U.S. EPA mixtures guidance documents identify a hierarchy of preference for toxicity assessment of mixtures: data on the mixture of interest are preferred over data on sufficiently similar mixtures, and data on individual components are preferred least. As discussed above, there are limited toxicity data on mixtures of weathered petroleum contamination from varying source materials. Likewise, there are no toxicity data on the petroleum fractions that have been defined for this purpose. However, toxicity data on mixtures of fraction constituents (i.e., representing subsets of the total fraction) and on individual constituents are available. For each fraction, toxicity data for mixtures and individual components that meet the structural requirements (aliphatic or aromatic, carbon number, and/or EC number) are evaluated to select an approach to toxicity assessment for that fraction. The evaluation takes into consideration the availability of mixture toxicity data and whether the mixture is sufficiently representative of the fraction, whether available component toxicity data are likely to encompass the range of potential toxic effects for members of the fraction, and the degree to which the component toxicity data suggest that members of the fraction exert similar effects at similar doses. The analytical data needed for each approach were also considered in selecting the most appropriate approach.

Based on the results of this analysis, the toxicity of each of the six aliphatic or aromatic hydrocarbon fractions is estimated in one or more of the following ways:

- Indicator Chemical Approach
- Hazard Index Approach
- Relative Potency Factor Approach
- Response-Addition Approach
- Integrated Addition Approach
- Surrogate Mixture Approach

Additional details of these approaches are described in Section 1.3.

Figure 1 shows the fraction definitions and the toxicity assessment approaches selected for each fraction for oral noncancer assessments. Options are presented for risk assessment when exposure media are analyzed only for the fraction total concentrations (Option 1) and when exposure media are analyzed both for the fraction total concentrations and for the individual component concentrations with toxicity values (Option 2).

Figure 2 illustrates the fraction definitions and the toxicity assessment approaches selected for each fraction for noncancer assessments following inhalation exposures. Options are presented for risk assessment when exposure media are analyzed only for the fraction total concentrations (Option 1) and when exposure media are analyzed both for the fraction total concentrations and for the individual component concentrations with toxicity values (Option 2).

Figure 3 shows the fraction definition and the approaches for both oral and inhalation cancer risk assessments. For two fractions, the aliphatic high carbon range fraction and the aromatic medium carbon range fraction, the data do not support a cancer risk assessment. For the aliphatic low carbon range fraction and the aliphatic medium carbon range fraction, the data do not support a cancer assessment by the oral route of exposure and only one option is offered for each fraction to evaluate cancer risks by the inhalation route of exposure. For the aromatic low carbon range fraction, only one option is offered for oral and inhalation exposure routes. For the aromatic high carbon range fraction, the following three options are offered: (Option 1) an indicator chemical approach when exposure media are analyzed only for the fraction total concentration; (Option 2) an RPF approach when exposure media are analyzed both for the fraction total concentration and for selected individual PAHs (i.e., components with RPFs); and (Option 3) an integrated addition approach when exposure media are analyzed for the fraction total concentration, for concentrations of selected individual PAHs that have RPFs, and for concentrations of other carcinogens that have cancer risk values but are not PAHs.

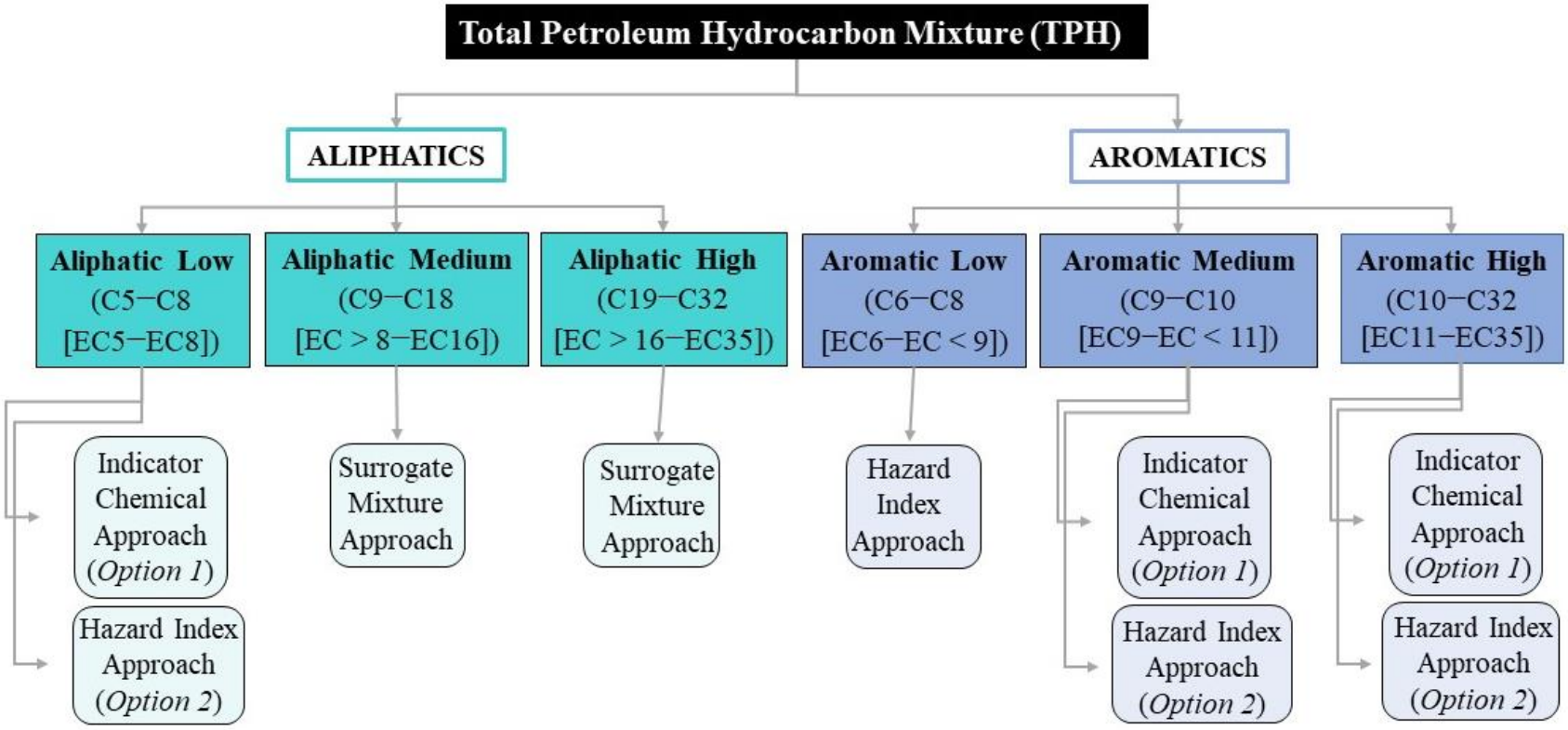


Figure 1. Overview of TPH Fractions and Assessment Methods for Oral Noncancer Assessment

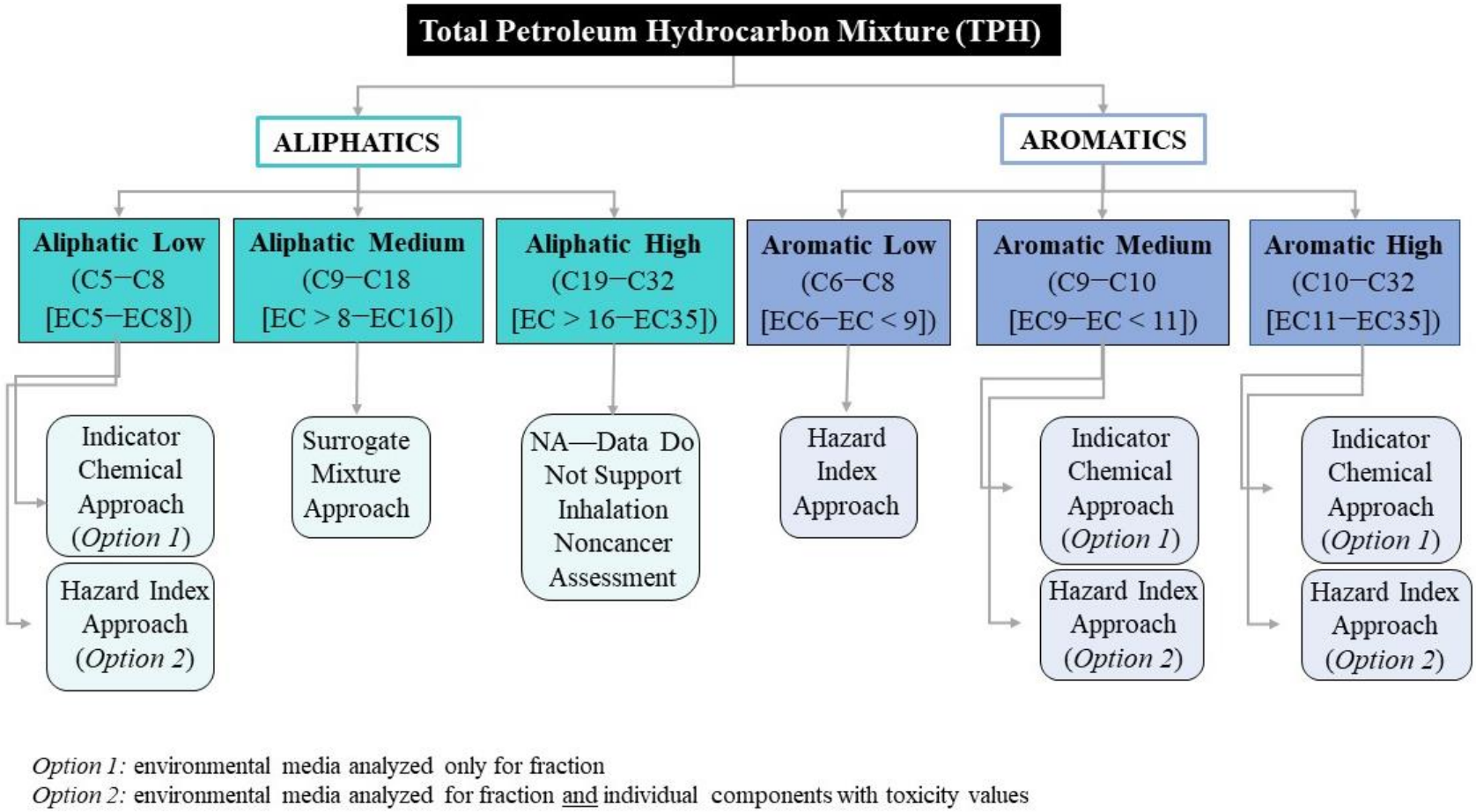


Figure 2. Overview of TPH Fractions and Assessment Methods for Inhalation Noncancer Assessment

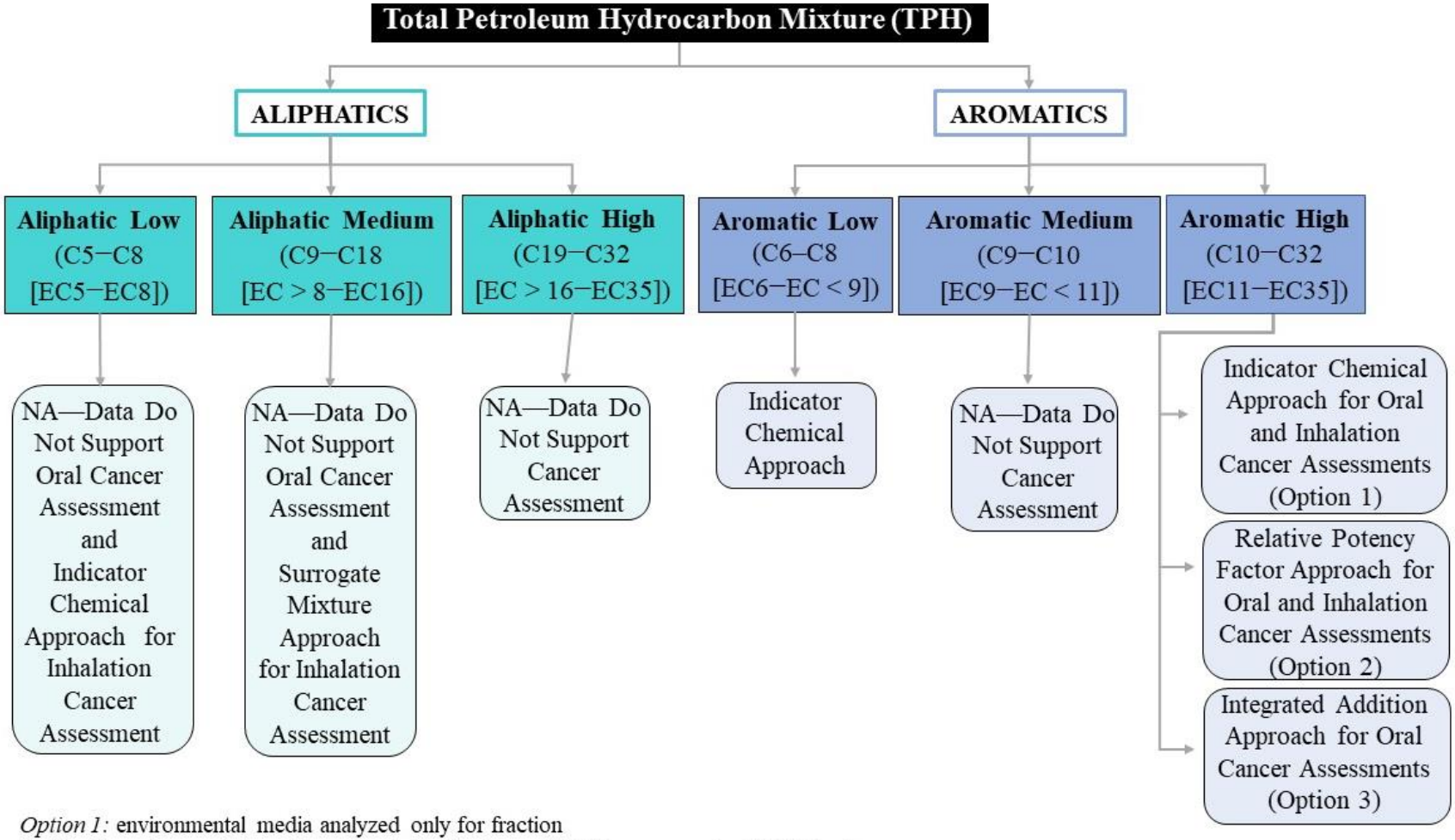


Figure 3. Overview of TPH Fractions and Assessment Methods for Cancer Assessment

The methods for assessing toxicity of the fractions are described in Section 1.3, followed by Sections 1.3.1–1.3.5, which provide details of the assessments for each fraction. Subsequent sections describe the implementation of the approach in noncancer and cancer risk assessment of petroleum contamination.

1.3. OVERVIEW OF MIXTURE ASSESSMENT METHODS

This section briefly describes the chemical mixtures risk assessment methods used in the TPH assessments. These methods are described in the U.S. EPA *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 2000, 1986), U.S. EPA *Feasibility of Performing Cumulative Risk Assessments for Mixtures of Disinfection By-Products in Drinking Water* (U.S. EPA, 2003a), and Agency for Toxic Substances and Disease Registry (ATSDR) *Framework for Assessing Health Impacts of Multiple Chemicals and Other Stressors* (ATSDR, 2018).

1.3.1. Indicator Chemical Approach

When the chemical composition of a mixture or a mixture fraction is not known, or toxicity measures are not available for 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 health risks in a health-protective manner; the chemical chosen as an indicator is among the best characterized toxicologically and likely among the most potent components of the mixture. The indicator chemical needs to have adequate dose-response data to indicate hazard potential or a dose-response relationship for noncancer outcomes, depending on the purpose of the assessment. Similarly, for cancer assessments, the indicator chemical needs to have adequate dose-response data to indicate cancer potential or to develop a dose-response relationship for cancer outcomes. The health risk value of the indicator chemical is integrated with exposure estimates for the mixture or mixture fraction to estimate health hazards associated with the fraction (i.e., calculate fraction-specific HI for a specific exposure pathway or a fraction-specific cancer risk estimate for a specific exposure pathway). This approach does not scale for potency of individual constituents; instead, it assumes that the toxicity of all measured members of the fraction can be adequately estimated by the health reference value of the indicator chemical.

1.3.2. Hazard Index Approach

The HI approach combines estimated population exposures with toxicity information to characterize the potential for toxicological effects. The HI is not a risk estimate, in that it is not expressed as a probability, nor is it an estimate of a toxicity measure. Instead, the HI is an indicator of potential hazard. In the HI approach, a hazard quotient (HQ) is calculated as the ratio of an estimate of exposure (E) to a reference value (RfV) for each mixture component chemical (i) (U.S. EPA, 1986). These HQs are summed to yield the HI for the mixture. In health risk assessments, U.S. EPA's preferred RfVs are the reference dose (RfD) for the oral exposure route and the reference concentration (RfC) for the inhalation exposure route.

$$HI = \sum_{i=1}^{n} HQ_i = \sum_{i=1}^{n} \frac{E_i}{RfV_i}$$

The HI is based on dose addition (U.S. EPA, 2000; Svendsgaard and Hertzberg, 1994); the hazard is evaluated as the potency-weighted sum of the component exposures. The HI is dimensionless, so *E* and the RfV have the same units.

1.3.3. 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 the class of chemicals comprising the mixture shares a known or suspected common mode of action (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.

$$\text{ICED} = \sum \text{RPF}_i D_i + D_{\text{IC}}$$

where:

IC	=	index chemical
ICED	=	index chemical equivalent dose of the mixture (e.g., mg/kg-day or mg/m^3)
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 or mg/m^3)
D_{IC}	=	dose of index chemical in the mixture (mg/kg-day or mg/m^3), given that the RPF value for the IC is 1

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

$$\begin{aligned} \text{RPF}_i &= \text{slope}_i \div \text{slope}_{\text{IC}} \\ &= \text{R/BMD}_{\text{R}-i} \div \text{R/BMD}_{\text{R}-\text{IC}} \\ &= \text{BMD}_{\text{R}-\text{IC}} \div \text{BMD}_{\text{R}-i} \end{aligned}$$

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 value for the IC (e.g., oral slope factor [OSF] in $[\text{mg/kg-day}]^{-1}$, or inhalation unit risk [IUR] in $[\text{mg/m}^3]^{-1}$).

1.3.4. Response-Addition Approach

The response-addition approach assumes simple independent action for mixture chemicals that cause the same effect, assuming that each impact is an independent response. In this method, the response to the mixture is predicted by summing the risk estimates for the mixture components under the law of statistical independence. Using r_i for the ith component risk, the formula for predicting the n-chemical response to the mixture probability (r_{mix}) for simple independent action is then:

$$r_{mix}(d_1,...,d_n) = 1 - \prod_{i=1}^{n}\left(1 - r_i(d_i)\right)$$

and for a binary mixture is:

$$\begin{aligned} r_{mix}(d_1,d_2) &= 1 - \left(1 - r_1(d_1)\right)\left(1 - r_2(d_2)\right) \\ &= r_1(d_1) + r_2(d_2) - r_1(d_1)p_2(d_2) \end{aligned}$$

1.3.5. 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 adverse 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-methylnaphtalene and 1,1-biphenyl) that are not characterized as PAH in this effort may cause cancer through different MOAs. For exposures to mixtures composed of such components and when required data are available, 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, 2007a, 2003a) 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, 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 and 1-methylnaphthalene are assumed to be independent from the MOAs of the PAHs. 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:

$$R_m = \sum R_j$$

where:

R_m = risk posed by the mixture
R_j = the risk posed by the jth subgroup (unitless)

1.3.6. Surrogate Mixture Approach

In some cases, chemical mixtures can be generated in a manner considered similar to a mixture (or mixture fraction) that might be encountered in the environment. Such mixtures subsequently can be tested toxicologically. When calculating an RfD, RfC, or slope factor for a whole mixture (i.e., the tested mixture), the general process is to assume the mixture can be treated the same as a single chemical and proceed with the established methodology for generating that estimate. Such RfDs, RfCs, or slope factors calculated for a whole mixture can be used as a surrogate for a mixture that was generated by a similar process and encountered in the environment (U.S. EPA, 2000).

The tested mixture needs to have adequate dose-response data to indicate hazard potential or a dose-response relationship for noncancer outcomes. Similarly, for cancer assessments, the tested mixture needs to have adequate dose-response data to indicate cancer potential or to develop a dose-response relationship for cancer outcomes. The health risk value of the tested mixture is integrated with exposure estimates for the mixture or mixture fraction to estimate health hazard associated with the fraction (i.e., calculate fraction specific HI for a specific exposure pathway or a fraction-specific cancer risk estimate for a specific exposure pathway).

2. METHODS OF FRACTION-SPECIFIC TOXICITY ASSESSMENT

2.1. LITERATURE SEARCHING AND DATA REVIEW

In 2009, the U.S. EPA compiled a list of individual hydrocarbons as a preliminary step in identifying potential surrogate compounds or mixtures to represent the toxicity of the fractions or compounds useful in a component-based method. The list included all individual hydrocarbons considered previously by the U.S. EPA National Center for Environmental Assessment (NCEA) Superfund Technical Support Center in the evaluation of hydrocarbons, as well as all those with toxicity data reviewed by the Massachusetts Department of Environmental Protection (MassDEP, 2003) or the TPHCWG (Edwards et al., 1997). Similarly, a list of mixtures, primarily hydrocarbon streams, was compiled from these sources. Searches were performed in the IRIS database at the time, Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 1997a), ATSDR toxicological profiles, Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1994, 1991a), and Drinking Water Standards and Health Advisories (DWSHA) list (U.S. EPA, 2006). Additionally, the California Environmental Protection Agency (CalEPA), National Toxicology Program (NTP), World Health Organization (WHO), and International Agency for Research on Cancer (IARC) were consulted for information. The U.S. EPA (2007b) High Production Volume (HPV) Challenge Program, and particularly the Petroleum HPV Testing Group publications, as well as the Organisation for Economic Co-operation and Development (OECD) HPV Program Screening Information Data Set (SIDS) documents were searched for relevant information. Additional pertinent individual compounds and mixtures encountered during this background search were added to the list for further consideration.

On the basis of the information found during these searches, compounds and mixtures that appeared to be possible candidates for use as surrogates were subjected to preliminary searching in PubMed and the Toxic Substances Control Act Test Submissions (TSCATS) database. If chosen for PPRTV assessment development on the basis of the results of the background searching or the preliminary searching, compounds and mixtures were then subjected to full literature searches of the other databases (through 2009). Details of the literature search methods for the compounds and mixtures selected for PPRTV assessment development are available in the individual documents (U.S. EPA, 2022a, b, c, d, 2009p, q, r).

For the fraction assessments that were updated in 2022 (aliphatic low carbon range fraction and aromatic medium and high carbon range fractions), only compounds or mixtures with existing U.S. EPA or ATSDR toxicity values were considered for use as potential indicator chemicals for derivation of the fraction-specific toxicity values, although toxicity data for other compounds were used for hazard identification and to assess consistency in toxic effects and potencies across the components and mixtures relevant to the fraction. Hazard identification and dose-response assessment for the updated fractions entailed the following steps: identifying mixtures and compounds that met structural criteria specific to each fraction and had available toxicity values from designated sources; searching published literature to identify other toxicity data relevant to the fraction; searching the reference list of pertinent reviews, OECD SIDS, and the Petroleum HPV Testing Group website to identify other mixtures or compounds with toxicity data that may inform hazard identification for the fraction; and evaluating all collated data to determine whether effects and/or potencies were consistent across the fraction. Additional details of the search methods for the updated fractions are available in the fraction-specific PPRTV assessments (U.S. EPA, 2022a, b, c, d, 2009p, q, r).

2.2. SELECTION OF APPROACH(ES) AND TOXICITY VALUE(S)

The method for selecting an approach and toxicity value(s) for the fraction was as follows. First, mixtures were preferred over individual compounds, provided that the mixture exhibited in vivo toxic effects similar to those exhibited by the individual fraction components. If suitable mixture data were lacking, but available component data indicated similar toxicity targets, a representative compound exhibiting in vivo effects and potency similar to those exhibited by other compounds in the fraction was chosen as an indicator chemical. In the event that components of the fraction varied widely in toxic effects or potency, the toxicity value for the most potent component was generally chosen as the indicator chemical for the fraction. Finally, if toxicity values were available for many or most of the individual compounds in a fraction, and these compounds are typically monitored at sites of aliphatic or aromatic hydrocarbon contamination, then a component approach would be considered.

3. TOXICITY VALUES FOR THE DEFINED TPH FRACTIONS

3.1. ALIPHATIC LOW CARBON RANGE FRACTION: C5−C8 (EC5−EC8)

The aliphatic low carbon range fraction includes straight-chain, branched, and cyclic alkanes and alkenes; examples include *n*-pentane, *n*-octane, 2-methylpentane, cyclohexane, and 1-hexene. Toxicity assessment and surrogate selection for the aliphatic low carbon range fraction is detailed in the PPRTV assessment for this fraction (U.S. EPA, 2022a). This section provides a summary of the approach and results; further detail is available in the PPRTV assessment.

Toxicity values were identified for seven aliphatic low carbon range compounds and one mixture. Tables 1 and 2 provide summaries of the oral and inhalation noncancer toxicity values, critical effects, and key studies. In February 2018 and again in August 2021, literature searches were conducted using a multistep process for the mixtures and individual compounds with toxicity values and for other mixtures and compounds that are relevant to the fraction. The primary toxicological endpoints identified for the fraction were neurological, hepatic, body weight, gastrointestinal [GI], respiratory, and developmental effects. Among members of the fraction that have undergone in vivo toxicity testing, the data available to assess consistency in effects are limited for effects on endpoints other than body weight. In addition to the scarcity of developmental toxicity data for members of the fraction, an important data limitation is the lack of chronic systemic toxicity information for all but three members of the fraction. Only cyclohexene, methylcyclohexane, and commercial hexane have been tested in comprehensive systemic toxicity studies in animals exposed for at least 1 year, all by the inhalation route of exposure. Furthermore, most of the oral toxicity studies are <13 weeks in duration, and few examined comprehensive endpoints.

Table 1. Available RfD Values for Aliphatic Low Carbon Range Fraction (C5−C8 [EC5−EC8])[a]

Indicator Chemical or Components	POD (mg/kg-d)	POD Type	UF_C	UF Components	RfD or p-RfD (mg/kg-d)[b]	Confidence in RfD or p-RfD	Critical Effect(s)	Species, Mode, and Duration	Reference
Subchronic									
n-Hexane (C6 [EC5.80])	785	LOAEL	3,000	UF_A, UF_D, UF_H, UF_L	0.3	Low	Reductions in motor nerve conduction velocity (nervous)	Rat, gavage, 8 wk	U.S. EPA (2009a); Ono et al. (1981)
Methylcyclopentane (C6 [EC5.89])	357	NOAEL	300	UF_A, UF_D, UF_H	0.4	Low	Reduced body weight (body weight)	Rat, gavage, 5 d/wk for 4 wk	U.S. EPA (2009i); Halder et al. (1985)
Cyclohexene (C6 [EC6.24])	**4.81**	**$BMDL_{1SD}$ (HED)**	**100**	**UF_A, UF_D, UF_H**	**0.05**	**Low**	**Increased total serum bilirubin (hepatic)**	**Rat, gavage, one-generation**	**MHLW (2001) as cited in U.S. EPA (2012a)**
n-Heptane (C7 [EC6.71])	3.13	$BMDL_{10}$	1,000	UF_A, UF_D, UF_H	*0.003*[b]	Low	Based on *n*-nonane as analogue; forestomach histopathology (GI)	Mouse, gavage, 13 wk	Dodd et al. (2003) as cited in U.S. EPA (2016a)
2,4,4-Trimethylpentene (C8 [EC6.80−6.90])	41.5	$BMDL_{10}$ (HED)	300	UF_A, UF_D, UF_H	*0.*[b]	Low	Increased relative liver weight (hepatic)	Rat, gavage, one-generation	Huntingdon Life Sciences (1997a) as cited in U.S. EPA (2015)

Table 1. Available RfD Values for Aliphatic Low Carbon Range Fraction (C5−C8 [EC5−EC8])[a]

Indicator Chemical or Components	POD (mg/kg-d)	POD Type	UF_C	UF Components	RfD or p-RfD (mg/kg-d)[b]	Confidence in RfD or p-RfD	Critical Effect(s)	Species, Mode, and Duration	Reference
Chronic									
Cyclohexene (C6 [EC6.24])	**4.81**	**$BMDL_{1SD}$ (HED)**	**1,000**	**UF_A, UF_D, UF_H, UF_S**	**0.005**	**Low**	**Increased total serum bilirubin (hepatic)**	**Rat, gavage, one-generation**	**MHLW (2001) as cited in U.S. EPA (2012a)**
n-Heptane (C7 [EC6.71])	3.13	$BMDL_{10}$	10,000	UF_A, UF_D, UF_H, UF_S	*0.0003*[b]	Low	Based on *n*-nonane as analogue; forestomach histopathology (GI)	Mouse, gavage, 13 wk	Dodd et al. (2003) as cited in U.S. EPA (2016a)
2,4,4-Trimethylpentene (C8 [EC6.80−6.90])	41.5	$BMDL_{10}$ (HED)	3,000	UF_A, UF_D, UF_H, UF_S	*0.01*[b]	Low	Increased relative liver weight (hepatic)	Rat, gavage, one-generation	Huntingdon Life Sciences (1997a) as cited in U.S. EPA (2015)

[a]**Bolded** rows show the compound and toxicity values selected as the indicator chemical for the fraction if analytical chemistry data do not identify concentrations of individual chemicals composing this fraction.
[b]Toxicity values are provisional values obtained from an existing PPRTV assessment. Values in *italics* are screening provisional values obtained from an existing PPRTV assessment. Screening provisional values are not assigned confidence statements; however, confidence in these values is presumed to be low. Screening provisional values are derived when the available data do not meet the requirements for deriving a provisional toxicity value.

BMDL = benchmark dose lower confidence limit; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; C = carbon; EC = equivalent carbon; GI = gastrointestinal; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; PPRTV = Provisional Peer-Reviewed Toxicity Value; p-RfD = provisional reference dose; RfD = reference dose; SD = standard deviation; UF = uncertainty factor; 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.

Table 2. Available RfC Values for Aliphatic Low Carbon Range Fraction (C5−C8 [EC5−EC8])[a]

Indicator Chemical or Components	POD (mg/kg-d)	POD Type (all are HECs)	UF_C	UF Components	RfC or p-RfC (mg/m^3)	Confidence in RfC or p-RfC	Critical Effect(s)	Species, Mode, and Duration	Reference
Subchronic									
n-Pentane (C5 [EC4.92])	3,658	NOAEL	300	UF_A, UF_D, UF_H	10	Low	No treatment-related effects	Rat, 6 h/d, 5 d/wk for 13 wk	McKee and Frank (1998) as cited in U.S. EPA (2009m)
Commercial hexane (C6)	804	NOAEL	30	UF_A, UF_H	27	Medium	Abnormal gait; decreased body weight; mild atrophy of sciatic and/or tibial nerve and skeletal muscle (nervous and body weight)	Rat, 22 h/d, 7 d/wk for 6 mo	IRDC (1992) as cited in U.S. EPA (2009e)
_n_-Hexane (C6 [EC5.80])	**215**	**$BMCL_{1SD}$**	**100**	**UF_A, UF_D, UF_H**	**2**	**Low**	**Peripheral neuropathy (nervous)**	**Rat, 12 h/d, 7 d/wk for 16 wk**	**Huang (1989) as cited in U.S. EPA (2009a)**
Cyclohexane (C6 [EC6.16])	1,822	$BMCL_{1SD}$	100	UF_A, UF_D, UF_H	18	Moderate	Reduced pup weight (developmental)	Rat, 6 h/d, 5 d/wk, two-generation	Kreckmann (2000) and Dupont HLR (1997a), both as cited in U.S. EPA (2010a)
n-Heptane (C7 [EC6.71])	1,170	$BMCL_{1SD}$	300	UF_A, UF_D, UF_H	4	Low	Loss of hearing sensitivity (nervous)	Rat, 6 h/d, 7 d/wk for 28 d	Simonsen and Lund (1995) as cited in U.S. EPA (2016a)

Table 2. Available RfC Values for Aliphatic Low Carbon Range Fraction (C5−C8 [EC5−EC8])[a]

Indicator Chemical or Components	POD (mg/kg-d)	POD Type (all are HECs)	UF_C	UF Components	RfC or p-RfC (mg/m^3)	Confidence in RfC or p-RfC	Critical Effect(s)	Species, Mode, and Duration	Reference
Chronic									
n-Pentane (C5 [EC4.92])	3,658	NOAEL	3,000	UF_A, UF_D, UF_H, UF_S	1	Low	No treatment-related effects	Rat, 6 h/d, 5 d/wk for 13 wk	McKee and Frank (1998) as cited in U.S. EPA (2009m)
Commercial hexane (C6)	17.59	$BMCL_{10}$	30	UF_A, UF_H	0.6	Medium	Nasal epithelial cell hyperplasia (respiratory)	Rat, 6 h/d, 5 d/wk for 2 yr	Daughtrey et al. (1999) and Biodynamics (1993), both as cited in U.S. EPA (2009e)
n-Hexane (C6 [EC5.80])	215	$BMCL_{1SD}$	300	UF_A, UF_D, UF_H, UF_S	0.7	Medium	Peripheral neuropathy (nervous)	Rat, 12 h/d, 7 d/wk for 16 wk	Huang et al. (1989) as cited in U.S. EPA (2005b)
Cyclohexane (C6 [EC6.16])	1,822	$BMCL_{1SD}$	300	UF_A, UF_D, UF_H, UF_S	6	Low-moderate	Reduced pup weight (developmental)	Rat, 6 h/d, 5 d/wk, 2-generatoin	Kreckmann (2000) and Dupont HLR (1997a), both as cited in U.S. EPA (2003e)
Cyclohexene (C6 [EC6.24])	360	NOAEL	300	UF_A, UF_D, UF_H	*1*[b]	Low	Spongiosis hepatis (hepatic)	Rat, 6 h/d, 5 d/wk for 104 wk	MHLW (2003) as cited in U.S. EPA (2012a)
***n*-Heptane (C7 [EC6.71])**	**1,170**	**$BMCL_{1SD}$**	**3,000**	**UF_A, UF_D, UF_H, UF_S**	**0.4**	**Low**	**Loss of hearing sensitivity (nervous)**	**Rat, 6 h/d, 7 d/wk for 28 d**	**Simonsen and Lund (1995) as cited in U.S. EPA (2016a)**

[a]**Bolded** rows show the compounds and toxicity values selected as the indicator chemicals for the fraction if analytical chemistry data do not identify concentrations of individual chemicals composing this fraction.
[b]Toxicity values are provisional values obtained from an existing PPRTV assessment. Values in *italics* are screening provisional values obtained from an existing PPRTV assessment. Screening provisional values are not assigned confidence statements; however, confidence in these values is presumed to be low. Screening provisional values are derived when the available data do not meet the requirements for deriving a provisional toxicity value.

BMCL = benchmark concentration lower confidence limit; $BMCL_{10}$ = 10% benchmark concentration lower confidence limit; C = carbon; EC = equivalent carbon; HEC = human equivalent concentration; NOAEL = no-observed-adverse-effect level; POD = point of departure; PPRTV = Provisional Peer-Reviewed Toxicity Value; p-RfC = provisional reference concentration; RfC = reference concentration; SD = standard deviation; UF = uncertainty factor; 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.

Available oral and inhalation toxicity data for aliphatic low carbon range compounds did not show much consistency across fraction members in terms of toxicological effects or potencies. Thus, there was no basis to identify a surrogate mixture or compound that is representative of the effects and potency of the fraction as a whole, so the most potent component compounds and mixtures were considered as the basis for indicator chemical selection.

Two options are presented for assessment of oral noncancer effects for this fraction. The first is for use when available analytical chemistry data do not identify concentrations of individual chemicals composing this fraction. In this case, the subchronic and chronic provisional reference doses (p-RfDs) (0.05 and 0.005 mg/kg-day, respectively) for cyclohexene are recommended as the indicator chemical for the aliphatic low carbon range fraction. The p-RfDs for cyclohexene are based on hepatic toxicity. The available oral toxicity data for aliphatic low carbon range compounds do not demonstrate significant consistency across fraction members in terms of toxicological effects or potencies. Therefore, there is no basis to identify an indicator chemical or mixture that is representative of the effects and potency of the fraction as a whole. Cyclohexene, among the most potent component compounds and mixtures considered in this fraction, is the selected indicator chemical (see discussion of method in Section 1.3.1). Although the RfDs for cyclohexene are not the lowest available, the subchronic and chronic p-RfD values for *n*-heptane (0.003 and 0.0003 mg/kg-day, respectively) are not recommended for the following three reasons. First, the *n*-heptane p-RfDs are screening values based on an read-across analysis and therefore carry additional uncertainty associated with the analogue approach. Second, the analogue upon which the values are based (*n*-nonane) is outside (C9 [EC9]) the carbon range of the fraction. Third, the chronic p-RfD for *n*-heptane is highly uncertain, derived with a composite uncertainty factor (UF_C) of 10,000. Evaluation of available data [see U.S. EPA (2022a) for further detail] suggests that use of the cyclohexene p-RfD values is reasonably anticipated to be protective for effects associated with exposure to other constituents of the fraction. These toxicity values are shown in bold in Table 1 to indicate their selection as the indicator chemicals for the fraction.

If the available analytical chemistry data quantify the concentrations of *n*-hexane, methylcyclopentane, cyclohexene, *n*-heptane, or 2,4,4-trimethylpentene separately from the remainder of the low carbon fraction, it is recommended that HQs for the individual chemicals with analytical data be calculated and an HI for the mixture be developed using the calculated HQs.

For subchronic oral exposures, the following subchronic p-RfDs can be used as the denominator in the HQ equations: *n*-hexane (0.3 mg/kg-day), methylcyclopentane (0.4 mg/kg-day), cyclohexene (0.05 mg/kg-day), *n*-heptane (0.003 mg/kg-day), and 2,4,4-trimethylpentene (0.1 mg/kg-day). In this alternative approach, the subchronic p-RfD (0.05 mg/kg-day) for cyclohexene is recommended for use with the remainder of the fraction, including any other fraction members analyzed individually.

For chronic oral exposures, the following chronic p-RfDs can be used in the denominator of the HQ equations: cyclohexene (0.005 mg/kg-day), *n*-heptane (0.0003 mg/kg-day), and 2,4,4-trimethylpentene (0.01 mg/kg-day). In this alternative approach, the chronic p-RfD (0.005 mg/kg-day) for cyclohexene is recommended for use with the remainder of the fraction, including any other fraction members analyzed individually.

As with the oral noncancer assessment, two options are presented for inhalation noncancer assessment of this fraction. If available analytical chemistry data do not identify concentrations of individual chemicals composing this fraction, the lowest subchronic and chronic provisional reference concentrations (p-RfCs) among the compounds in this fraction, for *n*-hexane and *n*-heptane, respectively, are recommended for the aliphatic low carbon range fraction. These toxicity values are shown in bold in Table 2 to indicate their selection as the indicator chemical for the fraction.

In cases where the available analytical chemistry data quantify the concentrations of *n*-pentane, *n*-hexane, cyclohexane, or *n*-heptane separately from the remainder of the low carbon fraction, it is recommended that HQs for the individual chemicals with analytical data be calculated and an HI for the mixture be developed using the calculated HQs.

For subchronic inhalation exposures, the following subchronic p-RfCs can be used as the denominator in the HQ equations: *n*-pentane (10 mg/m^3), *n*-hexane (2 mg/m^3), cyclohexane (18 mg/m^3), and *n*-heptane (4 mg/m^3). In this alternative approach, the subchronic p-RfC for *n*-hexane (2 mg/m^3) is recommended for use with the remainder of the fraction, including any other fraction members analyzed individually.

For chronic inhalation exposures, the following chronic p-RfCs can be used as the denominator in the HQ equations: *n*-pentane (1 mg/m^3), *n*-hexane (0.7 mg/m^3), cyclohexane (6 mg/m^3), cyclohexene (1 mg/m^3), and *n*-heptane (0.4 mg/m^3). In this alternative approach, the chronic p-RfC for *n*-heptane (0.4 mg/m^3) is recommended for use with the remainder of the fraction, including any other fraction members analyzed individually.

Few data with which to assess the carcinogenic potential of compounds and mixtures in the aliphatic low carbon range fraction are available. No human or animal studies examining carcinogenicity were located for any compound or mixture other than commercial hexane, *n*-hexane, cyclohexene, and 2,2,4-trimethylpentane. Only the data for commercial hexane were considered adequate to assess carcinogenic potential, resulting in a weight-of-evidence (WOE) descriptor of "*Suggestive Evidence for Carcinogenic Potential*" and a provisional IUR (p-IUR) of 2×10^{-4} $(mg/m^3)^{-1}$ for combined pituitary adenomas and adenocarcinomas in female mice (U.S. EPA, 2009e). None of the mixtures or constituents in this fraction had an OSF from the IRIS database, PPRTVs, HEAST, MassDEP, or TPHCWG. Thus, a provisional OSF (p-OSF) was not derived for the fraction. The only available IUR for members of the aliphatic low carbon range fraction is the screening value for commercial hexane (U.S. EPA, 2009e); this p-IUR is selected to assess inhalation carcinogenicity for this fraction. Table 3 shows the recommended cancer risk estimate for the aliphatic low carbon range fraction.

Table 3. Available Cancer Risk Estimates for Aliphatic Low Carbon Range Fraction (C5−C8 [EC5−EC8])[a]

Toxicity Type (units); Indicator Chemical	Species/Sex	Tumor Type	Cancer Risk Estimate	Reference
p-OSF $(mg/kg\text{-}d)^{-1}$	NDr			
p-IUR $(mg/m^3)^{-1}$; commercial hexane	**Mouse/F**	**Pituitary adenomas or adenocarcinomas**	***2 × 10^{-4}*** [b]	**Daughtrey et al. (1989) and Biodynamics (1993), both as cited in U.S. EPA (2009e)**

[a]**Bolded** row shows the compound and toxicity value selected as the indicator chemical for the fraction
[b]Toxicity values are provisional values obtained from an existing PPRTV assessment. Values in italics are screening provisional values obtained from an existing PPRTV assessment. Screening provisional values are not assigned confidence statements; however, confidence in these values is presumed to be low. Screening provisional values are derived when the available data do not meet the requirements for deriving a provisional toxicity value.

C = carbon; EC = equivalent carbon; F = female; NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor; PPRTV = Provisional Peer-Reviewed Toxicity Value.

3.2. ALIPHATIC MEDIUM CARBON RANGE FRACTION: C9−C18 (EC > 8−EC16)

The aliphatic medium carbon range fraction includes *n*-nonane, *n*-decane, and longer chain *n*-alkanes; a few *n*-alkenes (e.g., tridecene); branched chain alkanes and alkenes; and alkyl-substituted cycloalkanes. Toxicity values for compounds in this fraction are not available from the U.S. EPA's IRIS database, or from HEAST, ATSDR, MassDEP, or TPHCWG; PPRTV assessments for *n*-nonane and *n*-decane are available. Limited toxicity data are available for *n*-undecane (TERA, 2004). ATSDR toxicological profiles and inhalation Minimal Risk Levels (MRLs) are available for various jet fuels and kerosene, but these mixtures have a substantial aromatic content and are therefore not suitable to represent the toxicity of this fraction. The toxicity of this fraction may be better represented by dearomatized hydrocarbon streams[3] and solvents that fall within this carbon range and have minimal (<1.0%) aromatic content.

A PPRTV assessment for mid-range aliphatic hydrocarbon streams was prepared (U.S. EPA, 2009j) to synthesize the findings of these mixture studies and additional supporting toxicity studies on similar mixtures. Complete descriptions of the studies, as well as details of the derivation of toxicity values for the mixtures, are provided in the PPRTV assessment.

Tables 4, 5, and 6 list the available RfDs, RfCs, and cancer assessments for compounds or mixtures in this fraction. The mixture data are considered preferable to single component data, as previously discussed. The toxicity values for the mid-range aliphatic hydrocarbon stream mixture are the recommended values for this fraction and include subchronic and chronic p-RfCs. In addition, Table 4 contains screening oral toxicity values for mixture data that may be useful in evaluating this fraction, developed in Appendix A of U.S. EPA (2009j). Because the

[3]"Hydrocarbon streams" is a term used in petroleum production and refers to the specific industrial processing and refining steps applied to crude material. For example, a typical crude oil refinery may produce as many as 8−15 different streams of hydrocarbons that are eventually mixed into motor fuels; see API (2021a) and API (2021b).

toxicity data based on the three unpublished studies (Anonymous, 1990, 1991a, b as cited in U.S. EPA, 2009a) are not peer reviewed, only screening chronic or subchronic p-RfDs are available for the mixture. The surrogate mixture and oral and inhalation noncancer toxicity values selected to represent the fraction are shown in bold in Tables 4 and 5.

Table 4. Available RfD Values for Aliphatic Medium Carbon Range Fraction (C9−C18 [EC > 8−EC16)[a, b]

Surrogate Mixture or Components	POD	POD Type	UF_C	UF Components	RfD or p-RfD (mg/kg-d)	Confidence in RfD or p-RfD	Critical Effect(s) (system)	Species, Mode, and Duration	Reference
Subchronic									
n-Nonane (C9 [EC8.62])	3.13	$BMDL_{10}$	1,000	UF_A, UF_D, UF_H	0.003[c]	Low	Proliferative forestomach lesions (gastrointestinal)	Mouse, gavage, 7 d/wk for 90 d	Dodd et al. (2003) as cited in U.S. EPA (2009l)
n-Decane (C10 [EC9.57])	1,000	NOAEL	1,000	UF_A, UF_D, UF_H	*1.0*[c]	Low	No effects observed	Rat, gavage, 7 d/wk for 4−8 wk	Sasol (1995) as cited in U.S. EPA (2009k)
Mid-range aliphatic hydrocarbon stream	**100**	**NOAEL**	**1,000**	**UF_A, UF_D, UF_H**	***0.1***[c]	**Low**	**Liver, kidney, and hematologic effects**	**Rat, gavage, 7 d/wk for 13 wk**	**Anonymous (1990, 1991a) as cited in U.S. EPA (2009j)**
Chronic									
n-Nonane (C9 [EC8.62])	3.13	$BMDL_{10}$	10,000	UF_A, UF_D, UF_H, UF_S	*0.0003*[c]	Low	Proliferative forestomach lesions (gastrointestinal)	Mouse, gavage, 7 d/wk for 90 d	Dodd et al. (2003) as cited in U.S. EPA (2009l)
Mid-range aliphatic hydrocarbon stream	**100**	**NOAEL**	**10,000**	**UF_A, UF_D, UF_H, UF_S**	***0.01***[c]	**Low**	**Liver, kidney, and hematologic effects**	**Rat, gavage, 7 d/wk for 13 wk**	**Anonymous (1990, 1991a) as cited in U.S. EPA (2009j)**

[a]U.S. EPA (2009q).
[b]**Bolded** rows show the mixture and toxicity values selected as the surrogate mixture for the fraction.
[c]Toxicity values are provisional values obtained from an existing PPRTV assessment. Values in italics are screening provisional values obtained from an existing PPRTV assessment. Screening provisional values are not assigned confidence statements; however, confidence in these values is presumed to be low. Screening provisional values are derived when the available data do not meet the requirements for deriving a provisional toxicity value.

$BMDL_{10}$ = 10% benchmark dose lower confidence limit; C = carbon; EC = equivalent carbon; NOAEL = no-observed-adverse-effect level; POD = point of departure; PPRTV = Provisional Peer-Reviewed Toxicity Value; p-RfD = provisional reference dose; RfD = 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_S = subchronic-to-chronic uncertainty factor.

Table 5. Available RfC Values for Aliphatic Medium Carbon Range Fraction (C9−C18, EC > 8−EC16)[a, b]

Surrogate Mixture or Components	POD	POD Type (all are HECs)	UF_C	UF Components	RfC or p-RfC (mg/m^3)	Confidence in RfC or p-RfC	Critical Effect(s)	Species, Mode, and Duration	Reference
Subchronic									
n-Nonane (C9 [EC8.62])	66.4	NOAEL	300	UF_A, UF_D, UF_H	0.2[c]	Low	Salivation, lacrimation, and marginally depressed body weight (whole body effects)	Rat, 6 h/d, 5 d/wk for 13 wk	Carpenter et al. (1978) as cited in U.S. EPA (2009l)
Mid-range aliphatic hydrocarbon stream	**12**	**$BMCL_{10}$**	**100**	**UF_A, UF_D, UF_H**	**0.1[c]**	**Medium**	**Nasal goblet cell hypertrophy**	**Rat, 6 h/d, 5 d/wk for 13 wk**	**NTP (2004) as cited in U.S. EPA (2009j)**
Chronic									
n-Nonane (C9 [EC8.62])	66.4	NOAEL	3,000	UF_A, UF_D, UF_H, UF_S	0.02[c]	Low	Salivation, lacrimation, and marginally depressed body weight (whole body effects)	Rat, 6 h/d, 5 d/wk for 13 wk	Carpenter et al. (1978) as cited in U.S. EPA (2009l)
Mid-range aliphatic hydrocarbon stream	**12**	**$BMCL_{10}$**	**100**	**UF_A, UF_D, UF_H**	**0.1[c]**	Medium	**Nasal goblet cell hypertrophy and adrenal hyperplasia**	**Rat, 6 h/d, 5 d/wk for 13 wk**	**NTP (2004) as cited in U.S. EPA (2009j)**

[a]U.S. EPA (2009q).
[b]**Bolded** rows show the mixture and toxicity values selected as the surrogate mixture for the fraction.
[c]Toxicity values are provisional values obtained from an existing PPRTV assessment.

$BMCL_{10}$ = 10% benchmark concentration lower confidence limit; C = carbon; EC = equivalent carbon; HEC = human equivalent concentration; NOAEL = no-observed-adverse-effect level; POD = point of departure; PPRTV = Provisional Peer-Reviewed Toxicity Value; p-RfC = provisional reference concentration; RfC = 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_S = subchronic-to-chronic uncertainty factor.

Table 6. Available Cancer Risk Estimates for Aliphatic Medium Carbon Range Fraction (C9−C18 [EC > 8−EC16]) of Total Petroleum Hydrocarbons[a, b]

Toxicity Type (units); Surrogate Mixture	Species/Sex	Tumor Type	Cancer Value	Reference
p-OSF $(mg/kg\text{-}d)^{-1}$	NDr			
p-IUR $(mg/m^3)^{-1}$ Mid-range aliphatic hydrocarbon stream	**Rat/M**	**Benign or malignant adrenal pheochromocytoma**	***4.5 × 10^{-3}*** [c]	**NTP (2004) as cited in U.S. EPA (2009j)**

[a] U.S. EPA (2009q).
[b] **Bolded** row shows the mixture and toxicity value selected as the surrogate mixture for the fraction
[c] Toxicity values are provisional values obtained from an existing PPRTV assessment. Values in italics are screening provisional values obtained from an existing PPRTV assessment. Screening provisional values are not assigned confidence statements; however, confidence in these values is presumed to be low. Screening provisional values are derived when the available data do not meet the requirements for deriving a provisional toxicity value.

C = carbon; EC = equivalent carbon; M = male; NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor; PPRTV = Provisional Peer-Reviewed Toxicity Value.

As Table 6 shows, quantitative cancer risk assessments were not available for individual components of the fraction. The mid-range aliphatic hydrocarbon stream mixture data were considered adequate to develop a quantitative estimate of cancer risk from inhalation exposure. However, because the WOE indicates "*Suggestive Evidence of Carcinogenic Potential*," there is some uncertainty associated with the quantification. Appendix A of the PPRTV assessment document on the mid-range aliphatic hydrocarbon streams contains a screening p-IUR (U.S. EPA, 2009j). The screening p-IUR is listed in Table 6 (U.S. EPA, 2009j).

3.3. ALIPHATIC HIGH CARBON RANGE FRACTION: C19−C32 (EC > 16−EC35)

The aliphatic high carbon range fraction includes longer *n*-alkanes, such as eicosane, and branched and cyclic alkanes. Toxicity values are not available for the individual compounds. A search for toxicity information on eicosane in particular was desirable because MassDEP (1994) suggested it as a reference compound for this fraction, but data supportive of derivation of toxicity values were not identified. Food- and medicinal-grade mineral oils are pure (aromatic-free) mixtures of aliphatic hydrocarbons that correspond to this carbon range fraction and have data suitable for toxicity value derivation. Literature searches on mineral oils were performed and the medical literature on mineral oils was consulted. Subchronic and chronic p-RfDs as well as a cancer assessment, including a WOE of "*Inadequate Information to Assess the Carcinogenic Potential*" for white mineral oil, were derived in a PPRTV assessment (U.S. EPA, 2009s). Table 7 summarizes the resulting oral noncancer values (a quantitative cancer assessment was not performed). These toxicity values are recommended for assessment of this fraction using a surrogate mixture approach.

Table 7. Available RfD Values for Aliphatic High Carbon Range Fraction (C19−C32, EC > 16−EC35)[a, b]

Surrogate Mixture	POD	POD Type	UF_C	UF Components	RfD or p-RfD (mg/kg-d)	Confidence in RfD or p-RfD	Critical Effect(s)	Species, Mode, and Duration	Reference
Subchronic									
White mineral oils	**870**	**NOAEL**	**30**	**UF_D, UF_H**	**30[c]**	**Low**	**Lower end of human therapeutic dose range for laxative effects**	**Human (<1 yr of age) daily oral therapeutic use (870−2,600 mg/kg-d)**	**NASPGHN (2006) as cited in U.S. EPA (2009s)**
Chronic									
White mineral oils	**870**	**NOAEL**	**300**	**UF_D, UF_H, UF_S**	**3[c]**	**Low**	**Lower end of human therapeutic dose range for laxative effects**	**Human (<1 yr of age) daily oral therapeutic use (870−2,600 mg/kg-d)**	**NASPGHN (2006) as cited in U.S. EPA (2009s)**

[a]U.S. EPA (2009p).
[b]**Bolded** rows show the mixture and toxicity values selected as the surrogate mixture for the fraction.
[c]Toxicity values are provisional values obtained from an existing PPRTV assessment.

C = carbon; EC = equivalent carbon; NOAEL = no-observed-adverse-effect level; POD = point of departure; PPRTV = Provisional Peer-Reviewed Toxicity Value; p-RfD = provisional reference dose; RfD = 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_S = subchronic-to-chronic uncertainty factor.

3.4. AROMATIC LOW CARBON RANGE FRACTION: C6−C8 (EC6−EC < 9)

This fraction contains aromatic hydrocarbons in the C6−C8 range: benzene, toluene, ethylbenzene, and *o*-, *m*-, and *p*-xylenes (commonly referred to as BTEX) and styrene. It is unclear, however, whether styrene is a constituent of petroleum products. For example, styrene is not reported as a constituent of any of the petroleum mixtures including gasoline, kerosene, jet fuels, diesel fuel, fuel oils, lubricating and motor oils, and crude oil in Potter and Simmons (1998). Gustafson et al. (1997) lists styrene as a constituent for only one mixture, diesel, at a very low percentage of <0.002% (by weight), which may mean that it was detected but was below the quantitation limit. The reference provided for that information is a personal communication prepared for British Petroleum; thus, the information cannot readily be confirmed. Given the uncertainty as to whether styrene is likely to exist in sites of petroleum contamination, it was not considered in the assessment for this fraction.

Tables 8, 9, and 10 list U.S. EPA RfD assessments, RfC assessments, and a cancer assessment, respectively, that are available on the IRIS database for the individual compounds (BTEX) in this fraction. In addition, provisional toxicity values were derived for subchronic oral and inhalation exposure to BTEX (U.S. EPA, 2009b, d, g, t). Because BTEX components are routinely analyzed individually at sites of aromatic hydrocarbon contamination and noncancer toxicity values are available for these components, the recommendation for assessing the noncancer hazard associated with this fraction is to assess the BTEX components individually using an HI approach and their compound-specific toxicity values. For cancer assessments, benzene serves as an indicator chemical, because it is the only chemical in this fraction with IRIS OSF and IUR estimates. The OSF ($[1.5 \times 10^{-2}–5.5 \times 10^{-2}$ mg/kg-day$]^{-1}$) and the IUR ($[2.2 \times 10^{-3}–7.8 \times 10^{-3}$ µg/m$^3]^{-1}$) for benzene (U.S. EPA, 2003b) are used as indicators to estimate cancer risks for this fraction from exposures through the oral and inhalation routes, respectively.

Table 8. Available RfD Values for Aromatic Low Carbon Range Fraction (C6−C8, EC6−EC < 9)[a]

Components	POD	POD Type	UF_C	UF Components	RfD or p-RfD (mg/kg-d)	Confidence in RfD or p-RfD	Critical Effect(s)	Species, Mode, and Duration	Reference
Subchronic									
Benzene (C6 [EC6.14])	1.2[b]	$BMCL_{1SD}$	100	UF_H, UF_L	0.01[c]	Medium	Decreased lymphocyte count (hematologic)	Human occupational health study, 0.7−16 yr	Rothman et al. (1996) as cited in U.S. EPA (2009d)
Ethylbenzene (C8 [EC8.04])	48	$BMDL_{10}$	1,000	UF_A, UF_D, UF_H	0.05[c]	Medium	Centrilobular hepatocyte hypertrophy (hepatic)	Rat, gavage, 7 d/wk for 13 wk	Mellert et al. (2007) as cited in U.S. EPA (2009g)
Toluene (C7 [EC7.14])	238	$BMDL_{1SD}$	300	UF_A, UF_D, UF_H	0.8[c]	Medium	Increased kidney weight (urinary)	Rat, gavage, 5 d/wk for 13 wk	NTP (1990) as cited in U.S. EPA (2009b)
Xylenes (C8 [EC8.12−8.31])	440	$BMDL_{RD0.1}$	1,000	UF_A, UF_D, UF_H	0.4[c]	Low to medium	10% decrease in body weight (whole body effects)	Rat, gavage, 7 d/wk for 13 wk	Wolfe et al. (1988a) as cited in U.S. EPA (2009t)
Chronic									
Benzene (C6 [EC6.14])	1.2[b]	$BMCL_{1SD}$	300	UF_H, UF_L, UF_S	0.004	Medium	Decreased lymphocyte count (immune)	Human occupational health study, 0.7−16 yr	Rothman et al. (1996) as cited in U.S. EPA (2003b)
Ethylbenzene (C8 [EC8.04])	97.1	NOEL	1,000	UF_A, UF_H, UF_S	0.1	Low	Liver and kidney toxicity (hepatic, urinary)	Rat, gavage 5 d/wk for 26 wk	Wolf et al. (1956) as cited in U.S. EPA (1991b)
Toluene (C7 [EC7.14])	238	$BMDL_{1SD}$	3,000	UF_A, UF_D, UF_H, UF_S	0.08	Medium	Increased kidney weight (urinary)	Rat, gavage, 5 d/wk for 13 wk	NTP (1990) as cited in U.S. EPA (2005a)

Table 8. Available RfD Values for Aromatic Low Carbon Range Fraction (C6−C8, EC6−EC < 9)[a]

Components	POD	POD Type	UF_C	UF Components	RfD or p-RfD (mg/kg-d)	Confidence in RfD or p-RfD	Critical Effect(s)	Species, Mode, and Duration	Reference
Xylenes (C8 [EC8.12−8.31])	179	NOAEL	1,000	UF_A, UF_D, UF_H	0.2	Medium	Decreased body weight, increased mortality (other)	Rat, gavage, 5 d/wk for 103 wk	NTP (1986) as cited in U.S. EPA (2003c)

[a]U.S. EPA (2009r).
[b]Based on route-to-route extrapolation (inhalation to oral).
[c]Toxicity values are provisional values obtained from an existing PPRTV assessment.

BMCL = benchmark concentration lower confidence limit; BMDL = benchmark dose lower confidence limit; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; C = carbon; EC = equivalent carbon; NOAEL = no-observed-adverse-effect level; NOEL = no-observed-effect level; POD = point of departure; PPRTV = Provisional Peer-Reviewed Toxicity Value; p-RfD = provisional reference dose; RD = relative deviation; RfD = reference dose; SD = standard deviation; UF = uncertainty factor; 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.

Table 9. Available RfC Values for Aromatic Low Carbon Range Fraction (C6−C8, EC6−EC < 9)[a]

Components	POD	POD Type	UF_C	UF Components	RfC or p-RfC (mg/m^3)	Confidence in RfD or p-RfD	Critical Effect(s)	Species, Mode, and Duration	Reference
Subchronic									
Benzene (C6 [EC6.14])	8.2	$BMCL_{1SD}$	100	UF_H, UF_L	0.08[b]	Medium	Decreased lymphocyte count (hematologic)	Human occupational health study, 0.7−16 yr	Rothman et al. (1996) as cited in U.S. EPA (2009d)
Ethylbenzene (C8 [EC8.04])	868	LOAEL (HEC)	100	UF_A, UF_H, UF_L	9[b]	Medium	Histopathological evidence of ototoxicity without functional changes in audiometric threshold (other)	Rat, 6 h/d, 6 d/wk for 13 wk	Gagnaire et al. (2007) as cited in U.S. EPA (2009g)
Toluene (C7 [EC7.14])	46	NOAEL	10	UF_H	5[b]	High	Neurological effects in occupationally exposed workers (nervous)	Human occupational health studies, 1−36-yr exposure	Multiple human studies, as cited in U.S. EPA (2009b)
Xylenes (C8 [EC8.12−8.31])	39	NOAEL (HEC)	100	UF_A, UF_D, UF_H	0.4[b]	Medium	Impaired motor coordination (whole body effects)	Rat, 6 h/d, 5 d/wk for 13 wk	Korsak et al. (1994) as cited in U.S. EPA (2009t)
Chronic									
Benzene (C6 [EC6.14])	8.2	$BMCL_{1SD}$	300	UF_H, UF_L, UF_S	0.03	Medium	Decreased lymphocyte count (immune)	Human occupational health study, 0.7−16-yr exposure	Rothman et al. (1996) as cited in U.S. EPA (2003b)
Ethylbenzene (C8 [EC8.04])	434	NOAEL (HEC)	1,000	UF_A, UF_D, UF_H	1	Low	Developmental toxicity (developmental)	Rat and rabbit, 6−7 h/d, 7 d/wk on GDs 1−19 (rat) or GDs 1−24 (rabbit)	Andrew et al. (1981), Hardin et al. (1981) as cited in U.S. EPA (1991b)

Table 9. Available RfC Values for Aromatic Low Carbon Range Fraction (C6−C8, EC6−EC < 9)[a]

Components	POD	POD Type	UF_C	UF Components	RfC or p-RfC (mg/m^3)	Confidence in RfD or p-RfD	Critical Effect(s)	Species, Mode, and Duration	Reference
Toluene (C7 [EC7.14])	46	NOAEL	10	UF_H	5	High	Neurological effects in occupationally exposed workers (nervous)	Human occupational health studies, 1−36-yr exposure	Multiple human studies, as cited in U.S. EPA (2005a)
Xylenes (C8 [EC8.12−8.31])	39	NOAEL (HEC)	300	UF_A, UF_D, UF_H, UF_L	0.1	Medium	Impaired motor coordination (decreased rotarod performance) (nervous)	Rat, 6 h/d, 5 d/wk for 13 wk	Korsak et al. (1994) as cited in U.S. EPA (2003c)

[a]U.S. EPA (2009r).
[b]Toxicity values are provisional values obtained from an existing PPRTV assessment.

BMCL = benchmark concentration lower confidence limit; C = carbon; EC = equivalent carbon; GD = gestation day; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; PPRTV = Provisional Peer-Reviewed Toxicity Value; p-RfD = provisional reference dose; RfD = reference dose; SD = standard deviation; UF = uncertainty factor; 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.

Table 10. Available Cancer Risk Estimates for Aromatic Low Carbon Range Fraction (C6−C8 [EC6−EC < 9])[a]

Toxicity Type (units); Indicator Chemical	Species/Sex	Tumor Type	Cancer Value	Reference
OSF $(mg/kg\text{-}d)^{-1}$				
Benzene (C6 [EC6.14])	Human/M, F	Leukemia	1.5×10^{-2}–5.5×10^{-2}	Rinsky et al. (1981, 1987), Paustenbach et al. (1993), Crump and Allen (1984), Crump (1992, 1994), and U.S. EPA (1998) as cited in U.S. EPA (2003b)
IUR $(mg/m^3)^{-1}$				
Benzene (C6 [EC6.14])	Human/M, F	Leukemia	2.2×10^{-3}–7.8×10^{-3}	Rinsky et al. (1981, 1987), Paustenbach et al. (1993), Crump and Allen (1984), Crump (1992, 1994), and U.S. EPA (1998) as cited in U.S. EPA (2003b)

[a]U.S. EPA (2009r).
C = carbon; EC = equivalent carbon; F = female; IUR = inhalation unit risk; M = male; OSF = oral slope factor.

3.5. AROMATIC MEDIUM CARBON RANGE FRACTION: C9−C10 (EC9−EC < 11)

Constituents of the aromatic medium carbon range fraction include longer chain and multi-substituted benzenes (e.g., cumene [isopropylbenzene], *n*-propylbenzene, methylethylbenzenes, and TMBs). Toxicity assessment and surrogate selection for the aromatic medium carbon range fraction is detailed in the PPRTV assessment for this fraction (U.S. EPA, 2022d). This section provides a summary of the approach and results; further detail is available in the PPRTV assessment.

Toxicity values were identified for eight aromatic medium carbon range compounds and one mixture. Tables 11 and 12 provide a summary of the noncancer toxicity values, critical effects, and key studies. Literature searches, OECD SIDS, and the Petroleum HPV Testing Group website yielded relevant toxicity data for four additional compounds and one additional mixture[4] for use in hazard identification for the fraction. The primary toxicological endpoints identified for the fraction were neurological, hepatic, renal, body weight, hematological, endocrine, and developmental effects. The data available to assess consistency in effects across members of the fraction are limited for effects on endpoints other than body weight. There are no reliable human or animal data for three members of the fraction (*n*-propylbenzene, and *tert*- and *sec*-butylbenzene).[5] There are body-weight data for 11 members, and there are neurotoxicity data for 9 members. For all other primary toxicological endpoints, there are oral or inhalation data for 5−7 members of the fraction. Most of the animal data are from inhalation toxicity studies.

[4]The four additional aromatic medium carbon range compounds identified in the literature searches and tree-searching of reviews, OECD SIDS, and the Petroleum HPV Testing Group website are 1-methyl-4-ethylbenzene; 1,3-diethylbenzene; 1,4-diethylbenzene, and 1,2-diethylbenzene; the additional mixture is a mixture of diethylbenzenes.
[5]In the absence of human or animal data, screening toxicity values were derived using appropriate analogue chemicals (ethylbenzene and isopropylbenzene) in the PPRTV assessments of these compounds.

Comprehensive systematic toxicity was evaluated in rats and mice in subchronic and chronic inhalation studies for one member of the fraction (isopropylbenzene). In general, studies for other members of the fraction ranged in duration from 4 to 18 weeks; several of these studies (e.g., diethylbenzenes and TMBs) evaluated only neurological endpoints. Developmental inhalation toxicity studies were available for four members of the fraction (isopropylbenzene, 1,3,5- and 1,2,4-trimethylbenzene, and high flash aromatic naphtha [HFAN]).

Table 11. Available RfD Values for Aromatic Medium Carbon Range Fraction (C9−C10 [EC9−EC < 11])[a]

Indicator Chemical, Components or Mixture	POD (mg/kg-d)	POD Type	UF_C	UF Components	RfD or p-RfD (mg/kg-d)	Confidence in p-RfD or RfD	Critical Effect(s)	Species, Mode, and Duration	Primary Reference (source)
Subchronic									
n-Propylbenzene (C9 [EC8.94])	97.1	$NOEL_{ADJ}$	1,000	UF_A, UF_H, UF_S	*0.1*[b]	Low	Based on ethylbenzene as an analogue; increased liver and kidney weights (hepatic, urinary); histopathologic changes in kidney	Rat, gavage, 5 d/wk for 182 d	Wolf (1956) as cited in U.S. EPA (2009n)
1,3,5-Trimethylbenzene (C9 [EC9.15])	**3.5**	**BMDL (HED)**	**100**	**UF_A, UF_D, UF_H**	**0.04**	**Low**	**Decreased pain sensitivity in male Wistar rats[c] (nervous)**	**Rat, 6 h/d, 5 d/wk for 13 wk**	**Korsak and Rydzynski (1996) as cited in U.S. EPA (2016b)**
1,2,4-Trimethylbenzene (C9 [EC9.36])	**3.5**	**BMDL (HED)**	**100**	**UF_A, UF_D, UF_H**	**0.04**	**Low**	**Decreased pain sensitivity in male Wistar rats[c] (nervous)**	**Rat, 6 h/d, 5 d/wk for 13 wk**	**Korsak and Rydzynski (1996) as cited in U.S. EPA (2016b)**
tert-Butylbenzene (C10 [EC9.36])	110	$NOAEL_{ADJ}$	1,000	UF_A, UF_D, UF_H, UF_s	*0.1*[b]	Low	Based on isopropylbenzene as an analogue; increased kidney weight (urinary)	Rat, 5 d/wk for 194 d	Wolf (1956) as cited in U.S. EPA (2012d)
sec-Butylbenzene (C10 [EC9.57])	110	$NOAEL_{ADJ}$	1,000	UF_A, UF_D, UF_H, UF_S	*0.1*[b]	Low	Based on isopropylbenzene as an analogue; increased kidney weight (urinary)	Rat, 5 d/wk for 194 d	Wolf (1956) as cited in U.S. EPA (2012c)
1,2,3-Trimethylbenzene (C9 [EC9.65])	**3.5**	**BMDL (HED)**	**100**	**UF_A, UF_D, UF_H**	**0.04**	**Low**	**Decreased pain sensitivity in male Wistar rats[c] (nervous)**	**Rat, 6 h/d, 5 d/wk for 13 wk**	**Korsak and Rydzynski (1996) as cited in U.S. EPA (2016b)**

Table 11. Available RfD Values for Aromatic Medium Carbon Range Fraction (C9−C10 [EC9−EC < 11])[a]

Indicator Chemical, Components or Mixture	POD (mg/kg-d)	POD Type	UF_C	UF Components	RfD or p-RfD (mg/kg-d)	Confidence in p-RfD or RfD	Critical Effect(s)	Species, Mode, and Duration	Primary Reference (source)
n-Butylbenzene (C10 [EC9.96])	137	$BMDL_{10}$	1,000	UF_A, UF_D, UF_H	0.1[b]	Low	Increased incidence of hepatocellular hypertrophy in F_0 and F_1 parent male rats (hepatic)	Rat, gavage, 2-genearation	Izumi et al. (2005) as cited in U.S. EPA (2010b)
HFAN (C9−10)	85	$BMDL_{1SD}$	300	UF_A, UF_D, UF_H	*0.3*[b]	Low	Mild anemia, evidenced by a decrease in RBC count (hematological)	Dog, gelatin capsules, 13 wk	Bio/Dynamics Inc. (1990b) as cited in U.S. EPA (2009h)
Chronic									
Isopropylbenzene (C9 [EC8.66])	110	$NOAEL_{ADJ}$	1,000	UF_A, UF_D, UF_H, UF_S	0.1	Low−medium	Increased average kidney weight in female Wistar rats (urinary)	Rat, 5 d/wk for 194 d	Wolf (1956) as cited in U.S. EPA (1997b)
n-Propylbenzene (C9 [EC8.94])	97.1	$NOEL_{ADJ}$	1,000	UF_A, UF_H, UF_S	*0.1*[b]	Low	Based on ethylbenzene as an analogue; increased liver and kidney weights (hepatic, urinary)	Rat; gavage; 5 d/wk for 182 d	Wolf (1956) as cited in U.S. EPA (2009n)
1,3,5-Trimethylbenzene (C9 [EC9.15])	**3.5**	**BMDL (HED)**	**300**	**UF_A, UF_D, UF_H, UF_S**	**0.01**	**Low**	**Decreased pain sensitivity in male Wistar rats[c] (nervous)**	**Rat, 6 h/d, 5 d/wk for 13 wk**	**Korsak and Rydzynski (1996) as cited in U.S. EPA (2016b)**
1,2,4-Trimethylbenzene (C9 [EC9.36])	**3.5**	**BMDL (HED)**	**300**	**UF_A, UF_D, UF_H, UF_S**	**0.01**	**Low**	**Decreased pain sensitivity in male Wistar rats[c] (nervous)**	**Rat, 6 h/d, 5 d/wk for 13 wk**	**Korsak and Rydzynski (1996) as cited in U.S. EPA (2016b)**

Table 11. Available RfD Values for Aromatic Medium Carbon Range Fraction (C9−C10 [EC9−EC < 11])[a]

Indicator Chemical, Components or Mixture	POD (mg/kg-d)	POD Type	UF_C	UF Components	RfD or p-RfD (mg/kg-d)	Confidence in p-RfD or RfD	Critical Effect(s)	Species, Mode, and Duration	Primary Reference (source)
tert-Butylbenzene (C10 [EC9.36])	110	$NOAEL_{ADJ}$	1,000	UF_A, UF_D, UF_H, UF_S	*0.1*[b]	Low	Based on isopropylbenzene as an analogue; increased kidney weight (urinary)	Rat, 5 d/wk for 194 d	Wolf (1956) as cited in U.S. EPA (2012d)
sec-Butylbenzene (C10 [EC9.57])	110	$NOAEL_{ADJ}$	1,000	UF_A, UF_D, UF_H, UF_S	*0.1*[b]	Low	Based on isopropylbenzene as an analogue; increased kidney weight (urinary)	Rat, 5 d/wk for 194 d	Wolf (1956) as cited in U.S. EPA (2012c)
1,2,3-Trimethylbenzene (C9 [EC9.65])	**3.5**	**BMDL (HED)**	**300**	**UF_A, UF_D, UF_H, UF_S**	**0.01**	**Low**	**Decreased pain sensitivity in male Wistar rats[c] (nervous)**	**Rat, 6 h/d, 5 d/wk for 13 wk**	**Korsak and Rydzynski (1996) as cited in U.S. EPA (2016b)**
n-Butylbenzene (C10 [EC9.96])	137	$BMDL_{10}$	3,000	UF_A, UF_D, UF_H, UF_S	0.05[b]	Low	Increased incidence of hepatocellular hypertrophy in F_0 and F_1 parent male Crj:CD (SD) IGS rats (hepatic)	Rat, gavage, two-generation	Izumi et al. (2005) as cited in U.S. EPA (2010b)

Table 11. Available RfD Values for Aromatic Medium Carbon Range Fraction (C9−C10 [EC9−EC < 11])[a]

Indicator Chemical, Components or Mixture	POD (mg/kg-d)	POD Type	UF_C	UF Components	RfD or p-RfD (mg/kg-d)	Confidence in p-RfD or RfD	Critical Effect(s)	Species, Mode, and Duration	Primary Reference (source)
HFAN (C9−10)	85	$BMDL_{1SD}$	3,000	UF_A, UF_D, UF_H, UF_S	*0.03*[b]	Low	Mild anemia, evidenced by a decrease in RBC count (hematological)	Dog, gelatin capsules, 13 wk	Bio/Dynamics Inc. (1990b) as cited in U.S. EPA (2009h)

[a]**Bolded** row shows the compound and toxicity value selected as the indicator chemical for the fraction if analytical chemistry data do not identify concentrations of individual chemicals composing this fraction.
[b]Toxicity values are provisional values obtained from an existing PPRTV assessment. Values in *italics* are screening provisional values obtained from an existing PPRTV assessment. Screening provisional values are not assigned confidence statements; however, confidence in these values is presumed to be low. Screening provisional values are derived when the available data do not meet the requirements for deriving a provisional toxicity value.
[c]Toxicity values based on route-to-route extrapolation (inhalation to oral) using a modified PBPK model.

ADJ = adjusted; BMDL = benchmark dose lower confidence limit; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; C = carbon; EC = equivalent carbon; HED = human equivalent dose; HFAN = high-flash aromatic naphtha; NOAEL = no-observed-adverse-effect level; NOEL = no-observed-effect level; PBPK = physiologically based pharmacokinetic; POD = point of departure; PPRTV = Provisional Peer-Reviewed Toxicity Value; p-RfD = provisional reference dose; RBC = red blood cell; RfD = reference dose; SD = standard deviation; UF = uncertainty factor; 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.

Table 12. Available RfC Values for Aromatic Medium Carbon Range Fraction (C9−C10 [EC9−EC < 11])[a]

Indicator Chemical Components, or Mixture	POD	POD Type (all are HECs)	UF_C	UF Components	RfC or p-RfC (mg/m^3)	Confidence in p-RfC or RfC	Critical Effect(s)	Species, Mode, and Duration	Primary Reference (source)
Subchronic									
n-Propylbenzene (C9 [EC8.94])	434	NOAEL	300	UF_A, UF_D, UF_H	*1*[b]	Low	Based on ethylbenzene as an analogue; developmental toxicity (developmental)	Rat, 6−7 h/d, 7 d/wk for 3 wk prior to mating and GDs 1−19; rabbit, 6−7 h/d, 7 d/wk on GDs 1−24	Andrews (1981) and Hardin (1981), as cited in U.S. EPA (2009n)
1,3,5-Trimethylbenzene (C9 [EC9.15])	**18.15**	**BMCL**	**100**	**UF_A, UF_D, UF_H**	**0.2**	**Low−medium**	**Decreased pain sensitivity in male Wistar rats (nervous)**	**Rat, 6 h/d, 5 d/wk for 13 wk**	**Korsak and Rydzynski (1996) as cited in U.S. EPA (2016b)**
1,2,4-Trimethylbenzene (C9 [EC9.36])	**18.15**	**BMCL**	**100**	**UF_A, UF_D, UF_H**	**0.2**	**Low−medium**	**Decreased pain sensitivity in male Wistar rats (nervous)**	**Rat, 6 h/d, 5 d/wk for 13 wk**	**Korsak and Rydzynski (1996) as cited in U.S. EPA (2016b)**
1,2,3-Trimethylbenzene (C9 [EC9.65])	**18.15**	**BMCL**	**100**	**UF_A, UF_D, UF_H**	**0.2**	**Low−medium**	**Decreased pain sensitivity in male Wistar rats (nervous)**	**Rat, 6 h/d, 5 d/wk for 13 wk**	**Korsak and Rydzynski (1996) as cited in U.S. EPA (2016b)**
HFAN (C9−10)	125	LOAEL	300	UF_A, UF_H, UF_L	1[b]	Moderate	Decreased maternal body weight vs. controls (reproductive) in CD-1 mice	Mouse, 6 h/d, 7 d/wk on GDs 6−15	McKee et al. (1990) as cited in U.S. EPA (2009h)

Table 12. Available RfC Values for Aromatic Medium Carbon Range Fraction (C9−C10 [EC9−EC < 11])[a]

Indicator Chemical Components, or Mixture	POD	POD Type (all are HECs)	UF_C	UF Components	RfC or p-RfC (mg/m^3)	Confidence in p-RfC or RfC	Critical Effect(s)	Species, Mode, and Duration	Primary Reference (source)
Chronic									
Isopropylbenzene (C9 [EC8.66])	435	NOAEL	1,000	UF_A, UF_D, UF_H, UF_S	0.4	Medium	Increased kidney weights in female rats and adrenal weights in male and female F344 rats (endocrine, urinary)	Rat, 6 h/d, 5 d/wk for 13 wk	Cushman (1995) as cited in U.S. EPA (1997b)
n-Propylbenzene (C9 [EC8.94])	434	NOAEL	300	UF_A, UF_D, UF_H	*1*[b]	Low	Based on ethylbenzene as an analogue; developmental toxicity (developmental)	Rat, 6−7 h/d, 7 d/wk for 3 wk prior to mating and GDs 1−19; rabbit, 6−7 h/d, 7 d/wk on GDs 1−24	Andrews (1981) and Hardin (1981), as cited in U.S. EPA (2009n)
1,3,5-Trimethylbenzene (C9 [EC9.15])	**18.15**	**BMCL**	**300**	**UF_A, UF_D, UF_H, UF_S**	**0.06**	**Low−medium**	**Decreased pain sensitivity in male Wistar rats (nervous)**	**Rat, 6 h/d, 5 d/wk for 13 wk**	**Korsak and Rydzynski (1996) as cited in U.S. EPA (2016b)**
1,2,4-Trimethylbenzene (C9 [EC9.36])	**18.15**	**BMCL**	**300**	**UF_A, UF_D, UF_H, UF_S**	**0.06**	**Low−medium**	**Decreased pain sensitivity in male Wistar rats (nervous)**	**Rat, 6 h/d, 5 d/wk for 13 wk**	**Korsak and Rydzynski (1996) as cited in U.S. EPA (2016b)**
1,2,3-Trimethylbenzene (C9 [EC9.65])	**18.15**	**BMCL**	**300**	**UF_A, UF_D, UF_H, UF_S**	**0.06**	**Low−medium**	**Decreased pain sensitivity in male Wistar rats (nervous)**	**Rat, 6 h/d, 5 d/wk for 13 wk**	**Korsak and Rydzynski (1996) as cited in U.S. EPA (2016b)**

Table 12. Available RfC Values for Aromatic Medium Carbon Range Fraction (C9−C10 [EC9−EC < 11])[a]

Indicator Chemical Components, or Mixture	POD	POD Type (all are HECs)	UF_C	UF Components	RfC or p-RfC (mg/m^3)	Confidence in p-RfC or RfC	Critical Effect(s)	Species, Mode, and Duration	Primary Reference (source)
HFAN (C9−10)	125	LOAEL	1,000	UF_A, UF_H, UF_L, UF_S	0.1[b]	Moderate	Decreased maternal body weight vs. controls (reproductive) on GD 15 in CD-1 mice	Mouse, 6 h/d, 7 d/wk on GDs 6−15	McKee et al. (1990) as cited in U.S. EPA (2009h)

[a]**Bolded** row shows the compounds and toxicity value selected as the indicator chemical for the fraction if analytical chemistry data do not identify concentrations of individual chemicals composing this fraction.
[b]Toxicity values are provisional values obtained from an existing PPRTV assessment. Values in *italics* are screening provisional values obtained from an existing PPRTV assessment. Screening provisional values are not assigned confidence statements; however, confidence in these values is presumed to be low. Screening provisional values are derived when the available data do not meet the requirements for deriving a provisional toxicity value.

BMCL = benchmark concentration lower confidence limit; C = carbon; EC = equivalent carbon; GD = gestation day; HEC = human equivalent concentration; HFAN = high-flash aromatic naphtha; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; ; PPRTV = Provisional Peer-Reviewed Toxicity Value; p-RfC = provisional reference concentration; RfC = 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_S = subchronic-to-chronic uncertainty factor.

The data available to assess consistency in critical effects across members of the fraction are limited for effects on endpoints other than body weight. The potencies are comparable with RfDs being within 1 order of magnitude of one another. Given the limited data, the compounds that resulted in the lowest RfDs for these effects and target tissues were considered as the basis for indicator chemical selection. The subchronic and chronic p-RfDs (0.04 and 0.01 mg/kg-day, respectively) for TMBs are recommended as indicator chemicals for the aromatic medium carbon range fraction. The RfDs for TMBs are based on neurological effects (decreased pain sensitivity). While toxicological data from mixtures such as HFAN might be preferred in some cases, the p-RfD for HFAN is based on a screening value, and the Agency has more confidence in EPA's IRIS TMB oral assessments as the indicator chemical.

Options for oral noncancer assessment of this fraction are presented based on available analytical chemistry information.

If available analytical chemistry data do not identify concentrations of individual chemicals composing this fraction, the subchronic and chronic p-RfDs (0.04 and 0.01 mg/kg-day, respectively) for TMBs are recommended for the aromatic medium carbon range fraction (U.S. EPA, 2016b). Evaluation of available data suggests that use of the p-RfDs for TMBs is reasonably anticipated to be protective for effects associated with exposure to other constituents of the fraction. The indicator chemical and oral noncancer toxicity values selected to represent the fraction are shown in bold in Table 11.

If the available analytical chemistry data quantify the concentrations of TMBs, *n*-propylbenzene, *n*-butylbenzene, *sec*-butylbenzene, *tert*-butylbenzene, or isopropylbenzene separately from the remainder of the aromatic medium carbon range fraction, it is recommended that HQs for the individual chemicals with analytical data be calculated and an HI for the mixture be developed using the calculated HQs.

For subchronic oral exposures, the following subchronic RfDs or p-RfDs can be used as the denominator in the HQ equations: TMBs (0.04 mg/kg-day), *n*-propylbenzene (0.1 mg/kg-day), *n*-butylbenzene (0.1 mg/kg-day), *sec*-butylbenzene (0.1 mg/kg-day), and *tert*-butylbenzene (0.1 mg/kg-day). In this alternative approach, the subchronic RfD for TMBs (0.04 mg/kg-day) is recommended for use with the remainder of the fraction, including any other fraction members analyzed individually.

For chronic oral exposures, the following chronic RfDs or p-RfDs can be used as the denominator in the HQ equations: TMBs (0.01 mg/kg-day), isopropylbenzene (0.1 mg/kg-day), *n*-propylbenzene (0.1 mg/kg-day), *n*-butylbenzene (0.05 mg/kg-day), *sec*-butylbenzene (0.1 mg/kg-day), and *tert*-butylbenzene (0.1 mg/kg-day). In this alternative approach, the chronic RfD for TMBs (0.01 mg/kg-day) is recommended for use with the remainder of the fraction, including any other fraction members analyzed individually.

In some cases, toxicological data from mixtures such as HFAN might be preferred; however, the p-RfD for HFAN is based on a screening value. The Agency has more confidence in an HI approach as an alternative to the indicator chemical approach than for the surrogate mixture approach for this fraction.

Critical effects and values of RfCs for fraction members show consistency across the fraction with respect to the toxicological effects exerted (most frequently, neurological and developmental effects). The data show that an indicator chemical identifying effects on these targets would be reasonably anticipated to be representative of the effects of the fraction as a whole. Therefore, the compounds that resulted in the lowest RfCs for these effects were considered as the basis for surrogate selection.

As with oral noncancer assessment, two options for inhalation noncancer assessment are presented. If available analytical chemistry data do not identify concentrations of individual chemicals in this fraction, the subchronic and chronic p-RfCs (0.2 mg/m^3 and 0.06 mg/m^3, respectively) for TMBs (U.S. EPA, 2016b) are recommended as an indicator chemical for the aromatic medium carbon range fraction. The RfCs for TMBs are based on neurological effects (decreased pain sensitivity), and available data generally support the nervous system as a target of the aromatic medium carbon compounds. Use of these values is anticipated to be protective for exposure to other constituents based on available information. The indicator chemical and inhalation noncancer toxicity values selected to represent the fraction are shown in bold in Table 12.

Previously, in the PPRTV TPH mixtures document (U.S. EPA, 2009f), the HFAN subchronic and chronic p-RfCs were recommended for assessing noncancer hazards associated with inhalation route exposures to this fraction, based on a 2009 PPRTV assessment (U.S. EPA, 2009h). In 2016, the U.S. EPA IRIS Program published TMB subchronic and chronic p-RfCs of 0.2 and 0.06 mg/m^3, respectively (U.S. EPA, 2016b) that are lower than the respective HFAN values of 1 and 0.1 mg/m^3 (U.S. EPA, 2009h) (see Table 12). Because these are IRIS values rather than PPRTVs, these IRIS single chemical values should be used in the indicator chemical approach rather than HFAN-based surrogate mixture approach. The 2009 TPH mixture assessment indicates that the HFAN toxicity values are similar to values for other individual compounds in the fraction, which supports using HFAN as a surrogate for the fraction; however, the 2016 TMB values are much lower than the HFAN values and that logic is not applicable.

If the available analytical chemistry data quantify the concentrations of TMBs, *n*-propylbenzene, or isopropylbenzene separately from the remainder of the aromatic medium carbon range fraction, it is recommended that HQs for the individual chemicals with analytical data be calculated and a HI for the mixture be developed using the calculated HQs.

For subchronic inhalation exposures, the subchronic RfCs or p-RfCs for TMBs (0.2 mg/m^3) or *n*-propylbenzene (1.0 mg/m^3) can be used as the denominator in the HQ equations. In this alternative approach, the subchronic RfC for TMBs (0.2 mg/m^3) is recommended for use with the remainder of the fraction, including any other fraction members analyzed individually.

For chronic inhalation exposures, the following chronic RfCs or p-RfCs can be used in the denominator of the HQ equations: TMBs (0.06 mg/m^3), isopropylbenzene (0.4 mg/m^3), and *n*-propylbenzene (1 mg/m^3). In this alternative approach, the chronic RfC for TMBs (0.06 mg/m^3) is recommended for use with the remainder of the fraction, including any other fraction members analyzed individually.

Previously, in the PPRTV TPH mixtures document (U.S. EPA, 2009f), the HFAN subchronic and chronic p-RfCs were recommended for assessing noncancer hazards associated with inhalation route exposures to this fraction, based on a 2009 PPRTV assessment (U.S. EPA, 2009h). By definition, HFAN mixtures must contain a combined total of 75% TMB and ethyltoluene isomers (of which at least 22% is ethyltoluene and at least 15% is TMB) (U.S. EPA, 2009h). As noted previously, in 2016, the U.S. EPA IRIS Program published TMB subchronic and chronic p-RfCs of 0.2 and 0.06 mg/m^3, respectively (U.S. EPA, 2016b) that are lower than the HFAN values of 1 and 0.1 mg/m^3, respectively (U.S. EPA, 2009h) (see Table 12). Because these are IRIS values rather than PPRTVs, the U.S. EPA has more confidence in using these IRIS single chemical values in a hazard index approach rather than the HFAN values in surrogate mixture approach. The 2009 TPH mixture assessment indicates that the HFAN toxicity values are similar to values for other individual compounds in the fraction, which supports using HFAN as a surrogate for the fraction; however, the 2016 TMB values are much lower than the HFAN values and that logic is not applicable.

Few data are available to assess the carcinogenic potential of compounds and mixtures in the aromatic medium carbon range fraction. No human data were identified. Animal data are limited to studies of 1,2,4-trimethylbenzene and isopropylbenzene. Several limitations were identified in the only carcinogenicity study of 1,2,4-trimethylbenzene reported in U.S. EPA (2016b); these limitations included the use of one rodent species, treatment at a single dose level, and lack of quantitative mortality data. Only data from a newly identified study for isopropylbenzene (NTP, 2009) are considered adequate to sufficiently assess carcinogenic potential. This recently identified study was a 105-week chronic toxicity/carcinogenicity study of isopropylbenzene in rats and mice (NTP, 2009). Statistically significant increases in the incidence of respiratory epithelial adenomas of the nose in both sexes and renal adenoma or carcinoma (combined) in males were observed in rats. Increased interstitial cell adenomas were also reported in the male testis; however, the NTP report stated that these are possibly related to isopropylbenzene exposure. While the incidence of interstitial cell adenomas reported in the highest dose group in the male rats was significantly increased compared to the control group and there was a positive trend in the incidences reported among all exposed groups, the incidence in the high-dose group was within the range for historical chamber controls when studies with all exposure routes were considered. Interstitial cell hyperplasia and adenoma are common proliferative lesions in F344/N rats (i.e., the test species) and reportedly will develop in nearly all male rats of this strain that are allowed to complete their natural life span (NTP, 2009). In mice, the incidences of alveolar/bronchiolar adenomas were significantly increased in both sexes; increased incidences of hemangiosarcomas and follicular cell adenomas in males (possibly related to exposure) and hepatocellular adenomas or carcinomas in females were also noted. Based on these data, the study authors indicated that there was clear evidence of carcinogenicity in male rats and male and female mice, and some evidence of carcinogenic activity in female rats.

None of the mixtures or constituents in this fraction had an OSF or IUR from the IRIS database, PPRTVs, HEAST, MassDEP, or TPHCWG. At this time, the U.S. EPA has not formally evaluated the NTP (2009) study and has not estimated the cancer potency associated with the study results. Thus, a p-OSF or p-IUR was not derived for the fraction.

3.6. AROMATIC HIGH CARBON RANGE FRACTION: C10−C32 (EC11−EC35)

The aromatic high carbon range fraction contains PAHs (e.g., naphthalene, anthracene, BaP, BeP, dibenzo[*def,p*]chrysene) and benzenes with larger aliphatic substituents (e.g., *n*-hexylbenzene, phenylcyclohexane). This fraction is further subdivided for the purposes of this document. Unsubstituted 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. Noncancer toxicity assessment and surrogate selection for the aromatic high carbon range fraction is detailed in the PPRTV assessment for this fraction (U.S. EPA, 2022c). This section provides a summary of the approach and results; further detail is available in the PPRTV assessment.

Noncancer toxicity values were identified for 10 aromatic high carbon range compounds. Tables 13, 14, and 15 provide summaries of the toxicity values, critical effects, and key studies. Literature searches and searches of reviews, OECD SIDS and the Petroleum HPV Testing Group website yielded relevant toxicity data for five additional compounds and three defined mixtures[6] for use in hazard identification for the fraction. In addition, limited toxicity data that were not sufficient to derive a toxicity value are available in the PPRTV assessment for phenanthrene (U.S. EPA, 2009o). Critical effects identified with existing toxicity values were developmental effects (neurodevelopmental changes, fetal skeletal anomalies), respiratory effects (pulmonary alveolar proteinosis), increased liver weight, decreased red blood cells (RBCs), renal effects (nephropathy, decreased kidney weights, renal papillary mineralization), clinical signs of neurotoxicity, and decreased body weight. Additional potential targets identified based on literature searches include the adult and developing reproductive system and the GI system.

[6]The five additional aromatic medium carbon range compounds identified in the literature searches and tree-searching of reviews, OECD SIDS, and the Petroleum HPV Testing Group website are benzo[*b*]fluoranthene, benzo[*c*]fluorene, dibenzo[*def,p*]chrysene, 1,2,4-triethylbenzene, and 1,3,5-triethylbenzene; the additional mixtures are PAH mixtures containing 21, 16, or 9 PAHs.

Table 13. Available Subchronic RfD Values for Aromatic High Carbon Range Fraction (C10−C32 [EC11−EC35])[a]

Indicator Chemical or Components	POD (mg/kg-d)	POD Type	UF_C	UF Components	p-RfD (mg/kg-d)	Confidence in p-RfD	Critical Effect(s)	Species, Mode, and Duration	Reference
Benzo[*a*]pyrene[b] (C20 [EC29.95])	**0.092**	**$BMDL_{1SD}$**	**300**	**UF_A, UF_D, UF_H**	**0.0003**	**Medium**	**Neurobehavioral changes (developmental)**	**Rat, gavage, PNDs 5−11**	**Chen et al. (2012) as cited in U.S. EPA (2017)**
Benzo[*e*]pyrene (C20 [EC27.80])	0.092	$BMDL_{1SD}$	1,000	UF_A, UF_H, UF_D	*0.00009*[c]	NA	Based on benzo[*a*]pyrene as an analogue; neurobehavioral changes (developmental)	Rat, gavage, PNDs 5−11	U.S. EPA (2021b)
Naphthalene (C10 [EC11.57])	50	LOAEL	90	UF_A, UF_H, UF_L	0.6	NA	Clinical signs of toxicity and decreased body-weight gain (whole body effects)	Rat, gavage, GDs 6−15	NTP (1991) as cited in ATSDR (2005)
2-Methylnaphthalene (C11 [EC12.72])	3.5	$BMDL_{05}$	1,000	UF_A, UF_D, UF_H	0.004[c]	Low	Pulmonary alveolar proteinosis (respiratory)	Mouse, diet, 81 wk	Murata et al. (1997) as cited in U.S. EPA (2007c)
1,1-Biphenyl (C12 [EC13.45])	9.59	$BMDL_{05}$	100	UF_A, UF_H	0.1[c]	High	Increased incidence of fetal skeletal anomalies (developmental)	Rat, gavage, GDs 6−15	Khera et al. (1979) as cited in U.S. EPA (2011a)
Acenaphthene (C12 [EC14.76])	161	$BMDL_{10}$	1,000	UF_A, UF_D, UF_H	0.2[c]	Low	Increased relative liver weight in females (hepatic)	Mouse, gavage, 13 wk	U.S. EPA (1989) as cited in U.S. EPA (2011b)
Fluorene (C13 [EC15.68])	125	LOAEL	300	UF_A, UF_H, UF_L	0.4	NA	Increased relative liver weight (hepatic)	Mouse, gavage, 13 wk	U.S. EPA (1989) as cited in ATSDR (1995)
Anthracene (C14 [EC18.43])	1,000	NOEL	1,000	UF_A, UF_D, UF_H	1[c]	Low	No effects observed	Mouse, gavage, 13 wk	Wolfe (1989) as cited in U.S. EPA (2009c)

Table 13. Available Subchronic RfD Values for Aromatic High Carbon Range Fraction (C10−C32 [EC11−EC35])[a]

Indicator Chemical or Components	POD (mg/kg-d)	POD Type	UF_C	UF Components	p-RfD (mg/kg-d)	Confidence in p-RfD	Critical Effect(s)	Species, Mode, and Duration	Reference
Pyrene (C16 [EC22.45])	75	NOAEL	300	UF_A, UF_D, UF_H	0.3[c]	Low	Nephropathy and decreased kidney weights (urinary)	Mouse, gavage, 13 wk	U.S. EPA (1989) as cited in U.S. EPA (2007d)
Fluoranthene (C16 [EC21.11])	124	$BMDL_{10}$	1,000	UF_A, UF_D, UF_H	0.1[c]	Low	Nephropathy (urinary)	Mouse, gavage, 13 wk	U.S. EPA (1989) as cited in U.S. EPA (2012b)

[a]**Bolded** row shows the compound and toxicity value selected as the indicator chemical for the fraction if analytical chemistry data do not identify concentrations of individual chemicals composing this fraction.
[b]The chronic RfD for benzo[*a*]pyrene is based on a developmental exposure; therefore, it is also applicable to subchronic exposures and is listed here.
[c]Toxicity values are provisional values obtained from an existing PPRTV assessment. Values in *italics* are screening provisional values obtained from an existing PPRTV assessment. Screening provisional values are not assigned confidence statements; however, confidence in these values is presumed to be low. Screening provisional values are derived when the available data do not meet the requirements for deriving a provisional toxicity value.

BMDL = benchmark dose lower confidence limit; $BMDL_{05}$ = 5% benchmark dose lower confidence limit; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; C = carbon; EC = equivalent carbon; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; NA = not applicable, reference did not include confidence statement; NOAEL = no-observed-adverse-effect level; NOEL = no-observed-effect level; PND = postnatal day; POD = point of departure; PPRTV = Provisional Peer-Reviewed Toxicity Value; p-RfD = provisional reference dose; RfD = reference dose; SD = standard deviation; 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.

Table 14. Available Chronic RfD Values for Aromatic High Carbon Range Fraction (C10−C32 [EC11−EC35])[a]

Indicator Chemical or Components	POD (mg/kg-d)	POD Type	UF_C	UF Components	p-RfD or RfD (mg/kg-d)	Confidence in p-RfD or RfD	Critical Effect(s)	Species, Mode, and Duration	Reference
Benzo[*a*]pyrene[b] (C20 [EC29.95])	**0.092**	**$BMDL_{1SD}$**	**300**	**UF_A[c], UF_D, UF_H**	**0.0003**	**Medium**	**Neurobehavioral changes (developmental)**	**Rat, gavage, PNDs 5−11**	Chen et al. (2012) as cited in U.S. EPA (2017)
Benzo[*e*]pyrene (C20 [EC27.80])	0.092	$BMDL_{1SD}$	1,000	UFA, UFH, UFD	*0.00009*[d]	NA	Based on benzo[*a*]pyrene as an analogue; neurodevelopmental changes (developmental)	Rat, gavage, PNDs 5−11	U.S. EPA (2021b)
Naphthalene (C10 [EC11.57])	71	$NOAEL_{ADJ}$	3,000	UF_A, UF_D, UF_H, UF_S	0.02	Low	Decreased mean terminal body weight in males (other)	Rat, gavage, 5 d/wk, 13 wk	BCL (1980) as cited in U.S. EPA (1998)
2-Methylnaphthalene (C11 [EC12.72])	3.5	$BMDL_{05}$	1,000	UF_A, UF_D, UF_H	0.004	Low	Pulmonary alveolar proteinosis (respiratory)	Mouse, diet, 81 wk	Murata et al. (1997) as cited in U.S. EPA (2003d)
1-Methylnaphthalene (C11 [EC12.77])	71.6	LOAEL	10,000	UF_A, UF_D, UF_H, UF_L	*0.007*[d]	Low	Pulmonary alveolar proteinosis (respiratory)	Mouse, diet, 81 wk	Murata et al. (1993) as cited in U.S. EPA (2008)
1,1-Biphenyl (C12 [EC13.45])	13.9	$BMDL_{10}$ (HED)	30	UF_A, UF_H	0.5	Medium−high	Renal papillary mineralization in male F344 rats (urinary)	Rat, diet, 104 wk	Umeda et al. (2002) as cited in U.S. EPA (2013b)
Acenaphthene (C12 [EC14.76])	175	NOAEL	3,000	UF_A, UF_D, UF_H, UF_S	0.06	Low	Hepatotoxicity (hepatic)	Mouse, gavage, 13 wk	U.S. EPA (1989) as cited in U.S. EPA (1990a)
Fluorene (C13 [EC15.68])	125	NOAEL	3,000	UF_A, UF_D, UF_H, UF_S	0.04	Low	Decreased RBCs, packed cell volume, and hemoglobin (hematologic)	Mouse, gavage, 13 wk	U.S. EPA (1989) as cited in U.S. EPA (1990d)

Table 14. Available Chronic RfD Values for Aromatic High Carbon Range Fraction (C10−C32 [EC11−EC35])[a]

Indicator Chemical or Components	POD (mg/kg-d)	POD Type	UF_C	UF Components	p-RfD or RfD (mg/kg-d)	Confidence in p-RfD or RfD	Critical Effect(s)	Species, Mode, and Duration	Reference
Anthracene (C14 [EC18.43])	1,000	NOAEL	3,000	UF_A, UF_D, UF_H, UF_S	0.3	Low	No effects observed	Mouse, gavage, 13 wk	Wolfe (1989) as cited in U.S. EPA (1990b)
Pyrene (C16 [EC22.45])	75	NOAEL	3,000	UF_A, UF_D, UF_H, UF_S	0.03	Low	Kidney effects (renal tubular pathology, decreased kidney weights) (urinary)	Mouse, gavage, 13 wk	U.S. EPA (1989) as cited in U.S. EPA (1990e)
Fluoranthene (C16 [EC21.11])	125	NOAEL	3,000	UF_A, UF_D, UF_H, UF_S	0.04	Low	Nephropathy, increased liver weights, hematological alterations, and clinical effects (hepatic, urinary)	Mouse, gavage, 13 wk	U.S. EPA (1988) as cited in U.S. EPA (1990c)

[a]**Bolded** rows show the compound and toxicity value selected as the indicator chemical for the fraction if analytical chemistry data do not identify concentrations of individual chemicals composing this fraction.
[b]The chronic RfD for benzo[*a*]pyrene is based on a developmental exposure.
[c]Body-weight scaling to derive an HED was not performed because doses were administered directly to early postnatal animals (U.S. EPA, 2017).
[d]Toxicity values are provisional values obtained from an existing PPRTV assessment. Values in *italics* are screening provisional values obtained from an existing PPRTV assessment. Screening provisional values are not assigned confidence statements; however, confidence in these values is presumed to be low. Screening provisional values are derived when the available data do not meet the requirements for deriving a provisional toxicity value.

ADJ = adjusted; BMDL = benchmark dose lower confidence limit; $BMDL_{05}$ = 5% benchmark dose lower confidence limit; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; C = carbon; EC = equivalent carbon; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PND = postnatal day; POD = point of departure; PPRTV = Provisional Peer-Reviewed Toxicity Value; p-RfD = provisional reference dose; RBC = red blood cell; RfD = reference dose; SD = standard deviation; 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.

Table 15. Available RfC Values for Aromatic High Carbon Range Fraction (C10−C32 [EC11−EC35])[a]

Indicator Chemical or Components	POD (mg/m^3)	POD Type (all are HECs)	UF_C	UF Components	p-RfC or RfC (mg/m^3)	Confidence in p-RfC or RfC	Critical Effect(s)	Species, Frequency, and Duration	Reference
Subchronic									
1,1-Biphenyl (C12 [EC13.45])	1.23	$BMCL_{10}$[b]	300	UF_A, UF_D, UF_H	*0.004*[c]	Low	Congestion and edema of liver and kidneys (hepatic, urinary)	Mouse, 7 h/d, 5 d/wk for 13 wk	Cannon Laboratories Inc. (1977) as cited in U.S. EPA (2011a)
Benzo[*a*]pyrene[d] (C20 [EC29.95])	**0.0046**	**LOAEL[e]**	**3,000**	**UF_A, UF_D, UF_H, UF_L**	**0.000002**	**Low-medium**	**Decreased embryo/fetal survival (developmental)**	**Rat, 4 h/d on GDs 11−20**	**Archibong et al. (2002) as cited in U.S. EPA (2017)**
Benzo[*e*]pyrene (C20 [EC27.80])	0.0046	LOAEL	3,000	UF_A, UF_H, UF_D, UF_L	*0.000002*[c]	Low	Based on benzo[*a*]pyrene as an analogue; decreased embryo/fetal survival (developmental)	Rat, 4 h/d on GDs 11−20	Archibong et al. (2002) as cited in U.S. EPA (2021b)
Chronic									
Naphthalene (C10 [EC11.57])	9.3	LOAEL	3,000	UF_A, UF_D, UF_H, UF_L	0.003	Medium	Nasal effects: hyperplasia and metaplasia in respiratory and olfactory epithelium, respectively (nervous, respiratory)	Mouse, 6 h/d, 5 d/wk for 2 yr	NTP (1992) as cited in U.S. EPA (1998)
1,1-Biphenyl (C12 [EC13.45])	1.23	$BMCL_{10}$	3,000	UF_A, UF_D, UF_H, UF_S	*0.0004*[c]	Low	Congestion and edema of liver and kidneys (hepatic, urinary)	Mouse, 6 h/d, 7 d/wk for 13 wk	Cannon Laboratories Inc. (1977) as cited in U.S. EPA (2011a)
Benzo[*a*]pyrene (C20 [EC29.95])	**0.0046**	**LOAEL**	**3,000**	**UF_A, UF_D, UF_H, UF_L**	**0.000002**	**Low-medium**	**Decreased embryo/fetal survival (developmental)**	**Rat, 4 h/d on GDs 11−20**	**Archibong et al. (2002) as cited in U.S. EPA (2017)**

Table 15. Available RfC Values for Aromatic High Carbon Range Fraction (C10−C32 [EC11−EC35])[a]

Indicator Chemical or Components	POD (mg/m^3)	POD Type (all are HECs)	UF_C	UF Components	p-RfC or RfC (mg/m^3)	Confidence in p-RfC or RfC	Critical Effect(s)	Species, Frequency, and Duration	Reference
Benzo[*e*]pyrene (C20 [EC27.80])	0.0046	LOAEL	3,000	UF_A, UF_H, UF_D, UF_L	*0.000002*[c]	NA	Based on benzo[*a*]pyrene as an analogue; decreased embryo/fetal survival (developmental)	Rat, 4 h/d on GDs 11−20	Archibong et al. (2002) as cited in U.S. EPA (2021b)

[a]**Bolded** row shows the compound and toxicity value selected as the indicator chemical for the fraction if analytical chemistry data do not identify concentrations of individual chemicals composing this fraction.
[b]U.S. EPA derived the HEC in a PPRTV assessment based on consideration of the critical effect as extrarespiratory (using the RGDR for the extrarespiratory region).
[c]Toxicity values are provisional values obtained from an existing PPRTV assessment. Values in *italics* are screening provisional values obtained from an existing PPRTV assessment. Screening provisional values are not assigned confidence statements; however, confidence in these values is presumed to be low. Screening provisional values are derived when the available data do not meet the requirements for deriving a provisional toxicity value.
[d]Because the chronic RfC for benzo[*a*]pyrene is based on a developmental exposure, it is also applicable to subchronic exposures and is listed here.
[e]U.S. EPA derived the HEC in an IRIS assessment based on consideration of the critical effect as extrarespiratory (using the RGDR for the extrarespiratory region).

$BMCL_{10}$ = 10% benchmark concentration lower confidence limit; C = carbon; EC = equivalent carbon; GD = gestation day; HEC = human equivalent concentration; IRIS = Integrated Risk Information System; LOAEL = lowest-observed-adverse-effect level; NA = not applicable; POD = point of departure; PPRTV = Provisional Peer-Reviewed Toxicity Value; p-RfC = provisional reference concentration; RfC = reference concentration; RGDR = regional gas dose ratio; 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.

Human data and inhalation data for animals are scarce. Animal oral data to assess consistency in effects across members of the fraction are widely available for body-weight effects and moderate for other endpoints. Chronic systemic toxicity information is lacking for all but five members of the fraction: naphthalene and 1,1-biphenyl have been tested in comprehensive 2-year systemic toxicity studies in animals (inhalation and oral, respectively); 1- and 2-methylnaphthalene have been evaluated in comprehensive 81-week oral studies; and BaP was evaluated in a 2-year cancer bioassay with limited reporting of nonneoplastic findings.

Based on review of the available data [see (U.S. EPA, 2022c) for further details], there is evidence to suggest consistency in body-weight changes, neurological effects, hepatic effects, and hematological effects of some aromatic high carbon range fraction members, but not enough to indicate consistency across the entire fraction. Available data indicate that the kidney and bladder are particularly susceptible to 1,1-biphenyl toxicity, with data from other compounds generally showing increased incidence of age-related nephropathy. There is little evidence to indicate respiratory tract effects following oral exposure for compounds other than 1- and 2-methylnaphthalene (for which pulmonary findings are confounded by inhalation exposure via volatilization from feedstock), although there is limited evidence to suggest consistency in respiratory effects following inhalation exposure across compounds with lower carbon numbers (no data for fraction members with higher carbon numbers; C13−35). The available data are not adequate to provide confidence in an assessment of the consistency in effects for GI tract, reproductive toxicity, or developmental toxicity endpoints (including neurodevelopment and reproductive development).

The lowest oral subchronic and chronic RfD among the compounds in this fraction that is not a screening value is the chronic RfD for BaP (see Table 14); this value is recommended for chronic exposures to the aromatic high carbon range fraction if available analytical chemistry data do not identify concentrations of individual chemicals composing this fraction, and an indicator chemical approach is implemented. Although a subchronic toxicity value is not available for BaP, the chronic RfD is based on a developmental exposure, so the RfD value is applicable to subchronic exposures as well, if an indicator approach is implemented. In addition, extensive chronic toxicity information has been reported for BaP and the developmental endpoint is the most sensitive. Subchronic and chronic toxicity values for several other PAHs, except for those of BeP, which is a screening value, are considerably higher (several orders of magnitude in some cases) than the chronic RfD for BaP, raising the question of whether use of BaP as the indicator chemical for the fraction may be toxicologically relevant. However, emerging information on mixtures and other compounds shows effects at exposures comparable to (or even lower than) levels at which BaP induces toxicity, suggesting that use of BaP values for the whole fraction may be more appropriate than implied by comparisons limited to compounds with toxicity values. For example, recent studies suggest that other PAHs in this fraction may induce altered reproductive tract development (Kim et al., 2011), neurodevelopmental effects (Crepeaux et al., 2014; Crepeaux et al., 2013, 2012), transgenerational changes in immune function (Chu et al., 2013) or adiposity (Yan et al., 2014), or lethal transplacental carcinogenesis (Madeen et al., 2016; Benninghoff and Williams, 2013; Shorey et al., 2013; Shorey et al., 2012; Castro et al., 2009; Castro et al., 2008c; Castro et al., 2008a; Castro et al., 2008b) at very low exposure levels. These newer studies support the selection of BaP as the indicator chemical because it is the only indicator chemical candidate with an oral toxicity value that will be toxicologically relevant for most of these effects. However, users of the indicator chemical method should understand that there could be more uncertainty associated with the application of this toxicity value to the

aromatic high carbon range fraction than for its applications in assessments of BaP as an individual chemical in U.S. EPA (2017).

If the available analytical chemistry data quantify the concentrations of naphthalene, 2-methylnapthlalene, 1-methylnapthalene, 1,1-biphenyl, acenaphthene, fluorene, anthracene, pyrene, fluoranthene, or BaP separately from the remainder of the aromatic high carbon range fraction, it is recommended that HQs for the individual chemicals with analytical data be calculated and an HI for the mixture be developed using the calculated HQs.

For subchronic oral exposures, the following subchronic RfDs or p-RfDs can be used as the denominator in the HQ equations: naphthalene (0.6 mg/kg-day), 2-methylnaphthalene (0.004 mg/kg-day), 1,1-biphenyl (0.1 mg/kg-day), acenaphthene (0.2 mg/kg-day), fluorene (0.4 mg/kg-day), anthracene (1 mg/kg-day), pyrene (0.3 mg/kg-day), BeP (9×10^{-5} mg/kg-day), and fluoranthene (0.1 mg/kg-day). Additionally, the chronic RfD for BaP (0.0003 mg/kg-day) can be adopted for subchronic exposures because it is based on a developmental study (as discussed above). In this alternative approach, the chronic RfD for BaP (0.0003 mg/kg-day) is recommended for use with the remainder of the fraction, including any other fraction members analyzed individually.

For chronic oral exposures, the following chronic RfDs or p-RfDs can be used as the denominator in the HQ equations: naphthalene (0.02 mg/kg-day), 2-methylnaphthalene (0.004 mg/kg-day), 1-methylnaphthalene (0.007 mg/kg-day), 1,1-biphenyl (0.5 mg/kg-day), acenaphthene (0.06 mg/kg-day), fluorene (0.04 mg/kg-day), anthracene (0.3 mg/kg-day), pyrene (0.03 mg/kg-day), fluoranthene (0.04 mg/kg-day), BeP (9×10^{-5} mg/kg-day), and BaP (0.0003 mg/kg-day). In this alternative approach, the chronic RfD for BaP (0.0003 mg/kg-day) is recommended for use with the remainder of the fraction, including any other fraction members analyzed individually.

The lowest RfC among the compounds in this fraction is the chronic RfC for BaP (see Table 15)[7]; this value is recommended as the indicator chemical for chronic exposures to the aromatic high carbon range fraction if available analytical chemistry data do not identify concentrations of individual chemicals composing this fraction. Although a subchronic toxicity value is not available for BaP (the IRIS program did not develop subchronic values), the chronic RfC is based on a developmental exposure, so the RfC value is applicable to subchronic exposures as well. In addition, extensive chronic toxicity information has been reported for BaP and the developmental endpoint is the most sensitive. Several subchronic and/or chronic toxicity values for other PAHs are considerably higher (>2 orders of magnitude) than the chronic RfC for BaP, raising the question of whether use of BaP as the indicator chemical for the fraction may be overly conservative. However, emerging information (Crepeaux et al., 2014; Yan et al., 2014; Chu et al., 2013; Crepeaux et al., 2013, 2012) on mixtures shows neurodevelopmental effects at exposures lower than levels at which BaP induces toxicity, suggesting that use of BaP values for the whole fraction may be more appropriate than implied by comparisons limited to compounds with toxicity values.

[7]Both the subchronic and chronic p-RfCs for BeP are the same as those for BaP. The U.S. EPA's BeP p-RfCs were developed using a read-across approach where BaP was the selected analogue.

If the available analytical chemistry data quantify the concentrations of 1,1-biphenyl, naphthalene, BeP or BaP in the air separately from the remainder of the aromatic high carbon range fraction, it is recommended that HQs for the individual chemicals with analytical data be calculated and an HI for the mixture be developed using the calculated HQs.

For subchronic inhalation exposures, the subchronic p-RfCs for 1,1-biphenyl (0.004 mg/m^3) and BeP (2×10^{-6} mg/m^3) and the chronic RfC for BaP (2×10^{-6} mg/m^3) can be used as the denominator in the HQ equations; as discussed above, use of the chronic BaP value is appropriate because it is based on a developmental study. In this alternative approach, the chronic RfC for BaP (2×10^{-6} mg/m^3) is recommended for use with the remainder of the fraction, including any other fraction members analyzed individually.

For chronic inhalation exposures, the following chronic RfCs or p-RfCs can be used in the denominator of the HQ equations: naphthalene (0.003 mg/m^3), 1,1-biphenyl (0.0004 mg/m^3), BeP (2×10^{-6} mg/m^3), and BaP (2×10^{-6} mg/m^3). In this alternative approach, the chronic RfC for BaP (2×10^{-6} mg/m^3) is recommended for use with the remainder of the fraction, including any other fraction members analyzed individually.

Table 16 shows the available cancer risk estimates for components of the fraction. If analytical chemistry data do not identify concentrations of individual chemicals composing this fraction, an indicator chemical approach should be used. In this case, the BaP OSF should be integrated with an estimate of the oral exposure rates for the aromatic high carbon range fraction to estimate the oral cancer risk. The IUR should be estimated with the concentration of the fraction in the air to estimate the inhalation cancer risk. Table 17 shows the available RPF values for seven PAHs, with BaP serving as the IC. If analytical chemistry data identify individual concentrations of any of these seven PAH composing this fraction, an RPF approach should be used. In this case, the BaP OSF and IUR estimates can be integrated with estimates of the individual PAH exposure rates to estimate the oral or inhalation cancer risk associated with exposure to the fraction. If analytical chemistry data identify concentrations of individual of PAHs, subPAHs, and other carcinogenic fraction members with cancer risk values, an integrated addition approach should be used. The integrated addition approach assumes that the carcinogenic MOAs of the PAHs are independent of those of subPAH, 1-methylnaphthalene, and the other carcinogenic fraction member, 1,1-biphenyl. In this case, the RPF approach can be used to estimate cancer risk associated with the PAH portion of the fraction, and p-OSF values for 1-methylnaphthalene and 1,1-biphenyl can be integrated individually with their corresponding exposure rates. Response addition can then be used to sum risks across the three similarity groups (i.e., PAH, 1-methylnaphthalene, and 1,1-biphenyl) to estimate the oral cancer risk associated with exposure to the fraction. Because IURs (or p-IURs) were not identified for either 1-methylnaphthalene or 1,1-biphenyl, the integrated addition approach is only applicable to estimating oral cancer risks at this time.

Table 16. Available Cancer Risk Estimates for Aromatic High Carbon Range Fraction (C10−C32 [EC11−EC35])[a, b]

Toxicity Type (units); Indicator Chemical or Component	Species/Sex	Tumor Type	Cancer Value	Reference
OSF or p-OSF (mg/kg-d)$^{-1}$				
1-Methylnaphthalene (C11 [EC12.77])	Mouse/M	Lung adenomas or carcinomas	2.9×10^{-2} [c]	Murata et al. (1997) as cited in U.S. EPA (2008)
1,1-Biphenyl (C12 [EC13.45])	Mouse/F	Liver	8×10^{-3}	Umeda et al. (2005) as cited in U.S. EPA (2013b)
Benzo[*a*]pyrene (C20 [EC29.95])	**Rat/M, F; mouse/F**	**Forestomach, esophagus, tongue, and larynx tumors**	**1**	**Kroese et al. (2001), Beland and Culp (1998) as cited in U.S. EPA (2017)**
IUR (mg/m^3)$^{-1}$				
Benzo[*a*]pyrene (C20 [EC29.95])	**Hamster/M**	**Squamous cell neoplasia in the larynx, pharynx, trachea, nasal cavity, esophagus, and forestomach**	**6×10^{-1}**	**Thyssen et al. (1981) as cited in U.S. EPA (2017)**

[a]In the 2007 PPRTV assessment, a screening p-OSF of 0.7 (mg/kg-day)$^{-1}$ was derived for benz[*a*]anthracene using the RPF and OSF for benzo[*a*]pyrene at the time. Both the RPF for benz[*a*]anthracene (see Table 17) and the OSF for benzo[*a*]pyrene have since been updated, so this value is no longer relevant and is not presented herein.
[b]**Bolded** rows show the compound and toxicity values selected as the indicator chemical for the fraction if analytical chemistry data do not identify concentrations of individual chemicals composing this fraction.
[c]Toxicity value is a provisional value obtained from an existing PPRTV assessment.

C = carbon; EC = equivalent carbon; F = female; IUR = inhalation unit risk; M = male; NDr = not determined; OSF = oral slope factor; PPRTV = Provisional Peer-Reviewed Toxicity Value; p-OSF = provisional oral slope factor.

Table 17. RPFs in the U.S. EPA's 1993 Provisional Guidance

PAH (abbreviation)	RPF	Source(s)
Benzo[*a*]pyrene (BaP)	1	NA
Benz[*a*]anthracene (BaAC)	0.1	Bingham and Falk (1969)
Benz[*e*]acephenanthrylene (BeAPE)[a]	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]Formerly benzo[*b*]fluoranthene.

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

4. IMPLEMENTATION OF THE APPROACH

To estimate health risk or hazard for the entire hydrocarbon mixture, the estimates for all six of the aromatic and aliphatic fractions are summed using an appropriate additivity method, following relevant U.S. EPA guidance for risk assessment of mixtures (U.S. EPA, 2000, 1989, 1986). U.S. EPA (2000) recommends use of dose-addition methods for characterization of potential risk from exposure to a mixture of chemicals that are toxicologically similar.[8] Dose-addition methods are commonly used in noncancer risk assessment using the HI approach, and in cancer risk assessment using RPFs or toxic equivalency factors. Response-addition is recommended for mixture components that act on different systems or produce effects that do not influence each other, and, thus, can be assumed to act independently. Response-addition methods are commonly used in cancer risk assessment, wherein risks are estimated for individual compounds using corresponding dose-response curves and summed to yield an estimate of risk for the mixture.

Sections 4.1 and 4.2 briefly describe the methods for noncancer hazard assessment and cancer risk assessment, respectively, using the fraction approach for petroleum hydrocarbon mixtures.

4.1. FRACTION-BASED NONCANCER RISK ASSESSMENT

Noncancer health hazard assessment for the entire hydrocarbon mixture using the fraction approach is performed at a screening level using the HI approach. The quantitative exposure information for these individual chemicals or fractions is based on analytical data from the hazardous waste sites. Figure 4−Figure 7 provide graphic illustrations of how noncancer risk assessments are carried out using the toxicity values for the total petroleum hydrocarbon fractions under two scenarios: Option 1 (see Figures 4 and 5), where environmental media have been analyzed for the total fraction concentration only; and Option 2 (see Figures 6 and 7), where environmental media have been analyzed for the total fraction concentration as well as individual fraction components. For the sake of completeness, Figure 4−Figure 7 show summation across all six fractions, but, depending on the source of the mixture and weathering and transport, exposure may not include all fractions.

[8]U.S. EPA (2000) defines “similar components” as single chemicals that cause the same biologic activity or are expected to cause a type of biologic activity based on chemical structure. Evidence of similarity may include similarly shaped dose-response curves, or parallel log dose-probit-response curves for quantal data on the number of animals (people) responding, and the same mechanism of action or toxic endpoint. These components may also be expected to have comparable characteristics for fate, transport, physiologic processes, and toxicity.

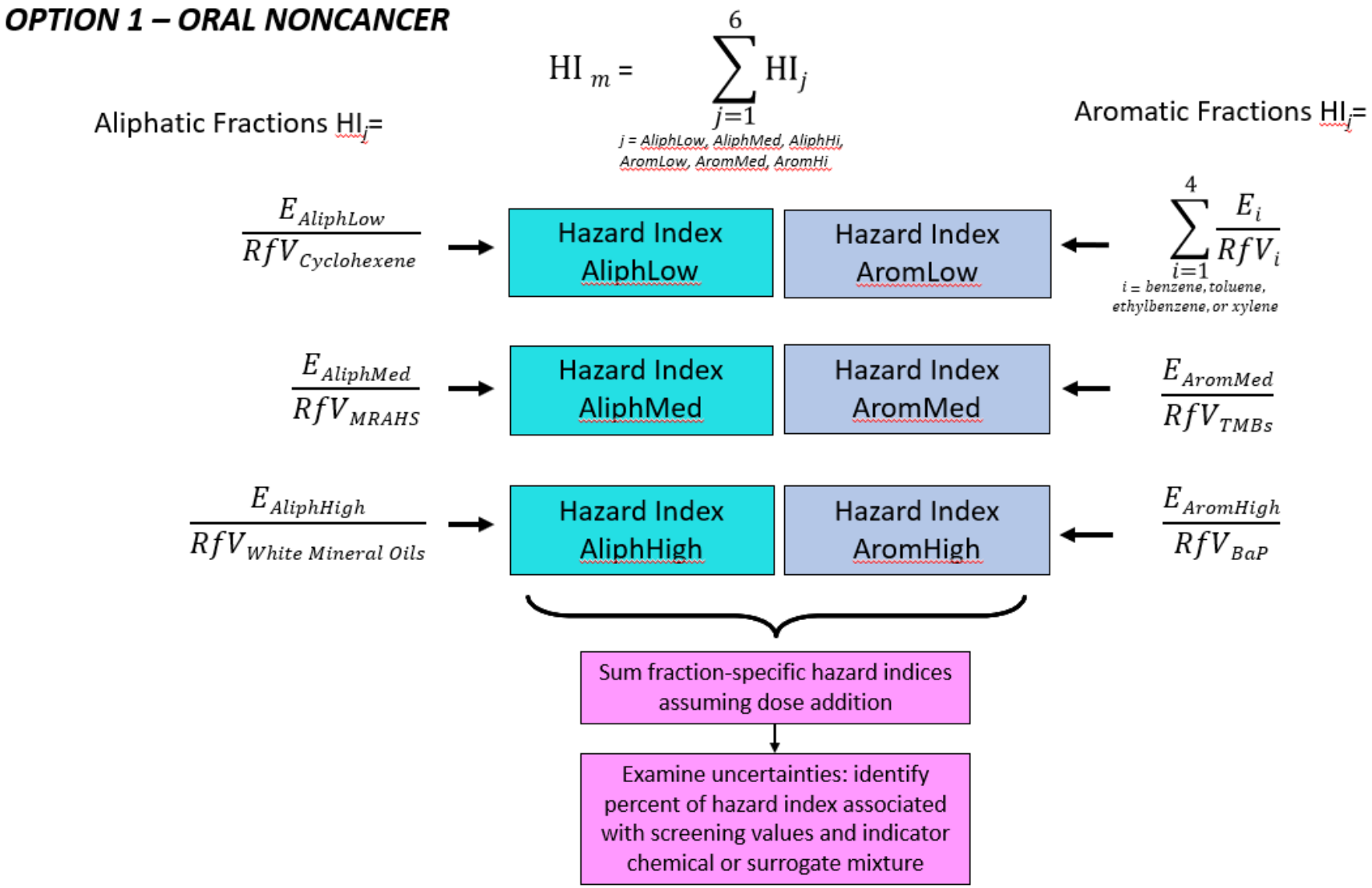


Figure 4. Fraction-Based Oral Noncancer Risk Assessment for Complex Mixtures of Aliphatic and Aromatic Hydrocarbons: Option 1

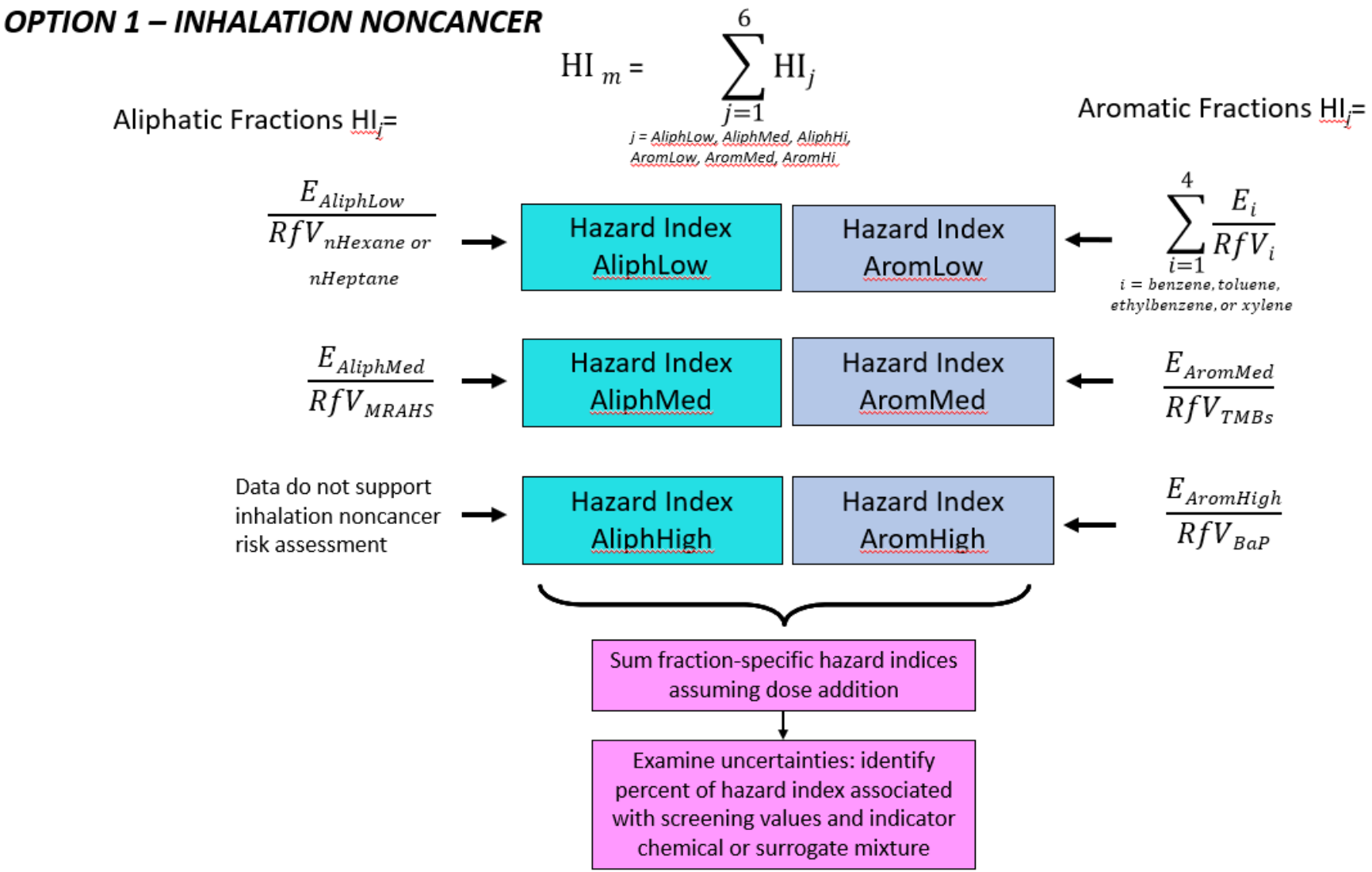


Figure 5. Fraction-Based Inhalation Noncancer Risk Assessment for Complex Mixtures of Aliphatic and Aromatic Hydrocarbons: Option 1

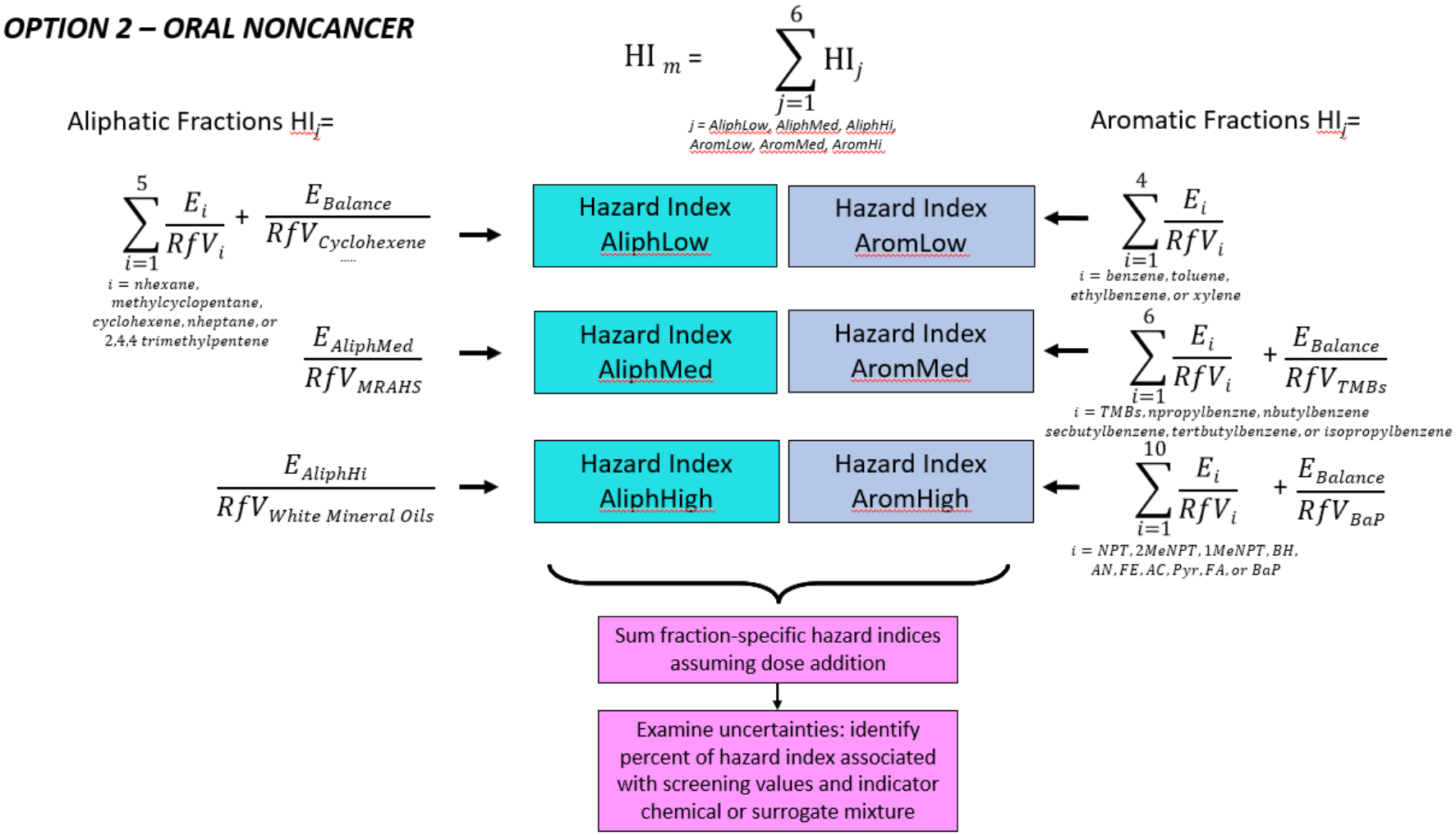


Figure 6. Fraction-Based Oral Noncancer Risk Assessment for Complex Mixtures of Aliphatic and Aromatic Hydrocarbons: Option 2

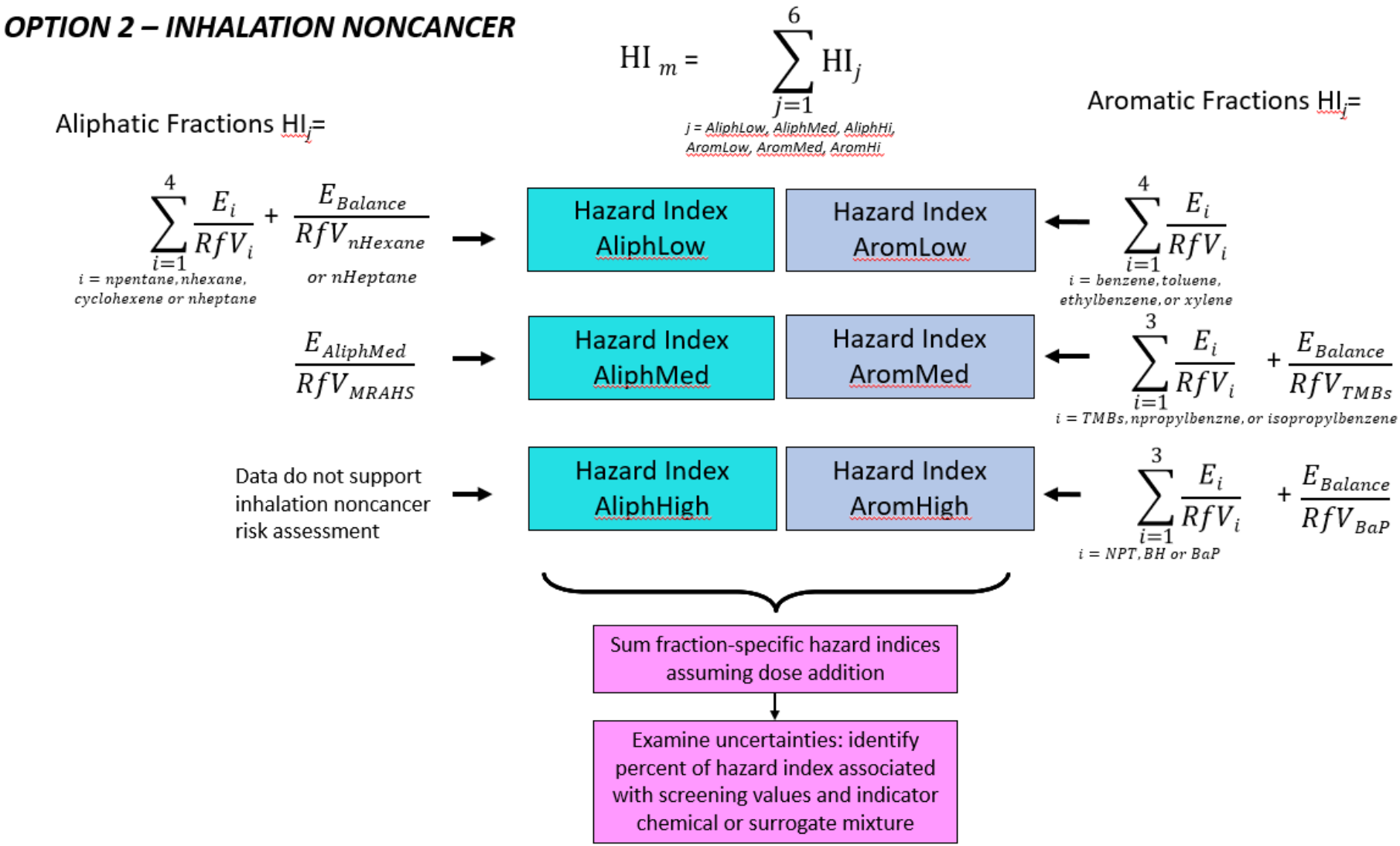


Figure 7. Fraction-Based Inhalation Noncancer Risk Assessment for Complex Mixtures of Aliphatic and Aromatic Hydrocarbons: Option 2

where:

HI_m	=	Screening Hazard Index for the whole mixture
HI_j	=	Hazard Index calculated for the *j*th fraction (*j* = AliphLow [aliphatic low], AliphMed [aliphatic medium], AliphHi [Aliphatic High], AromLow [aromatic low], AromMed [Aromatic Medium], and AromHi [aromatic high])
E_j	=	Daily oral dose (mg/kg-day) or inhalation exposure concentration (mg/m^3) for the *j*th fraction
E_i	=	Daily oral dose (mg/kg-day) or inhalation exposure concentration (mg/m^3) for the *i*th component
$E_{Balance}$	=	Daily oral dose (mg/kg-day) or inhalation exposure concentration (mg/m^3) for portion of fraction not evaluated as individual components
RfV	=	Reference value: reference dose (RfD, mg/kg-day) or reference concentration (RfC, mg/m^3) for indicator chemical or surrogate mixture
MRAHS	=	Mid-range aliphatic hydrocarbon streams

The steps involved in noncancer risk assessment of the hydrocarbon mixture using Option 1 are as follows:

Oral

1) Aliphatic low, medium, and high carbon range fractions and aromatic medium and high carbon range fractions:
   a. Combine exposure estimate (mg/kg-day) for the fraction with the appropriate duration (subchronic or chronic) RfD from Table 18 to estimate HI for each fraction.
2) Aromatic low carbon range fraction:
   a. Combine individual exposure estimates for components with their corresponding toxicity values in Table 18 to calculate HIs for each component; sum HIs across the components.
3) Sum HIs across all fractions assessed at the site.

Inhalation

1) Aliphatic low and medium carbon range fractions and aromatic medium and high carbon range fractions:
   a. Combine exposure estimate (mg/m^3) for the fraction with the appropriate duration (subchronic or chronic) RfC from Table 18 to estimate HI for each fraction.
2) Aromatic low carbon range fraction:
   a. Combine individual exposure estimates for components with their corresponding toxicity values in Table 18 to calculate HIs for each component; sum HIs across the components.
3) Sum HIs across all fractions assessed at the site. Note: data do not support inhalation noncancer assessment for the aliphatic high carbon range fraction.

Table 18. Fraction-Specific Noncancer Toxicity Values for Option 1: Exposure Media Analyzed for BTEX and Fractions

Secondary Fraction	Assessment Method	Subchronic RfD or p-RfD (mg/kg-d)[a]	Chronic RfD or p-RfD (mg/kg-d)[a]	Subchronic RfC or p-RfC (mg/m^3)	Chronic RfC or p-RfC (mg/m^3)
Aliphatic					
Low carbon range (C5−C8 [EC5−EC8])[b]	Indicator chemical	0.05 (cyclohexene)	0.005 (cyclohexene)	2 (*n*-hexane)	0.4 (*n*-heptane)
Medium carbon range (C9−C18 [EC > 8−EC16])	Surrogate mixture	*0.1 (mid-range aliphatic hydrocarbon streams)*	*0.01 (mid-range aliphatic hydrocarbon streams)*	0.1 (mid-range aliphatic hydrocarbon streams)	0.1 (mid-range aliphatic hydrocarbon streams)
High carbon range (C19−C32 [EC > 16−EC35])	Surrogate mixture	30 (white mineral oil)	3 (white mineral oil)	NA	NA
Aromatic					
Low carbon range (C6−C8 [EC6−EC < 9])	Hazard Index	Benzene: 0.01 Toluene: 0.8 Ethylbenzene: 0.05[c] Xylenes: 0.4	Benzene: 0.004 Toluene: 0.08 Ethylbenzene: 0.1[c] Xylenes: 0.2	Benzene: 0.08 Toluene: 5 Ethylbenzene: 9 Xylenes: 0.4	Benzene: 0.03 Toluene: 5 Ethylbenzene: 1 Xylenes: 0.1
Medium carbon range (C9−C10 [EC9−EC < 11])[b]	Indicator chemical	0.04 (trimethylbenzenes)	0.01 (trimethylbenzenes)	0.2 (trimethylbenzenes)	0.06 (trimethylbenzenes)
High carbon range (C10−C32 [EC11−EC35])[b]	Indicator chemical	0.0003 (benzo[*a*]pyrene)	0.0003 (benzo[*a*]pyrene)	0.000002 (benzo[*a*]pyrene)	0.000002 (benzo[*a*]pyrene)

[a]Risk estimates in *italics* are PPRTV screening values. Screening values are not assigned confidence statements; however, confidence in these values is presumed to be low. Screening values are derived when the data do not meet all requirements for deriving a provisional toxicity value. Screening values are derived using the same methodologies and undergo the same development and review processes (i.e., internal and external peer review, etc.) as provisional values; however, there is generally more uncertainty associated with these values.

[b]Risk estimates(s) updated in 2022 as part of this TPH approach (U.S. EPA, 2022a, c, d).

[c]The subchronic p-RfD for ethylbenzene is lower than the chronic value because it was derived using data that were not available when the IRIS RfD was derived.

BTEX = benzene, toluene, ethylbenzene, and xylenes; C = carbon; EC = equivalent carbon; IRIS = Integrated Risk Information System; NA = not applicable; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; RfC = reference concentration; RfD = reference dose.

The steps involved in noncancer risk assessment of the hydrocarbon mixture using Option 2 are as follows:

Oral

1) Aliphatic medium and high carbon range fractions:
   a. Combine exposure estimate (mg/kg-day) for the fraction with the appropriate duration (subchronic or chronic) RfD from Table 19 to estimate HI for each fraction.
2) Aromatic low carbon range fraction:
   a. Combine individual exposure estimates for components with their corresponding toxicity values in Table 19 to calculate HIs for each component; sum HIs across the components.
3) Aliphatic low and aromatic medium and high carbon range fractions:
   a. Combine individual exposure estimates for components with their corresponding toxicity values in Table 19 to calculate component-specific HIs.
   b. Subtract doses or concentrations (mg/kg-day) of all components assessed individually (by route and exposure duration) from the estimated dose or concentration of the total fraction to estimate the exposure concentration for the balance of the fraction.
   c. Combine the exposure estimate (mg/kg-day) for the balance of the fraction with the appropriate duration (subchronic or chronic) RfD for the surrogate shown in Table 19.
   d. Sum the HIs for the components with the HI calculated for the remaining fraction mass to estimate the HI for the fraction.
4) Sum HIs across all fractions assessed at the site.

Inhalation

1) Aliphatic medium range fraction:
   a. Combine exposure estimate (mg/m^3) for the fraction with the appropriate duration (subchronic or chronic) RfC from Table 19 to estimate HI for each fraction.
2) Aromatic low carbon range fraction:
   a. Combine individual exposure estimates for components with their corresponding toxicity values in Table 19 to calculate HIs for each component; sum HIs across the components.
3) Aliphatic low and aromatic medium and high carbon range fractions:
   a. Combine individual exposure estimates for components with their corresponding toxicity values in Table 19 to calculate component-specific HIs.
   b. Subtract doses or concentrations (mg/m^3) of all components assessed individually (by route and exposure duration) from the estimated dose or concentration of the total fraction to estimate the exposure concentration for the balance of the fraction.
   c. Combine the exposure estimate (mg/m^3) for the balance of the fraction with the appropriate duration (subchronic or chronic) RfC for the surrogate shown in Table 19.
   d. Sum the HIs for the components with the HI calculated for the remaining fraction mass to estimate the HI for the fraction.
4) Sum HIs across all fractions assessed at the site. Note: data do not support inhalation noncancer assessment for the aliphatic high carbon range fraction.

Table 19. Fraction-Specific Noncancer Toxicity Values for Option 2: Analytical Data Available for Individual Components and Fractions

Fraction and Carbon Range	Assessment Method	Subchronic RfD or p-RfD (mg/kg-d)[a]	Chronic RfD or p-RfD (mg/kg-d)[a]	Subchronic RfC or p-RfC (mg/m^3)[a]	Chronic RfC or p-RfC (mg/m^3)[a]
Aliphatic					
Low (C5−C8 [EC5−EC8])[b]	Hybrid	Components: Cyclohexene: 0.05 *n-Heptane: 0.003* *n*-Hexane: 0.3 Methylcyclopentane: 0.4 *2,4,4-Trimethylpentene: 0.1* Surrogate for balance of fraction:[c] 0.05 (cyclohexene)	Components: Cyclohexene: 0.005 *n-Heptane: 0.0003* *2,4,4-Trimethylpentene: 0.01* Surrogate for balance of fraction:[c] 0.05 (cyclohexene)	Components: Cyclohexane: 18 *n*-Heptane: 4 *n*-Hexane: 2 *n*-Pentane: 10 Surrogate for balance of fraction:[c] 2 (*n*-hexane)	Components: Cyclohexane: 6 *Cyclohexene: 1* *n*-Heptane: 0.4 *n*-Hexane: 0.7 *n*-Pentane: 1 Surrogate for balance of fraction:[c] 0.4 (*n*-heptane)
Medium (C9−C18 [EC > 8−EC16])	Surrogate mixture	*0.1* *(mid-range aliphatic hydrocarbon streams)*	*0.01* *(mid-range aliphatic hydrocarbon streams)*	0.1 (mid-range aliphatic hydrocarbon streams)	0.1 (mid-range aliphatic hydrocarbon streams)
High (C19−C32 [EC > 16−EC35])	Surrogate mixture	30 (white mineral oil)	3 (white mineral oil)	NA	NA
Aromatic					
Low (C6−C8 [EC6−EC < 9])	Hazard Index	Benzene: 0.01 Toluene: 0.8 Ethylbenzene: 0.05 Xylenes: 0.4	Benzene: 0.004 Toluene: 0.08 Ethylbenzene: 0.1 Xylenes: 0.2	Benzene: 0.08 Toluene: 5 Ethylbenzene: 9 Xylenes: 0.4	Benzene: 0.03 Toluene: 5 Ethylbenzene: 1 Xylenes: 0.1
Medium (C9−C10 [EC9−EC < 11])[b]	Hybrid	Components *n-Propylbenzene: 0.1* *tert-Butylbenzene: 0.1* *sec-Butylbenzene: 0.1* *n*-Butylbenzene: 0.1 Trimethylbenzenes: 0.04 Surrogate for balance of fraction:[c] 0.04 (trimethylbenzenes)	Components Isopropylbenzene: 0.1 *n-Propylbenzene: 0.1* *tert-Butylbenzene: 0.1* *sec-Butylbenzene: 0.1* *n*-Butylbenzene: 0.05 Trimethylbenzenes: 0.01 Surrogate for balance of fraction:[c] 0.01 (trimethylbenzenes)	Components: *n-Propylbenzene: 1* Trimethylbenzenes: 0.2 Surrogate for balance of fraction:[c] 0.2 (trimethylbenzenes)	Components: Isopropylbenzene: 0.4 *n-Propylbenzene: 1* Trimethylbenzenes: 0.06 Surrogate for balance of fraction:[c] 0.06 (trimethylbenzenes)

Table 19. Fraction-Specific Noncancer Toxicity Values for Option 2: Analytical Data Available for Individual Components and Fractions

Fraction and Carbon Range	Assessment Method	Subchronic RfD or p-RfD (mg/kg-d)[a]	Chronic RfD or p-RfD (mg/kg-d)[a]	Subchronic RfC or p-RfC (mg/m^3)[a]	Chronic RfC or p-RfC (mg/m^3)[a]
High (C10−C32 [EC11−EC35])[b]	Hybrid	Components: Acenaphthene: 0.2 Anthracene: 1 Benzo[*a*]pyrene: 0.0003 1,1-Biphenyl: 0.1 Fluoranthene: 0.1 Fluorene: 0.4 2-Methylnaphthalene: 0.004 Naphthalene: 0.6 Pyrene: 0.3 Surrogate for balance of fraction:[c] 0.0003 (benzo[*a*]pyrene)	Components: Acenaphthene: 0.06 Anthracene: 0.3 Benzo[*a*]pyrene: 0.0003 1,1-Biphenyl: 0.5 Fluoranthene: 0.04 Fluorene: 0.04 *1-Methylnaphthalene: 0.007* 2-Methylnaphthalene: 0.004 Naphthalene: 0.02 Pyrene: 0.03 Surrogate for balance of fraction:[c] 0.0003 (benzo[*a*]pyrene)	Components: *1,1-Biphenyl: 0.004* Benzo[*a*]pyrene: 0.000002; Benzo[*e*]pyrene: 0.000002 Surrogate for balance of fraction:[c] 0.000002 (benzo[*a*]pyrene)	Components: *1,1-Biphenyl: 0.0004* Benzo[*a*]pyrene: 0.000002; Benzo[*e*]pyrene: 0.000002; Naphthalene: 0.003 Surrogate for balance of fraction:[c] 0.000002 (benzo[*a*]pyrene)

[a]Toxicity values in *italics* are PPRTV screening values. Screening values are not assigned confidence statements; however, confidence in these values is presumed to be low. Screening values are derived when the data do not meet all requirements for deriving a provisional toxicity value. Screening values are derived using the same methodologies and undergo the same development and review processes (i.e., internal and external peer review, etc.) as provisional values; however, there is generally more uncertainty associated with these values.
[b]Fraction toxicity value(s) updated in 2022 (U.S. EPA, 2022a, c, d).
[c]Balance of fraction in any given exposure medium equals the total fraction mass concentration minus the sum of the mass concentrations of the individual components listed.

C = carbon; EC = equivalent carbon; NA = not applicable; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; RfC = reference concentration; RfD = reference dose.

There may be circumstances in which a combination of Options 1 and 2 are used. For example, if there are analytical data for individual components of the aromatic medium carbon range fraction, but not the aromatic high carbon range fraction, Option 2 would be used for the medium fraction, while Option 1 would be used for the high fraction.

4.2. FRACTION-BASED CANCER RISK ASSESSMENT

Cancer health risk assessment for the entire hydrocarbon mixture using the fraction approach is performed using a combination of dose- and response-addition methods. Dose-addition methods are used in application of the RPFs to cancer risk assessment of PAHs that lack cancer risk values. Response addition is used for the components with corresponding OSFs or IURs. Figures 8 and 9 provide graphic illustrations of how oral and inhalation cancer risk assessments are carried out using the toxicity values for petroleum fractions. For the sake of completeness, Figures 8 and 9 show summation of all fractions, but exposure at some sites may be limited to fewer fractions. Figure 10 details three options for estimating oral cancer risk for exposure to the aromatic high carbon range fraction.

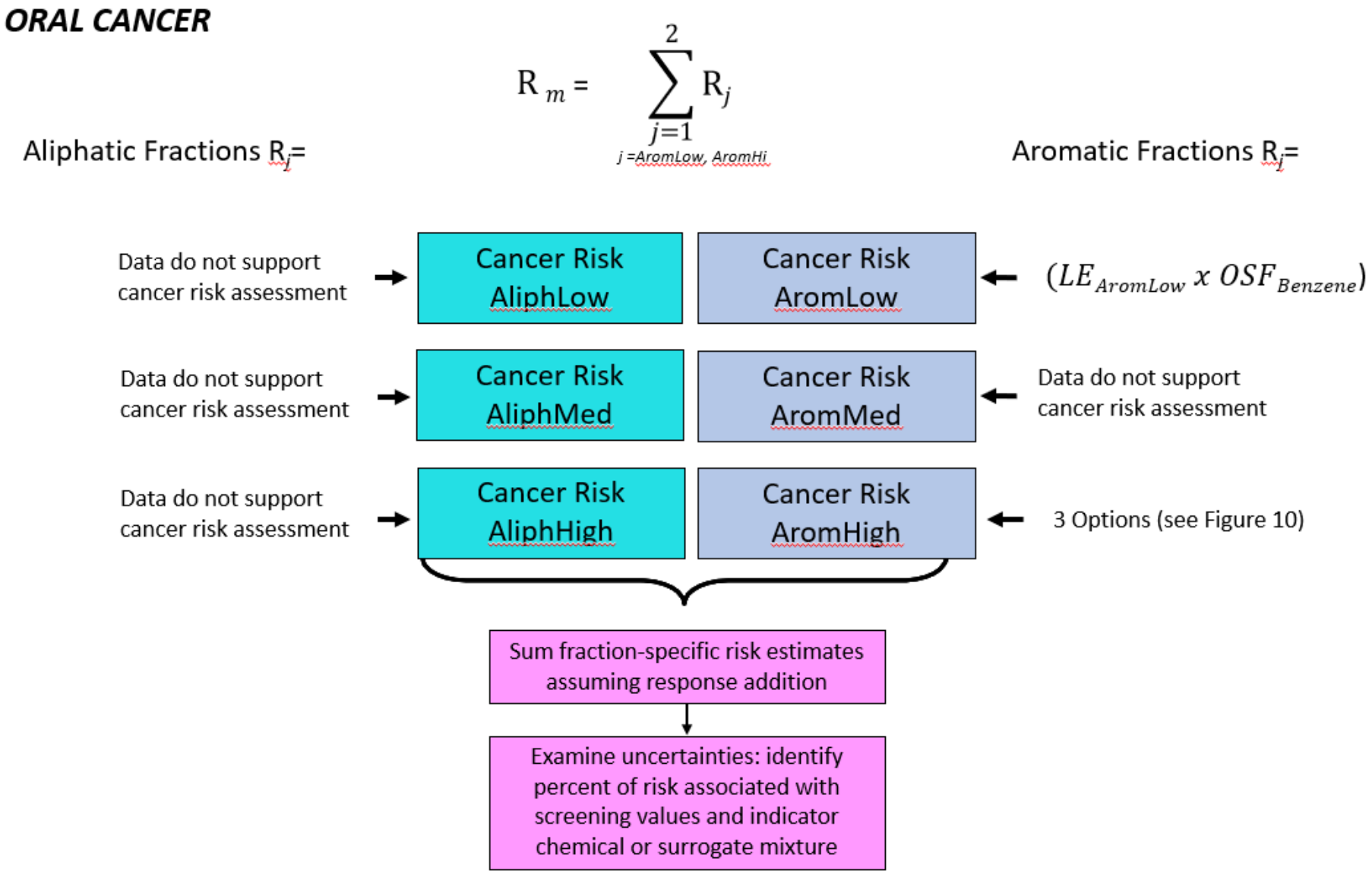


Figure 8. Fraction-Based Oral Cancer Risk Assessment for Complex Mixtures of Aliphatic and Aromatic Hydrocarbons

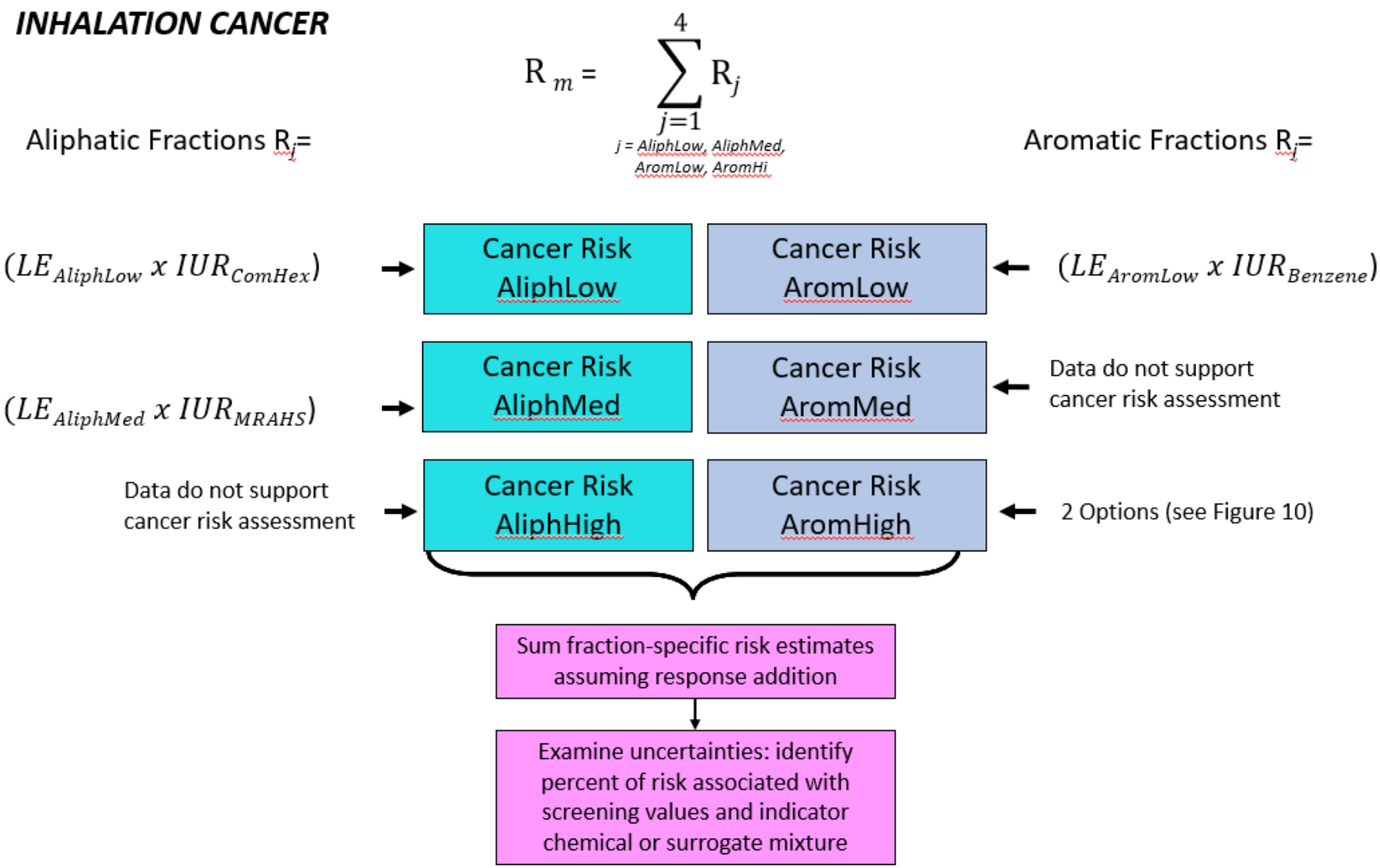


Figure 9. Fraction-Based Inhalation Cancer Risk Assessment for Complex Mixtures of Aliphatic and Aromatic Hydrocarbons

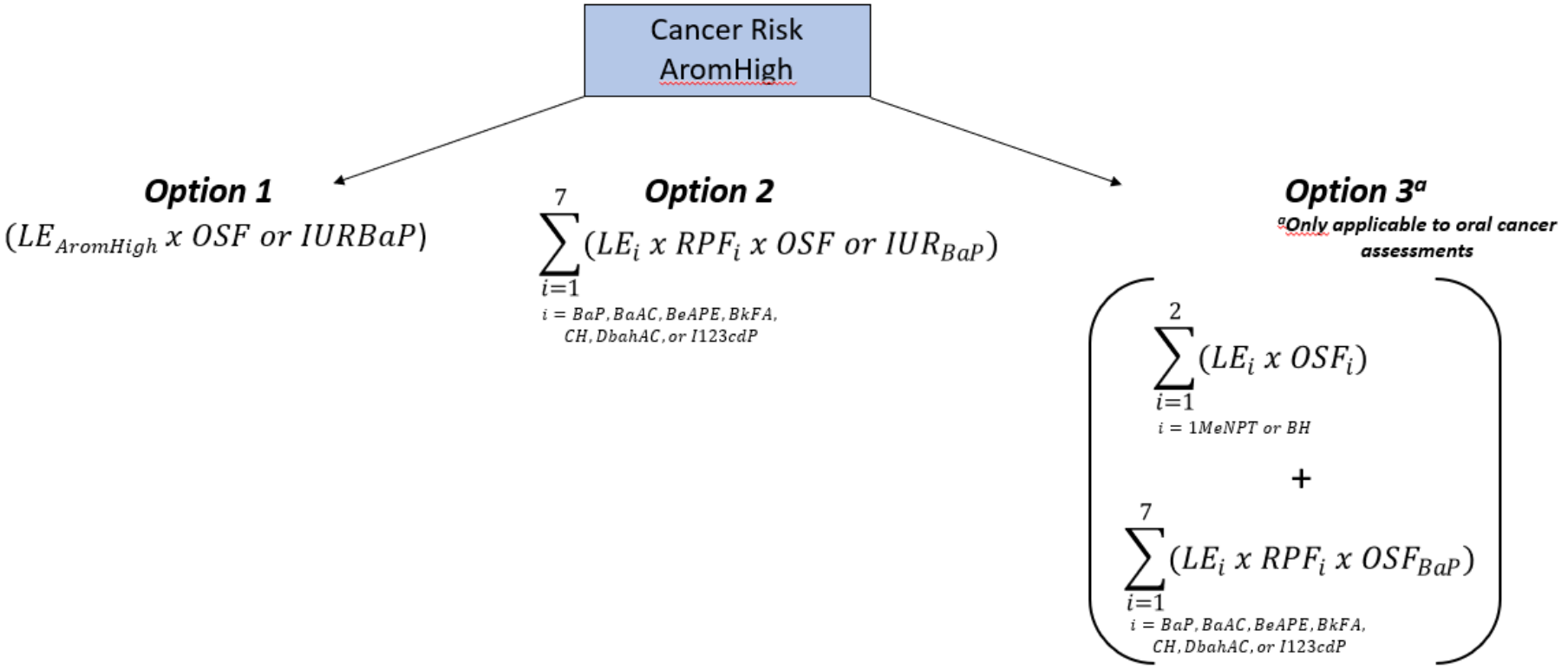


Figure 10. Options for Oral Cancer Risk Assessment for the Aromatic High Carbon Range Fraction

where:

Rm	=	Risk associated with the mixture
R_j	=	Risk associated with the *j*th fraction (*j* = AliphLow [aliphatic low], AliphMed [aliphatic medium], AromLow [aromatic low], AromHi [aromatic high])
LE_j	=	Lifetime oral dose (mg/kg-day) or inhalation exposure concentration (mg/m^3) for the *j*th fraction
LE_i	=	Lifetime oral dose (mg/kg-day) or inhalation exposure concentration (mg/m^3) for the *i*th component
OSF_i	=	Cancer oral slope factor (OSF $[mg/kg\text{-}day]^{-1}$) for indicator chemical or surrogate mixture
IUR_i	=	Inhalation unit risk (IUR $[mg/m^3]^{-1}$) for indicator chemical or surrogate mixture
Comhex	=	Commercial hexane
MRAHS	=	Mid-range aliphatic hydrocarbon streams
RPF_i	=	Relative potency factor for the *i*th PAH

The steps involved in cancer risk assessment of the hydrocarbon mixture are shown below for oral and inhalation exposures.

Oral:

1) Aliphatic low, medium, and high carbon range fractions and aromatic medium carbon range fraction:
   a. Data do not currently support direct cancer assessment.
2) Aromatic low carbon range fraction:
   a. Combine individual lifetime oral exposure estimate (mg/kg-day) for aromatic low carbon range fraction with the OSF for benzene in Table 20 to estimate risk for the fraction.
3) Aromatic high carbon range fraction:

Option 1:

a. Combine oral exposure estimate (mg/kg-day) for fraction with the OSF for benzo[*a*]pyrene in Table 20 to estimate risk for the fraction.

Option 2:

a. For PAHs with RPFs, multiply each individual exposure estimate by its corresponding RPFs from Table 21 and the OSF for benzo[*a*]pyrene to estimate risks.
b. Sum risks across the PAHs.

Option 3:

a. Combine individual exposure estimates (mg/kg-day) for components with OSFs in Table 20 to estimate risks.
b. For PAHs[9] with RPFs, multiply each individual exposure estimate by its corresponding RPF from Table 21 and the OSF for benzo[*a*]pyrene to estimate risks.
c. Sum risks across the PAHs, subPAH, and other carcinogenic fraction member with OSFs.

4) Sum risks across aromatic low and high carbon range fractions (if assessed at the site).

Inhalation:

1) Aliphatic low and medium carbon range fractions:
   a. Combine inhalation exposure estimate (mg/m^3) for each fraction with its corresponding IUR from Table 20 to estimate risk for each fraction.
2) Aromatic low carbon range fraction:
   a. Combine individual exposure estimate (mg/m^3) for the aromatic low carbon range fraction with the IUR for benzene in Table 20 to estimate risk for the fraction.

[9]Recall that, in this document, 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 PAH excludes their alkyl substituted derivatives.

3) Aromatic high carbon range fraction:

Option 1:

a. Combine inhalation exposure estimate (mg/m^3) for fraction with the IUR for benzo[*a*]pyrene in Table 20 to estimate risk for the fraction.

Option 2:

a. For PAHs with RPFs, multiply each individual exposure estimate by its corresponding RPFs from Table 21 and the IUR for benzo[*a*]pyrene to estimate risks.
b. Sum risks across the PAHs.

5) Sum risks across all fractions assessed at the site.

Table 20. Fraction-Specific Cancer Toxicity Values

Fraction and Carbon Range	Assessment Method	OSF $(mg/kg\text{-}d)^{-1}$ [a]	IUR $(mg/m^3)^{-1}$ [a]
Aliphatic			
Low (C5−C8 [EC5−EC8])[b]	Surrogate mixture	NA; data do not support cancer risk assessment	*2.0×10^{-4}* (*commercial hexane*)
Medium (C9−C18 [EC > 8−EC16])	Surrogate mixture	NA; data do not support cancer risk assessment	*4.5×10^{-3}* (*mid-range aliphatic hydrocarbon streams*)
High (C19−C32 [EC > 16−EC35])	NA; data do not support cancer risk assessment		
Aromatic			
Low (C6−C8 [EC6−EC < 9])	Indicator chemical	Benzene: 1.5×10^{-2}–5.5×10^{-2}	Benzene: 2.2×10^{-3}–7.8×10^{-3}
Medium (C9−C10 [EC9−EC < 11])[b]	NA; data do not support cancer risk assessment		
High (C10−C32 [EC11−EC35])[b]	Indicator Chemical (Option 1); Relative Potency Factor (Option 2); Integrated Addition (Option 3)	1,1-Biphenyl: 8×10^{-3} *1-Methylnaphthalene: 2.9×10^{-2}* Benzo[*a*]pyrene: 1 See relative potency values in Table 20	Benzo[*a*]pyrene: 6×10^{-1}

[a]Toxicity values in *italics* PPRTV are screening values. Screening values are not assigned confidence statements; however, confidence in these values is presumed to be low. Screening values are derived when the data do not meet all requirements for deriving a provisional toxicity value. Screening values are derived using the same methodologies and undergo the same development and review processes (i.e., internal and external peer review, etc.) as provisional values; however, there is generally more uncertainty associated with these values.
[b]Toxicity value(s) updated in 2022 (U.S. EPA, 2022a, b, d).

C = carbon; EC = equivalent carbon; IUR = inhalation unit risk; NA = not applicable; OSF = oral slope factor; PAH = polycyclic aromatic hydrocarbon; RPF = relative potency factor.

Table 21. RPFs for PAH Carcinogenicity		
PAH (abbreviation)	**RPF**	**Data Source(s) for RPF Values**
Benzo[*a*]pyrene (BaP)	1	
Benz[*a*]anthracene (BaAC)	0.1	Bingham and Falk (1969)
Benz[*e*]acephenanthrylene (BeAPE)[a]	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]Formerly benzo[*b*]fluoranthene.

PAH = polycyclic aromatic hydrocarbon; RPF = relative potency factor.

4.3. UNCERTAINTY ASSESSMENT

Mixture risk assessment with dose- or response-addition is a default approach that is used to evaluate potential health risks when whole mixture toxicity data are not available. Application of the petroleum fraction method, using both dose- and response-addition approaches, involves assumptions that may be difficult to substantiate for complex mixtures of petroleum contaminants, including:

1) The surrogate mixture or component(s) represents the toxicity of the entire fraction.
2) Synergistic or potentiating toxicological interactions among chemicals are less likely to happen at low environmental contamination levels.
3) Compounds act through independent modes of toxic action when compounds are evaluated using response addition, OR there is a common mode of toxic action for compounds evaluated using dose-addition.

Whenever possible, these assumptions should be evaluated and verified as part of the risk assessment process, and the results should be articulated as part of the final risk characterization. This PPRTV assessment, and the companion documents on individual compounds, mixtures, or fractions, can provide information pertaining to the first assumption. The second assumption can be evaluated through literature review. If two or more chemicals at a site are detected at high exposure concentrations, the toxicology literature should be consulted for information on toxicological interactions among these chemicals. If interactions are demonstrated, especially if synergism or potentiation is shown, this information should be described in the risk characterization along with the quantitative risk or hazard estimates. The assumptions regarding modes of toxic action may be informed by review of the toxicity assessments (IRIS toxicological reviews, PPRTV assessment documents, or ATSDR toxicological profiles) for the most important contaminants. For further guidance, details, and discussion, see U.S. EPA (2000) and the other references cited above.

An important source of uncertainty is the use of an indicator compound or surrogate mixture to represent the toxicity of an untested mixture or portion of a mixture. Therefore, the U.S. EPA suggests that risk assessors characterize the percentage of the estimated risk or of the HI that is calculated using an indicator chemical or surrogate mixture approach. To that end, the U.S. EPA suggests that when a hybrid approach (as described above) is used, risk assessors estimate the risk associated with the measured amount of the surrogate compound (e.g., TMBs for the aromatic medium carbon range or BaP for the aromatic high carbon range) separately from the balance of the fraction, as a means of explicitly characterizing the more uncertain portion associated with the balance of the fraction. For example, when a hybrid approach is used for the chronic inhalation toxicity of the aromatic medium carbon range fraction, risks or HIs would be calculated separately for isopropylbenzene, *n*-propylbenzene, and TMBs, before using the toxicity value of TMBs to estimate the risk or HI associated with the balance of the fraction.

The quality of the underlying toxicity data used to develop either a provisional or screening RfD, a provisional or screening RfC, or a provisional or screening OSF or IUR is an additional source of uncertainty. To convey the difference in quality in the mixture risk assessment, the U.S. EPA suggests that risk assessors identify the percentage of the estimated risk or of the HI that is associated with screening toxicity estimates (i.e., screening OSFs, screening p-RfDs, or screening p-RfCs) and the percentage based on provisional estimates (i.e., p-OSFs, p-IURs, or p-RfDs). Such examinations of mixture risk estimates are consistent with mixture risk assessment practices (Rice et al., 2005; U.S. EPA, 2000).

APPENDIX A. CHEMICAL SYNONYMS AND ABBREVIATIONS

Table A-1. Chemical Synonyms and Abbreviations

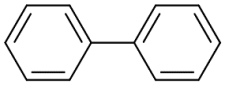
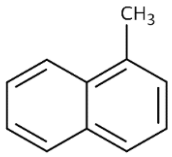
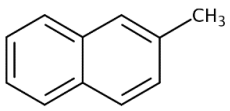
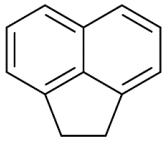
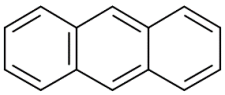
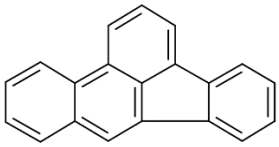
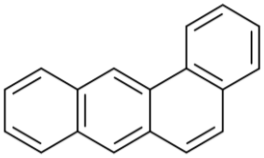
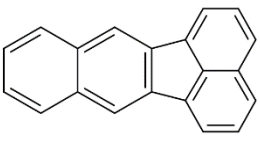
Chemical Name (common synonyms[a])	CASRN	Abbreviation	Structure	Molecular Weight (g/mol)
Aromatic High Carbon Range				
1,1-Biphenyl (biphenyl; 1,1′-biphenyl; 1,1-biphenyl)	92-52-4	BH		154.212
1-Methylnaphthalene (naphthalene, 1-methyl-)	90-12-0	1MeNPT		142.201
2-Methylnaphthalene (naphthalene, 2-methyl-)	91-57-6	2MeNPT		142.201
Acenaphthene (acenaphthylene, 1,2-dihydro-; 1,2-dihydroacenaphthylene; 1,8-ethylenenaphthalene)	83-32-9	ANL		154.212
Anthracene (anthracin; paranaphthalene)	120-12-7	AC		178.234
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		252.316
Benz[*a*]anthracene (tetraphene; benzo[*b*]phenanthrene; 1,2-benzanthracene; 2,3-benzophenanthrene; 1,2-benzanthrene; naphthanthracene)	56-55-3	BaAC		228.294
Benzo[*k*]fluoranthene (dibenzo[*b*,*jk*]fluorene; 8,9-benzofluoranthene; 11,12-benzofluoranthene; 2,3:1′,8′-biaphthylene)	207-08-9	BkFA		252.316

Table A-1. Chemical Synonyms and Abbreviations

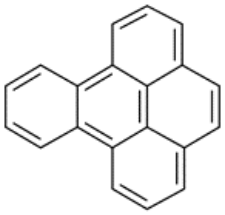
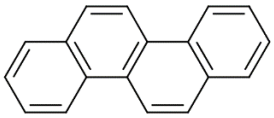
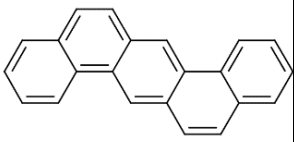
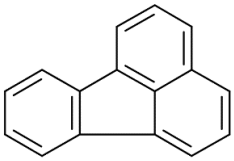
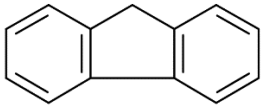
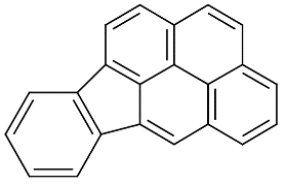
Chemical Name (common synonyms[a])	CASRN	Abbreviation	Structure	Molecular Weight (g/mol)
Benzo[*a*]pyrene (benzo[*pqr*]tetraphene; benzo[*def*]chrysene; 1,2-benzpyrene;benzene 3,4-benzopyren; 4,5-benzpyrene; 6,7-benzopyrene)	50-32-8	BaP		252.316
Benzo[*e*]pyrene	192-97-2	BeP		252.316
Chrysene (benzo[*a*]phenanthrene; 1,2-benzophenanthrene)	218-01-9	CH		228.294
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		278.354
Fluoranthene (clustercarbon; idryl; benzo[*jk*]fluorene; 1,2-[1,8-naphthalenediyl]benzene; benz[*a*]acenaphthylene; 1,2-benzoacenaphyhylene)	206-44-0	FA		202.256
Fluorene (9H-fluorene; 2,3-benzidene; *o*-biphenylenemethane; diphenylenemethane; 2,2'-methylenebiphenyl; *o*-biphenylmethane)	86-73-7	FE		166.223
Indeno[*1,2,3cd*]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		276.338

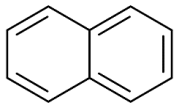
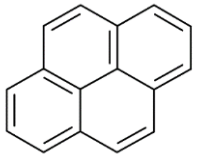
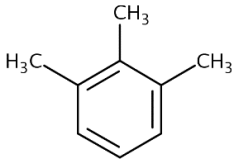
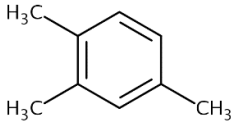
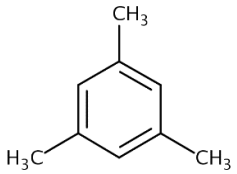
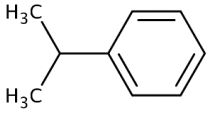
Table A-1. Chemical Synonyms and Abbreviations				
Chemical Name (common synonyms[a])	**CASRN**	**Abbreviation**	**Structure**	**Molecular Weight (g/mol)**
Naphthalene (naphthalin)	91-20-3	NPT		128.174
Pyrene (benzo[*def*]phenanthrene; pyren)	129-00-0	Pyr		202.256
Aromatic Medium Carbon Range				
1,2,3-Trimethylbenzene (benzene, 1,2,3-trimethyl-)	526-73-8	1,2,3-TMB		120.195
1,2,4-Trimethylbenzene (benzene, 1,2,4-trimethyl-)	95-63-6	1,2,4-TMB		120.195
1,3,5-Trimethylbenzene (benzene, 1,3,5-trimethyl-)	108-67-8	1,3,5-TMB		120.195
Isopropylbenzene (cumene; [propan-2-yl]benzene; benzene, [1-methylethyl]-)	98-82-8			120.195

Table A-1. Chemical Synonyms and Abbreviations

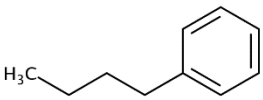
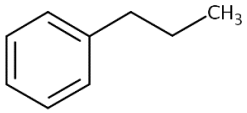
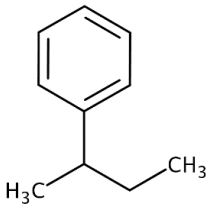
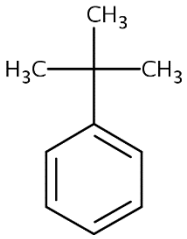
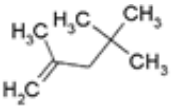
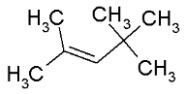
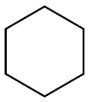
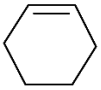
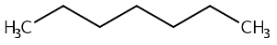
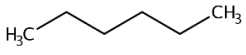
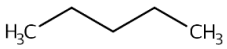
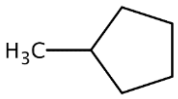
Chemical Name (common synonyms[a])	CASRN	Abbreviation	Structure	Molecular Weight (g/mol)
HFAN (light aromatic solvent naphtha [petroleum]; solvent naphtha, petroleum, light aromatic; super high flash naphtha; aromatic solvent; solvent, aromatic petroleum; solvent naphtha; light aromatic solvent naphtha; low boiling point naphtha–unspecified; solvent naphtha [petroleum], light aromatic)	64742-95-6		Various	Various
***n*-Butylbenzene** (benzene, butyl-)	104-51-8			134.222
***n*-Propylbenzene** (propylbenzene; benzene, propyl-)	103-65-1			120.195
***sec*-Butylbenzene** ([butan-2-yl]benzene; benzene, [1-methylpropyl]-)	135-98-8			134.222
***tert*-Butylbenzene** (benzene, [1,1-dimethylethyl]-)	98-06-6			134.222
Aliphatic Low Carbon Range				
2,4,4-Trimethylpentene	2516-77-08 (mixture of two isomers, 107-39-1 and 107-40-4)		 and 	112.22

Table A-1. Chemical Synonyms and Abbreviations

Chemical Name (common synonyms[a])	CASRN	Abbreviation	Structure	Molecular Weight (g/mol)
Commercial hexane (NOCAS_872521)	Various		Various	Various
Cyclohexane	110-82-7			84.162
Cyclohexene	110-83-8			82.146
***n*-Heptane** (heptane)	142-82-5			100.205
***n*-Hexane** (hexane)	110-54-3			86.178
***n*-Pentane** (pentane; norpar 55)	109-66-0			72.151
Methylcyclopentane (cyclopentane, methyl-)	96-37-7			84.162

[a]Synonyms are listed according to National Institute of Standards and Technology (NIST, 2020) and include valid synonyms from U.S. EPA CompTox Chemicals Dashboard; accessed 03-30-2020 (U.S. EPA, 2021a).

U.S. EPA = U.S. Environmental Protection Agency.

APPENDIX B. REFERENCES

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