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Provisional Peer-Reviewed Toxicity Values for

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

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

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https://www.epa.gov/pprtv

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Center for Public Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
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Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA Office of Research and Development (ORD) Center for Public Health and Environmental Assessment (CPHEA) website at https://ecomments.epa.gov/pprtv.

TABLE OF CONTENTS

COMMONLY USED ABBREVIATIONS AND ACRONYMS

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

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

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

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund program. PPRTVs are derived after a review of the relevant scientific literature using established U.S. Environmental Protection Agency (U.S. EPA) guidance on human health toxicity value derivations.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

Currently available PPRTV assessments can be accessed on the U.S. EPA's PPRTV website at https://www.epa.gov/pprtv. PPRTV assessments are eligible to be updated on a 5-year cycle and revised as appropriate to incorporate new data or methodologies that might impact the toxicity values or affect the characterization of the chemical's potential for causing adverse human-health effects. Questions regarding nomination of chemicals for update can be sent to the appropriate U.S. EPA's eComments Chemical Safety web page (https://ecomments.epa.gov/chemicalsafety/).

QUALITY ASSURANCE

This work was conducted under the U.S. EPA Quality Assurance (QA) program to ensure data are of known and acceptable quality to support their intended use. Surveillance of the work by the assessment managers and programmatic scientific leads ensured adherence to QA processes and criteria, as well as quick and effective resolution of any problems. The QA manager, assessment managers, and programmatic scientific leads have determined under the QA program that this work meets all U.S. EPA quality requirements. This PPRTV was written with guidance from the CPHEA Program Quality Assurance Project Plan (PQAPP), the QAPP titled *Program Quality Assurance Project Plan (PQAPP) for the Provisional Peer-Reviewed Toxicity Values (PPRTVs) and Related Assessments/Documents (L-CPAD-0032718-QP)*, and the PPRTV development contractor QAPP titled *Quality Assurance Project Plan—Preparation of Provisional Toxicity Value (PTV) Documents (L-CPAD-0031971-QP)*. As part of the QA system, a quality product review is done prior to management clearance. A Technical Systems Audit may be performed at the discretion of the QA staff.

All PPRTV assessments receive internal peer review by at least two CPHEA scientists and an independent external peer review by at least three scientific experts. The reviews focus on whether all studies have been correctly selected, interpreted, and adequately described for the purposes of deriving a provisional reference value. The reviews also cover quantitative and qualitative aspects of the provisional value development and address whether uncertainties associated with the assessment have been adequately characterized.

DISCLAIMERS

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

Other U.S. EPA programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

QUESTIONS REGARDING PPRTVS

Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA ORD CPHEA website at https://ecomments.epa.gov/pprtv.

1. INTRODUCTION

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

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

1.1. DEFINITION OF THE AROMATIC HIGH CARBON RANGE FRACTION

The aromatic high carbon range fraction includes aromatic hydrocarbons with a carbon (C) range of C10−C32 (contains between 10 and 32 carbons, inclusive) and an equivalent carbon (EC)[1] number index range of EC11−EC35 that occur in, or co-occur with, petroleum contamination. Hydrocarbons with a carbon number greater than C32 are not included in the aromatic high carbon range fraction due to limited bioavailability driving a lack of toxicity observed in in vivo studies, limited potential for transport via groundwater flow and via volatilization to the air, and incompatibility with existing standard analytical methods (Boogaard et al., 2017; Shell Global Solutions International et al., 2017; Gustafson et al., 1997). While the aromatic medium carbon range fraction also includes C10 compounds, the aromatic medium carbon range fraction is restricted to those compounds with EC9−EC < 11. For this reason, naphthalene (C10, EC11.57) is included in the aromatic high carbon range fraction. The EC index is equivalent to the retention time of the compound on a boiling-point gas chromatography (GC) column (nonpolar capillary column), normalized to the *n*-alkanes (NJ DEP, 2010). EC numbers are the physical characteristic that underpin analytical separation of petroleum components. EC numbers are useful because they are more closely related to environmental mobility than carbon number. For instance, two chemicals with similar carbon numbers but different structures (e.g., aliphatic vs. aromatic) could partition differently into environmental media and, ultimately, have different environmental fates. Grouping based on EC numbers provides a consistent basis for logically placing petroleum hydrocarbon compounds into fractions, because EC measures correlate with physicochemical properties such as water

[1]Based on an empirical relationship, the EC value can be estimated from a compound's boiling point (BP; °C) using the following equation: $EC = 4.12 + 0.02\ (BP) + 6.5 \times 10^{-5}\ (BP)^2$; see Gustafson et al. (1997).

solubility, vapor pressure, Henry's law constant, and soil adsorption coefficient (log K_{oc}). Toxicological considerations also are a consideration when defining the aromatic high carbon range fraction. Substituted benzenes (C9−C10; contained within the aromatic medium carbon fraction) were grouped separately from polycyclic aromatic hydrocarbons (PAHs), naphthalenes, and 1,1-biphenyl (contained within the aromatic high carbon range fraction), which generally exhibit greater carcinogenicity and noncancer toxicity. Individual compounds in this fraction have a backbone consisting of one or more aromatic rings, which can be substituted with alkane, alkene, and other nonaromatic ring structures. Example compounds include 1,2,4-triethylbenzene, 2-methylnaphthalene, fluorene, and benzo[*a*]pyrene (BaP). Compounds with two to six fused unsubstituted aromatic rings without anything other than carbon or hydrogen in their composition are characterized as PAHs. The selection of relevant compounds and mixtures is described in Section 2 and Appendices A and B.

1.2. OVERVIEW OF PHYSICOCHEMICAL PROPERTIES AND ENVIRONMENTAL FATE

The systematic chemical names, synonyms [following guidance in NIST (2020b)], CASRNs, chemical abbreviations, chemical structures, and molecular weights for chemicals in this document are listed in Table 1 and in Appendix B of U.S. EPA (2022). The physicochemical properties for members of the aromatic high carbon range fraction that have noncancer toxicity values compiled from the CompTox Chemicals Dashboard (U.S. EPA, 2021a) are provided in Table 2. Section 2 details how the fraction members with toxicity values were identified. The representative chemicals identified are 1,1-biphenyl and eight PAHs, including naphthalene, and two methyl-substituted naphthalene compounds (CASRNs 91-57-6 and 90-12-0). These chemicals are all solids except for 1-methylnaphthalene (CASRN 90-12-0), which is a liquid at room temperature; they have moderate to low water solubility and vapor pressure. Members of this fraction are expected to have little to no mobility in soil based on measured K_{oc} data; however, the K_{oc} for naphthalene suggests potential mobility in some soil types. Volatilization of members of this fraction from water and moist soil will be moderate based upon the measured Henry's law constant values for the representative compounds. Volatilization from dry soil surfaces will be low to moderate based upon the measured vapor pressure values. Measured aerobic and anaerobic biodegradation data are available for the representative compounds. Under aerobic conditions, the nine PAHs are expected to have slow removal by biodegradation in unacclimated systems and more rapid biodegradation in acclimated systems. Acclimation periods (days to months) have been observed prior to the onset of microbial degradation in tests using soil not previously exposed to PAHs. It is thought that this occurs because small population(s) of organisms capable of PAH degradation must attain sufficient densities before detectable PAH reduction is observed (Mihelcic and Luthy, 1988). 1,1-Biphenyl undergoes biodegradation more readily than the many PAHs, as demonstrated in a modified test where 1,1-biphenyl achieved 66% of its theoretical biochemical oxygen demand (BOD) after 14 days (compared to 0–2% after 28 days for naphthalene and acenaphthalene) (ECHA, 2019; OECD, 2009; CITI, 1992). Under anaerobic conditions, biodegradation is slow for all fraction members. Members of the aromatic high carbon range fraction do not contain hydrolysable functional groups; therefore, the rate of hydrolysis is expected to be negligible for all fraction members. In the atmosphere, the rate of photooxidation is expected to be moderate for fraction members. Many of the fraction members, except, for example, 1,1-biphenyl, contain chromophores that absorb light at wavelengths >290 nm, and are therefore expected to be susceptible to direct photolysis by sunlight (NLM, 2017a, b, c, e, f, g, 2015a, b, 2014, 2005). When the fraction members occur in the atmosphere in the particulate phase, they will be physically removed by wet and dry deposition.

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

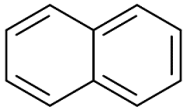
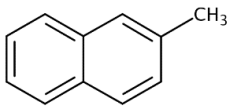
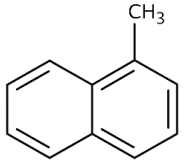
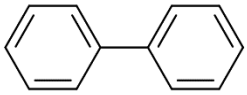
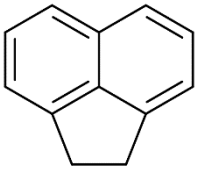
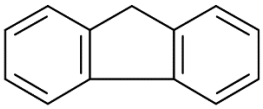
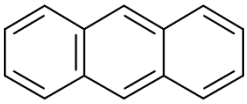
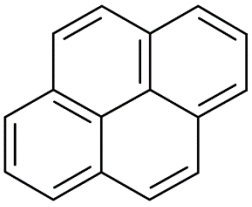
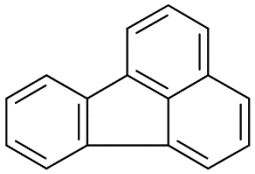
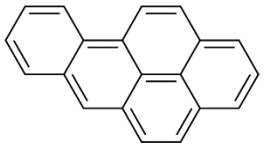
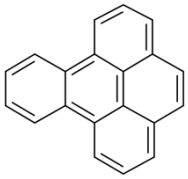
Chemical (common synonyms[b])	CASRN	Abbreviation	Structure	Molecular Weight (g/mol)
Naphthalene (naphthalin)	91-20-3	NPT		128.174
2-Methylnaphthalene (naphthalene, 2-methyl-)	91-57-6	2MeNPT		142.201
1-Methylnaphthalene (naphthalene, 1-methyl-)	90-12-0	1MeNPT		142.201
1,1-Biphenyl (biphenyl; 1,1′-biphenyl)	92-52-4	BH		154.212
Acenaphthene (acenaphthylene, 1,2-dihydro-; 1,2-dihydroacenaphthylene; 1,8-ethylenenaphthalene)	83-32-9	ANL		154.212
Fluorene (9H-fluorene; 2,3-benzidene; *o*-biphenylenemethane; diphenylenemethane; 2,2′-methylenebiphenyl; *o*-biphenylmethane)	86-73-7	FE		166.223
Anthracene (anthracin; paranaphthalene)	120-12-7	AC		178.234
Pyrene (benzo[*def*]phenanthrene; pyren)	129-00-0	Pyr		202.256

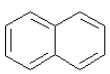
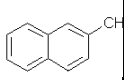
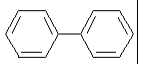
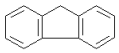
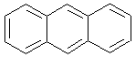
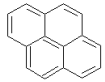
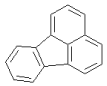
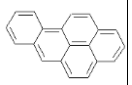
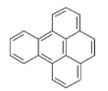
Table 1. Synonyms and Abbreviations for Chemicals in this PPRTV Assessment[a]

Chemical (common synonyms[b])	CASRN	Abbreviation	Structure	Molecular Weight (g/mol)
Fluoranthene (ClusterCarbon; idryl; benzo[*jk*]fluorene; 1,2-[1,8-naphthalenediyl]benzene; benz[*a*]acenaphthylene; 1,2-benzoacenaphyhylene)	206-44-0	FA		202.256
Benzo[*a*]pyrene (benzo[*pqr*]tetraphene; benzo[*def*]chrysene; 1,2-benzpyrene; 3,4-benzopyren; 4,5-benzpyrene; 6,7-benzopyrene)	50-32-8	BaP		252.316
Benzo[*e*]pyrene	192-97-2	BeP		252.316

[a]Only chemicals with toxicity values are listed.
[b]Synonyms are listed according to NIST (2020b) and include valid synonyms from U.S. EPA CompTox Chemicals Dashboard; accessed 03-30-2020; U.S. EPA (2021a).

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

Table 2. Physicochemical Properties of Aromatic High Carbon Range Chemicals with Noncancer Toxicity Values[a]

Chemical	NPT	2MeNPT	1MeNPT	BH	ANL	FE	AC	Pyr	FA	BaP	BeP
Structure											
CASRN	91-20-3	91-57-6	90-12-0	92-52-4	83-32-9	86-73-7	120-12-7	129-00-0	206-44-0	50-32-8	192-97-2
Molecular formula	$C_{10}H_8$	$C_{11}H_{10}$	$C_{11}H_{10}$	$C_{12}H_{10}$	$C_{12}H_{10}$	$C_{13}H_{10}$	$C_{14}H_{10}$	$C_{16}H_{10}$	$C_{16}H_{10}$	$C_{20}H_{12}$	$C_{20}H_{12}$
EC number[b]	11.57	12.72	12.77	13.45	14.76	15.68	18.43	22.45	21.11	29.95	27.80
Molecular weight (g/mol)	128.174	142.201	142.201	154.212	154.212	166.223	178.234	202.256	202.256	252.316	252.316
Melting point (°C)	80.3	33.7	−3.10	69.8	93.9	115	215	150	108	177	178
Boiling point (°C)	218	241	242	255	279	295	340	399	380	495	469*
Vapor pressure (mm Hg at 25°C)	8.50×10^{-2}	5.50×10^{-2}	6.70×10^{-2}	8.93×10^{-3}	2.15×10^{-3}	6.00×10^{-4}	6.53×10^{-6}	4.50×10^{-6}	9.22×10^{-6}	5.49×10^{-9}	5.70×10^{-9}
Henry's law constant (atm-m^3/mole at 25°C)	4.4×10^{-4}	5.18×10^{-4}	5.14×10^{-4}	3.08×10^{-4}	1.84×10^{-4}	9.62×10^{-5}	5.56×10^{-5}	1.19×10^{-5}	8.86×10^{-6}	4.57×10^{-7}	1.07×10^{-6}*
Water solubility (mol/L at 25°C)	2.47×10^{-4}	1.74×10^{-4}	1.95×10^{-4}	4.60×10^{-5}	4.64×10^{-5}	1.15×10^{-5}	3.38×10^{-7}	6.65×10^{-7}	1.24×10^{-6}	8.40×10^{-9}	1.89×10^{-8}
Log K_{ow}	3.30	3.86	3.87	4.01	3.92	4.18	4.45	4.88	5.16	6.13	6.44
Log K_{oa}	5.19	5.83*	5.01*	6.15	6.31	6.79	7.55	8.80	8.88	9.61*	10.3*
Log K_{oc}	2.96	3.60	3.36	3.27	3.59	3.70	4.31	4.90	4.80	5.95	5.67*

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

AC = anthracene; ANL = acenaphthene; BaP = benzo[*a*]pyrene; BeP = benzo[*e*]pyrene; BH = biphenyl; BP = boiling point; EC = equivalent carbon; FA = fluoranthene; FE = fluorene; K_{oa} = octanol-air partition coefficient; K_{oc} = soil adsorption coefficient; K_{ow} = octanol-water partition coefficient; 1MeNPT = 1-methylnaphthalene; 2MeNPT = 2-methylnaphthalene; NPT = naphthalene; Pyr = pyrene; TPHCWG = Total Petroleum Hydrocarbon Criteria Working Group; U.S. EPA = U.S. Environmental Protection Agency.

1.3. OVERVIEW OF MIXTURE ASSESSMENT METHODS

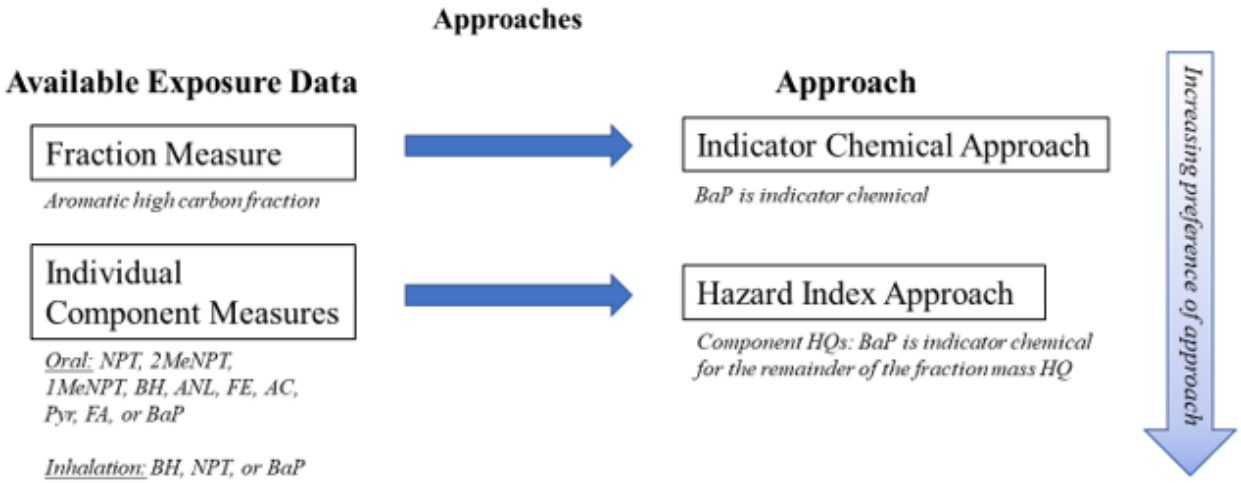
A number of different approaches have been developed and used to estimate risks and hazards posed by exposures to chemical mixtures encountered in the environment. The two approaches utilized in this PPRTV assessment are the indicator chemical approach and the hazard index (HI) approach. The choice of approaches is based on the available analytical chemistry.

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

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

Chemical mixture assessments are conducted most appropriately with quantitative dose-response information resulting from comparable exposures to the mixture of concern. If the dose-response data are insufficient to develop a health reference value for the specific mixture of concern in the environment, the second option recommended by the U.S. EPA *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 2000, 1986) is a "sufficient similarity" approach that uses a health reference value from a characterized surrogate mixture to estimate the hazards or risks associated with exposures to the mixture of concern. This method requires chemistry and toxicity data on both the potential surrogate mixture and the mixture of concern (e.g., an in vitro endpoint that is related to the apical endpoint observed in an epidemiological study or whole animal study), and a health reference value (e.g., from an in vivo study) on the surrogate mixture. If the chemistry and toxicity data indicate that the mixtures are "sufficiently similar" to one another, then the health reference value for the surrogate mixture can be used as a proxy for the mixture of concern. No data were identified that were suitable to implement a whole mixture approach.

The choice of a chemical mixtures risk assessment method is driven by the available data. Starting with the method requiring the least information and then discussing the method requiring more information, the following subsections summarize the indicator chemical approach and the HI approach. Figure 1 summarizes the two approaches and the preference for using each approach.



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

AC = anthracene; ANL = acenaphthene; BaP = benzo[*a*]pyrene; BH = 1,1-biphenyl; FA = fluoranthene; FE = fluorene; HQ = hazard quotient; 1MeNPT = 1-methylnaphthalene; 2MeNPT = 2-methylnaphthalene; NPT = naphthalene; Pyr = pyrene.

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

1.3.1. Indicator Chemical Approach

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

1.3.2. Hazard Index Approach

The HI approach combines estimated population exposures with toxicity information to characterize the potential for adverse 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 (e.g., percentage decrement in enzyme activity). Instead, the HI is an indicator of potential hazard. In the HI approach, a hazard quotient (HQ) is calculated as the ratio of human exposure (*E*) to a health 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, and the reference concentration (RfC) for the inhalation exposure route.

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

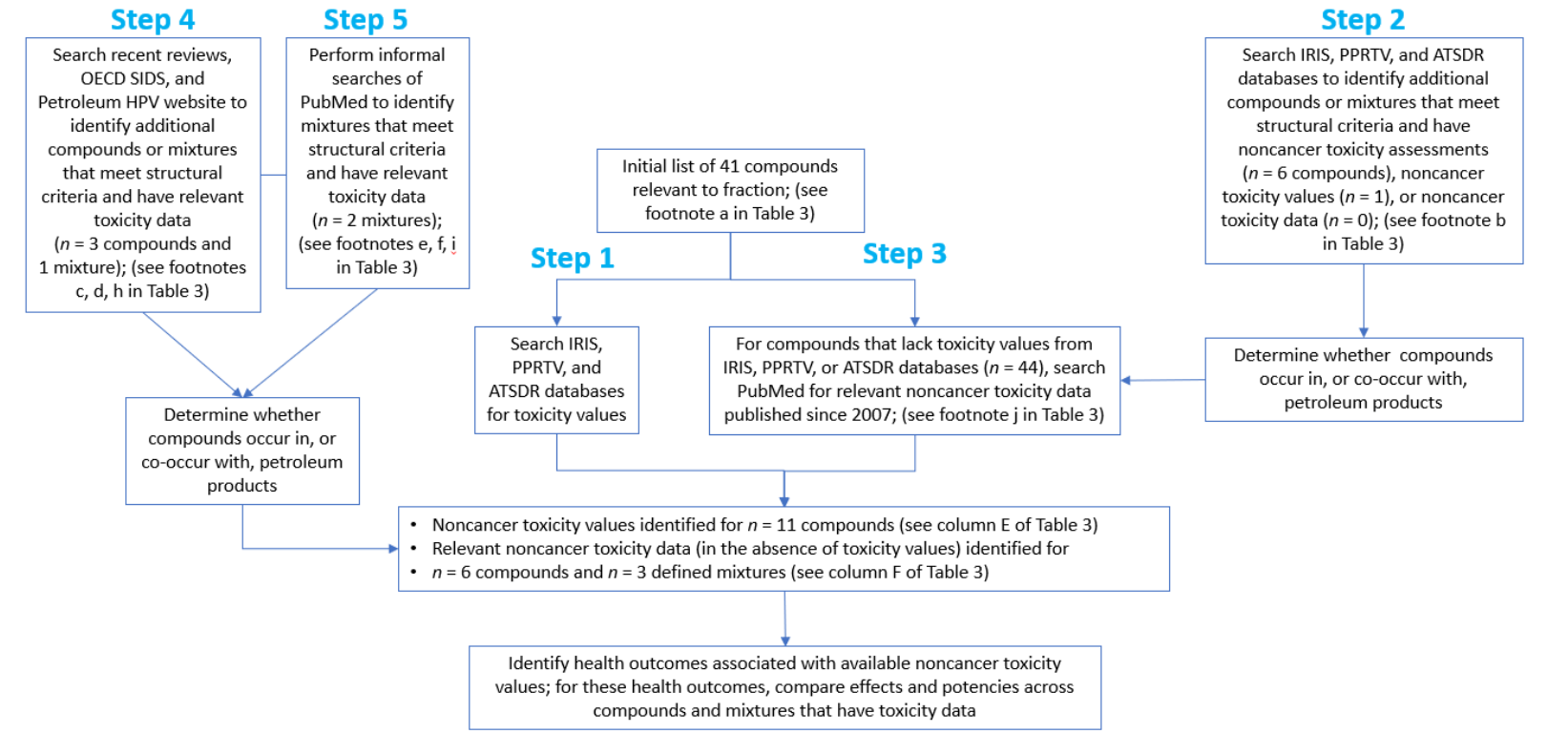
The HI is based on dose addition (U.S. EPA, 2000; Svendsgaard and Hertzberg, 1994); the hazard is evaluated as the potency-weighted sum of the component exposures. The HI is dimensionless, so *E* and the RfV must be in the same units.

2. SUMMARY OF TOXICITY AND DOSE-RESPONSE ASSESSMENT APPROACH FOR NONCANCER EFFECTS

The indicator chemical approach and the HI approach are used for hazard assessment for the aromatic high carbon range fraction. Both approaches require toxicity and dose-response assessment data. These data depend upon the identification of component chemicals and mixtures with existing toxicity values, and the identification of hazard information. The approach for identifying this information is outlined here and described in additional detail in subsequent sections. Mixtures and compounds that met structural criteria (see definition of the fraction in Section 1.1) and had available toxicity values from designated sources were identified, as was relevant hazard information.

Literature searches were performed for the mixtures and compounds with toxicity values and for other mixtures and compounds that are relevant to the fraction. These literature searches were conducted in February 2018 and date-limited to assessments and literature published after 2007[2]. These literature searches were updated most recently in August 2021. The literature searches were designed for several purposes. First, the literature searches were to determine whether new information suggested that toxicity values for mixtures or compounds relevant to the fraction (see definition of the fraction, in Section 1.1) should be updated from those identified in the U.S. EPA (2009b) PPRTV assessment for mixtures of aliphatic and aromatic hydrocarbons. Second, the literature searches were to determine whether new noncancer toxicity values or data on other mixtures or compounds meeting the structural criteria of the fraction might alter the overall understanding of the toxicity of the fraction. Third, a search of recent comprehensive reviews was conducted on the toxicity of petroleum components or classes of compounds relevant to the fraction, as well as Organisation for Economic Co-operation and Development (OECD) Screening Information Data Set (SIDS) assessments3 and the Petroleum High Production Volume (HPV) Testing Group website, to identify other mixtures or compounds with toxicity data that may inform hazard identification for the fraction. Toxicity data criteria included human studies of any duration by oral, inhalation, and dermal exposure, and animal studies of oral or inhalation exposure lasting at least 28 days (or any duration of gestational exposure). Mixture toxicity data were considered relevant only if the mixture composition under study was quantitatively defined to enable assessment of relevance to the fraction. Figure 2 shows a schematic depiction of the process, and further detail is provided below.

[2]The literature searches were date-limited to studies published from 2007 forward in order to capture studies that were published since the searches performed for the 2009 PPRTV assessment for TPH mixtures (U.S. EPA, 2009b).
[3]The OECD Existing Chemicals Database (https://hpvchemicals.oecd.org) was reviewed for C10−C13 aromatic solvents.



Compound Structural Criteria:	Mixture Structural Criteria:	Toxicity Data Criteria:
10 ≤ C ≤ 32 *and* 11 ≤ EC < 35 aromatic	≥99% of the mixture consists of aromatic compounds (≤1% aliphatic) *and* ≥90% of mixture consists of compounds meeting structural criteria (left) and highly toxic lower aromatic carbons (e.g., benzene) are not present	Human: any duration, oral, inhalation, or dermal exposure Animal: oral or inhalation exposure for at least 28 days or any duration during gestation Mixture toxicity data considered relevant only if mixture composition quantitatively defined to enable assessment of relevance to the fraction

ATSDR = Agency for Toxic Substances and Disease Registry; C = carbon; EC = equivalent carbon; HPV = High Production Volume: IRIS = Integrated Risk Information System; OECD = Organisation for Economic Co-operation and Development; PPRTV = Provisional Peer-Reviewed Toxicity Value; RfC = reference concentration; RfD = reference dose; SIDS = Screening Information Data Set.

Compounds and mixtures relevant to the aromatic high carbon range fraction with available toxicity values or data were identified. Table 3 lists individual compounds and mixtures and links them to their corresponding identification source during the literature search process. Table 3 also indicates compounds with available toxicity values, or in the absence of toxicity values, available toxicity data.

Figure 2. Selection of Compounds and Mixtures for Aromatic High Carbon Range Fraction Hazard Identification and Noncancer Dose-Response Assessment

2.1. IDENTIFICATION OF RELEVANT MIXTURES AND COMPOUNDS WITH NONCANCER TOXICITY VALUES

In Step 1 of the assessment (see Figure 2), the U.S. EPA identified constituents of the fraction that have existing toxicity values from any of the sources considered for the U.S. EPA (2009b) PPRTV assessment for *Complex Mixtures of Aliphatic and Aromatic Hydrocarbons*; these included assessments on the Integrated Risk Information System [IRIS], PPRTV assessments, Agency for Toxic Substances and Disease Registry [ATSDR] Minimal Risk Levels [MRLs], Massachusetts Department of Environmental Protection [MassDEP], the Total Petroleum Hydrocarbon Criteria Working Group [TPHCWG], and Health Effects Assessment Summary Tables [HEAST]). Of these sources, only IRIS, PPRTVs, and ATSDR MRLs have been updated since 2009, so only these sources were consulted for updated toxicity values. Beginning with an initial list of 41 chemicals considered relevant to the fraction [see the full list in Table 3 as well as a description of the approach and results in Wang et al. (2012)], the IRIS, PPRTVs, and ATSDR MRLs were reviewed for noncancer toxicity values. At least one subchronic or chronic oral reference value or subchronic or chronic inhalation reference value was available for 11 chemicals (acenaphthene, anthracene, BaP, benzo[*e*]pyrene [BeP], 1,1-biphenyl, fluoranthene, fluorene, 1-methylnaphthalene, 2-methylnaphthalene, naphthalene, and pyrene). Table 4 shows the noncancer toxicity values available for the 11 relevant compounds.

Table 3. Chemicals and Mixtures Identified in Literature Searches

CASRN	Chemical Name	Literature Search Identification Source	PubMed Searches Performed	Toxicity Values Identified	Toxicity Data Identified
92-52-4	1,1-Biphenyl	Initial list of 41[a]	X	X	
26137-53-1	1,2,3-Trimethyl-4-propenyl-naphthalene	Updated PPRTV, IRIS, and ATSDR MRL databases[b]	X		
877-44-1	1,2,4-Triethylbenzene	Recent reviews of petroleum toxicity[c, d]			X
527-53-7	1,2,3,5-Tetramethylbenzene	Initial list of 41[a]	X		
575-41-7	1,3-Dimethylnaphthalene	Initial list of 41[a]	X		
102-25-0	1,3,5-Triethylbenzene	Recent reviews of petroleum toxicity[c, d]			X
202-94-8	11H-Benzo[*b,c*]aceanthrylene	Initial list of 41[a]	X		
90-12-0	1-Methylnaphthalene	Initial list of 41[a]	X	X	
Various	16-PAH mixture	Informal PubMed searches[e, f]	X		X
243-17-4	2,3-Benzofluorene	Updated PPRTV, IRIS, and ATSDR MRL databases[b]	X		
581-42-0	2,6-Dimethylnaphthalene	Initial list of 41[a]	X		
91-57-6	2-Methylnaphthalene	Initial list of 41[a]	X	X	
Various	21-PAH mixture[g]	Recent reviews of petroleum toxicity[c, h]			X
202-98-2	4H-Cyclopenta[*d,e,f*]chrysene	Initial list of 41[a]	X		

Table 3. Chemicals and Mixtures Identified in Literature Searches

CASRN	Chemical Name	Literature Search Identification Source	PubMed Searches Performed	Toxicity Values Identified	Toxicity Data Identified
Various	9-PAH mixture	Informal PubMed searches[e, i]	X		X
83-32-9	Acenaphthene	Initial list of 41[a]	X	X	
208-96-8	Acenaphthylene	Updated PPRTV, IRIS, and ATSDR MRL databases[b]	X		
191-26-4	Anthanthrene	Initial list of 41[a]	X		
120-12-7	Anthracene	Initial list of 41[a]	X	X	
56-55-3	Benzo[*a*]anthracene	Initial list of 41[a]	X		
50-32-8	Benzo[*a*]pyrene	Initial list of 41[a]; oral and inhalation toxicity values[j]		X	
205-99-2	Benzo[*b*]fluoranthene	Initial list of 41[a]	X		X
205-12-9	Benzo[*c*]fluorene	Recent reviews of petroleum toxicity[c, h]			X
192-97-2	Benzo[*e*]pyrene	Updated PPRTV, IRIS, and ATSDR MRL databases[b]; oral and inhalation toxicity values[j]		X	
191-24-2	Benzo[*ghi*]perylene	Initial list of 41[a]	X		
207-08-9	Benzo[*k*]fluoranthene	Initial list of 41[a]	X		
199-54-2	Benzo[*e*]aceanthrylene	Initial list of 41[a]	X		
202-33-5	Benzo[*j*]aceanthrylene	Initial list of 41[a]	X		
205-82-3	Benzo[*j*]fluoranthene	Initial list of 41[a]	X		
211-91-6	Benzo[*l*]aceanthrylene	Initial list of 41[a]	X		
218-01-9	Chrysene	Initial list of 41[a]	X		
191-07-1	Coronene	Updated PPRTV, IRIS, and ATSDR MRL databases[b]	X		
27208-37-3	Cyclopenta[*c,d*]pyrene	Initial list of 41[a]	X		
191-30-0	Dibenzo[*a,l*]pyrene	Initial list of 41[a]	X		X
215-58-7	Dibenzo[*a,c*]anthracene	Initial list of 41[a]	X		
5385-75-1	Dibenzo[*a,e*]fluoranthene	Initial list of 41[a]	X		
192-65-4	Dibenzo[*a,e*]pyrene	Initial list of 41[a]	X		
53-70-3	Dibenzo[*a,h*]anthracene	Initial list of 41[a]	X		
189-64-0	Dibenzo[*a,h*]pyrene	Initial list of 41[a]	X		
189-55-9	Dibenzo[*a,i*]pyrene	Initial list of 41[a]	X		
206-44-0	Fluoranthene	Initial list of 41[a]	X	X	
86-73-7	Fluorene	Initial list of 41[a]	X	X	
193-39-5	Indeno[1,2,3-*c,d*]pyrene	Initial list of 41[a]	X		

Table 3. Chemicals and Mixtures Identified in Literature Searches

CASRN	Chemical Name	Literature Search Identification Source	PubMed Searches Performed	Toxicity Values Identified	Toxicity Data Identified
91-20-3	Naphthalene	Initial list of 41[a]; oral and inhalation toxicity values[j]		X	
193-09-9	Naphtho[2,3-*e*]pyrene	Initial list of 41[a]	X		
1078-71-3	*n*-Heptylbenzene	Initial list of 41[a]	X		
1077-16-3	*n*-Hexylbenzene	Initial list of 41[a]	X		
2189-60-8	*n*-Octylbenzene	Initial list of 41[a]	X		
538-68-1	*n*-Pentylbenzene	Initial list of 41[a]	X		
198-55-0	Perylene	Updated PPRTV, IRIS, and ATSDR MRL databases[b]	X		
85-01-8	Phenanthrene	Initial list of 41[a]	X		X
827-52-1	Phenylcyclohexane	Initial list of 41[a]	X		
129-00-0	Pyrene	Initial list of 41[a]	X	X	

[a]The U.S. EPA developed the initial list of 41 chemicals relevant to the aromatic medium carbon range. The list included all individual hydrocarbons considered previously by the U.S. EPA's STSC in the evaluation of hydrocarbons, as well as all those with toxicity data reviewed by the MassDEP (MassDEP, 2003) or the TPHCWG (Edwards et al., 1997).
[b]During review of the updated IRIS, PPRTV, and ATSDR MRL databases, these compounds were identified in the PPRTV database as meeting structural criteria for inclusion and having toxicity assessments.
[c]These compounds/mixtures were identified in Mckee et al. (2015) and Baxter and Warshawsky (2012), reviews of petroleum toxicity.
[d]Toxicity data for these compounds were found in Tshala-Katumbay et al. (2006).
[e]These mixtures were identified in PubMed searches using the terms "'polycyclic aromatic hydrocarbons' AND mixture AND (rat or mouse or hamster or rabbit)."
[f]Toxicity data for this mixture were found in Crepeaux et al. (2014); (Crepeaux et al., 2013, 2012).
[g]The 21-PAH mixture includes 1- and 2-methylnaphthalene, which are substituted PAHs (subPAHs). For simplicity, it is referred to as a 21-PAH mixture rather than a 19-PAH and 2-subPAH mixture.
[h]Toxicity data for these compounds/mixtures were found in Weyand et al. (2004).
[i]Toxicity data for this mixture were found in Yan et al. (2014) and Chu et al. (2013).
[j]Because these compounds had IRIS, PPRTV, or ATSDR toxicity values for both oral and inhalation routes, no additional literature searches were performed.

ATSDR = Agency for Toxic Substances and Disease Registry; IRIS = Integrated Risk Information System; MassDEP = Massachusetts Department of Environmental Protection; MRL = minimal risk level; PAH = polycyclic aromatic hydrocarbon; PPRTV = Provisional Peer-Reviewed Toxicity Value; STSC = Superfund Technical Support Center; TPHCWG = Total Petroleum Hydrocarbon Criteria Working Group; U.S. EPA = U.S. Environmental Protection Agency.

Table 4. Summary of Available Noncancer Toxicity Values for Constituents of Aromatic High Carbon Range (C10−C32, EC11−EC35) Fraction[a, b]

CASRN	Name	C	EC	Oral Reference Dose (mg/kg-d)		Inhalation Reference Concentration (mg/m^3)	
				Subchronic	Chronic	Subchronic	Chronic
91-20-3	Naphthalene	10	11.57	0.6 (ATSDR)	0.02 (IRIS)	–	0.003 (IRIS)
91-57-6	2-Methyl-naphthalene	11	12.72	0.004 (PPRTV)	0.004 (IRIS)	–	–
90-12-0	1-Methyl-naphthalene	11	12.77	–	0.007* (PPRTV)	–	–
92-52-4	1,1-Biphenyl	12	13.45	0.1 (PPRTV)	0.5 (IRIS)	0.004* (PPRTV)	0.0004* (PPRTV)
83-32-9	Acenaphthene	12	14.76	0.2 (PPRTV)	0.06 (IRIS)	–	–
86-73-7	Fluorene	13	15.68	0.4 (ATSDR)	0.04 (IRIS)	–	–
120-12-7	Anthracene	14	18.43	1 (PPRTV)	0.3 (IRIS)	–	–
129-00-0	Pyrene	16	22.45	0.3 (PPRTV)	0.03 (IRIS)	–	–
206-44-0	Fluoranthene	16	21.11	0.1 (PPRTV)	0.04 (IRIS)	–	–
192-97-2	Benzo[*e*]pyrene[c]	20	27.80	0.00009* (PPRTV)	0.00009* (PPRTV)	0.000002* (PPRTV)	0.000002* (PPRTV)
50-32-8	Benzo[*a*]pyrene	20	29.95	0.0003[d] (IRIS)	0.0003 (IRIS)	0.000002[d] (IRIS)	0.000002 (IRIS)

[a]Toxicity values shown were selected from the following sources in order of preference: IRIS, PPRTVs, ATSDR, HEAST, MassDEP, or TPHCWG.
[b]Appendix B of the TPH mixture PPRTV (U.S. EPA, 2022, 2021c) assessment provides a table containing all chemicals with toxicity values listed in any of the individual TPH fractions. The table lists the chemical name used in PPRTV assessments and its corresponding acronym, common synonyms listed in U.S. EPA's CompTox Chemicals Dashboard, CASRN, structure, and molecular weight.
[c]The screening subchronic and chronic p-RfDs and the screening subchronic and chronic p-RfCs are derived using an alternative analogue approach in the PPRTV assessment (U.S. EPA, 2021b).
[d]The chronic RfD and RfC values for benzo[*a*]pyrene are based on a developmental exposure; therefore, they are also applicable to subchronic exposures and are listed here.
*Screening toxicity value.

ATSDR = Agency for Toxic Substances and Disease Registry; C = carbon; EC = equivalent carbon; HEAST = Health Effects Assessment Summary Tables; IRIS = Integrated Risk Information System; MassDEP = Massachusetts Department of Environmental Protection; PPRTV = Provisional Peer-Reviewed Toxicity Value; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; TPH = total petroleum hydrocarbon; TPHCWG = Total Petroleum Hydrocarbon Criteria Working Group; U.S. EPA = U.S. Environmental Protection Agency.

In Step 2 (see Figure 2), other assessments in the IRIS, PPRTV, and ATSDR databases were reviewed to determine whether there were any other compounds or mixtures not in the initial list that met the structural criteria for inclusion (C10−C32 and EC11−EC35 aromatics). Searches of the IRIS and ATSDR databases did not identify any additional compounds, but review of the PPRTV database identified five additional compounds that met structural criteria for inclusion and had toxicity assessments: acenaphthylene, 2,3-benzofluorene, coronene, perylene, and 1,2,3-trimethyl-4-propenylnaphthalene. None of these PPRTV assessments

included toxicity value derivations or any relevant toxicity data. The U.S. EPA derived a toxicity value for BeP, a compound that met structural criteria for inclusion in the fraction.

2.2. IDENTIFICATION OF OTHER RELEVANT TOXICITY DATA

Among the 47 compounds outlined above (41 chemicals in the U.S. EPA's initial list plus 6 chemicals [acenaphthylene, BeP, 2,3-benzofluorene, coronene, perylene, and 1,2,3-trimethyl-4-propynylnaphthalene] found during the search of PPRTV database), there were 11 compounds with noncancer toxicity values (see Table 4). Four of these compounds (BaP, BeP, naphthalene, and 1,1-biphenyl) had IRIS or PPRTV toxicity values for both oral and inhalation routes; no additional literature searches were performed for these compounds. For the remaining 44 members, literature searches in PubMed were conducted in Step 3 (see Figure 2) to identify any new studies that fill data gaps. The literature searches were date-limited to studies published from 2007 forward in order to capture studies that were published since the searches performed for the 2009 PPRTV assessment for TPH mixtures (U.S. EPA, 2009b). This search was updated most recently in August 2021. A summary of the literature search strategy is provided in Appendix A. As detailed in Appendix A, studies considered relevant to hazard identification included animal studies using inhalation or oral exposure routes, in which exposures continued for at least 28 days (or any duration of gestational exposure), at least one health outcome was assessed, and an untreated or vehicle control group was included. Human studies of any duration in which exposure was known or presumed to be through oral, inhalation, or dermal routes and at least one health outcome was assessed were considered relevant.

The update literature search identified 11 epidemiological studies of noncancer effects in humans exposed to undefined PAH mixtures: Agarwal et al. (2017); Alhamdow et al. (2017); Mortamais et al. (2017); Sram et al. (2017); Yang et al. (2017); Yin et al. (2017); Ranjbar et al. (2015); Clark et al. (2012); Wang et al. (2016); Xu et al. (2010); and Suresh et al. (2009). These studies were primarily focused on cardiovascular, immune, and neurological or neurodevelopmental outcomes. New animal studies identified in the searches and considered relevant include an oral developmental study of benzo[*b*]fluoranthene (Kim et al., 2011), a 28-day oral neurobehavioral study of fluorene (Peiffer et al., 2016), and a 28-day inhalation study of 2-methylnaphthalene (Swiercz et al., 2011).

The literature searches also identified oral studies of dibenzo[*def,p*]chrysene (also known as dibenzo[*a,l*]pyrene) (Fish and Benninghoff, 2017a, b; Madeen et al., 2016; Shorey et al., 2013; Shorey et al., 2012; Castro et al., 2009; Castro et al., 2008c; Castro et al., 2008a; Castro et al., 2008b). Dibenzo[*def,p*]chrysene was not reported as a constituent of petroleum products in Gustafson et al. (1997). However, because only the 16 PAHs with noncancer or cancer toxicity values have historically been measured in most environmental media (U.S. EPA, 2021d; Keith, 2015), the lack of detections reported by Gustafson et al. (1997) may not reflect the actual composition of the mixture. In addition, detection limits at the time may not have been low enough to reveal very low concentrations of PAHs such as dibenzo[*def,p*]chrysene. For example, NLM (2017d) reported that dibenzo[*def,p*]chrysene "occurs as a result of incomplete burning of fossil fuels, wood, diesel oils and gasoline fuels." Therefore, it was considered to be relevant to petroleum contamination.

In Step 4 (see Figure 2), to determine whether additional relevant compounds or mixtures had been tested for repeat-dose and/or reproductive/developmental toxicity since 2007, recent reviews of petroleum toxicity (Mckee et al., 2015; Baxter and Warshawsky, 2012), an OECD (2012) SIDS dossier, and the Petroleum HPV Testing Group website were searched.

Searches of the Mckee et al. (2015) and Baxter and Warshawsky (2012) reviews identified three additional compounds with relevant (oral or inhalation, at least 28 days of exposure or any duration during development) animal toxicity data: 1,2,4-triethylbenzene, 1,3,5-triethylbenzene, and benzo[*c*]fluorene. Both of the triethylbenzenes were tested for neurotoxicity in a study of mice exposed orally for 5 weeks (Tshala-Katumbay et al., 2006). Benzo[*c*]fluorene, as well as a mixture of 21 PAHs, was tested for oral carcinogenicity in mice (Weyand et al., 2004); a few noncancer endpoints were reported. The 21-PAH mixture included one compound that was outside the carbon range (indan, C9); however, it was present at <1% in the mixture. The mixture composition is shown in Appendix B (see Table B-1). A subchronic oral study (Dalbey et al., 2014) of heavy paraffinic distillate aromatic extract in rats was located on the Petroleum HPV Testing Group website. However, this mixture included compounds outside the fraction range (as high as C50) and contained approximately 15% aliphatic compounds. Thus, it did not meet structural requirements for the aromatic high carbon range fraction and was not considered further.

Finally, in Step 5 (see Figure 2), PubMed searches using the terms "polycyclic aromatic hydrocarbons' AND mixture AND (rat or mouse or hamster or rabbit)" were performed to determine whether any oral or inhalation animal studies of mixtures that met inclusion criteria were available. Mixtures considered relevant to the fraction met the following criteria (see Figure 2):

1. at least 90% of the mixture consisted of identified compounds within the C10−C32 and/or EC11−EC35 ranges, and highly toxic lower aromatic carbons (e.g., benzene) were not present.
2. 99% of the mixture consisted of aromatic compounds (≤1% aliphatic).
3. the mixture had been tested in animals in at least one repeat-dose (≥28 days) or reproductive/developmental toxicity study using inhalation or oral exposure routes and included an untreated or vehicle control group.
4. human mixture studies of any duration by oral, inhalation, and dermal exposure, and animal studies of oral or inhalation exposure lasting at least 28 days (or any duration of gestational exposure).

In addition, mixture studies were considered relevant only if the composition of the test material was clearly defined.

The PubMed searches identified three neurodevelopmental studies of oral exposure to a 16-PAH mixture (Crepeaux et al., 2014, 2013, 2012), and two studies of inhalation exposure to a nebulized 9-PAH mixture during gestation or lactation, examining adiposity (Yan et al., 2014) and immune (Chu et al., 2013) endpoints in offspring. Compositions of the 16- and 9-PAH mixtures are shown in Appendix B (see Tables B-2 and B-3, respectively).

In summary, relevant toxicity data for compounds or mixtures that lack toxicity values were identified from reviews or literature searches for five compounds (benzo[*b*]fluoranthene, benzo[*c*]fluorene, dibenzo[*def,p*]chrysene, 1,2,4-triethylbenzene, and 1,3,5-triethylbenzene) and three defined mixtures (21-, 16-, and 9-PAH mixtures). 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, 2009c), bringing the total number of compounds with available toxicity data but no existing toxicity values to six.

2.3. METHODS FOR INDICATOR CHEMICAL SELECTION

Only compounds or mixtures with at least one U.S. EPA or ATSDR toxicity value (see Table 4) 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 effects and potency across the components of the fraction. The method for selecting indicator chemicals was adapted from the 2009 complex TPH mixtures document (U.S. EPA, 2009b). First, mixtures were preferred over individual compounds, provided that the mixture exhibited in vivo toxic effects and potency similar to those exhibited by the individual fraction components.

If suitable mixture data were lacking, but available component data indicated similar toxicity targets and potency, a representative compound exhibiting in vivo toxic effects and potency similar to those exhibited by other compounds in the fraction was chosen. In the event that components of the fraction varied widely in toxic effects or potency, the toxicity value for the most toxic component was selected as an 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 a site of hydrocarbon contamination, then an indicator chemical would be considered. In the case of studies where the exposures or doses occurred during fetal development, chronic toxicity values were considered representative of both chronic and subchronic exposures and were used as the subchronic toxicity value of the indicator chemical if they included the most sensitive endpoint.

3. REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER)

Compound-specific IRIS and PPRTV assessment documents, supplemented by the literature search findings for additional chemicals that met the structural criteria (described above) and review articles (Mckee et al., 2015; Baxter and Warshawsky, 2012; OECD, 2012; ATSDR, 2005) were assessed to evaluate the available noncancer toxicity data for compounds in the aromatic high carbon range fraction. Critical effects identified with existing toxicity values include 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 gastrointestinal (GI) system. Table 5 presents an overview of the human and animal data available to evaluate these primary toxicological endpoints for each aromatic high carbon range fraction compound and three relevant mixtures. As Table 5 shows, 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.

Table 5. Overview of Human and Animal Data Availability for Evidence Integration[a]

CASRN	Name	Rings	C	EC	Body Weight	Hemato-logical	Neuro-logical	Hepatic	Renal/ Bladder	Respir-atory	Gastro-intestinal	Repro-ductive	Develop-mental
91-20-3	**Naphthalene**	2	10	11.57	O, I	H, O, I	O, I	O, I	O, I	O, I	O, I	O, I	O
877-44-1	1,2,4-Triethylbenzene	1	12	11.57	O		O						
102-25-0	1,3,5-Triethylbenzene	1	12	11.62	O		O						
91-57-6	**2-Methylnaphthalene**	2	11	12.72	O, I	O, I	O, I	O, I	O, I	O, I	I	O, I	
90-12-0	**1-Methylnaphthalene**	2	11	12.77	O	O	O	O	O	O		O	
92-52-4	**1,1-Biphenyl**	2	12	13.45	O, I	O	H	H, O, I	O, I	O, I	O	O	O
83-32-9	**Acenaphthene**	2	12	14.76	O	O	O	O	O	O	O	O	
86-73-7	**Fluorene**	2	13	15.68	O	O	O	O	O	O	O	O	
85-01-8	Phenanthrene	3	14	18.37	O								
120-12-7	**Anthracene**	3	14	18.43	O	O	O	O	O	O	O	O	
205-12-9	Benzo[*c*]fluorene	3	17	21.45	O						O		
129-00-0	**Pyrene**	4	16	22.45	O	O	O	O	O	O	O	O	
206-44-0	**Fluoranthene**	3	16	21.11	O	O	O	O	O	O	O	O	
205-99-2	Benzo[*b*]fluoranthene	4	20	25.04	O								O
50-32-8	**Benzo[*a*]pyrene**	4	20	29.95	O, I	O	H, O	O	O	O	O	H, O, I	H, O, I
192-97-2	**Benzo[*e*]pyrene[b]**	4	20	27.80				O					
191-30-0	Dibenzo[*def,p*]chrysene	6	24	33.69									O
NA	16-PAH mixture	2−6	10−22	11.57−32.62									O
NA	9-PAH mixture	4−6	16−22	22.45−32.62									I
NA	21-PAH mixture	1−6	9−22	11.57−32.62	O						O		

[a]Includes human and animal studies meeting inclusion criteria. **Bolded** compounds have at least one oral or inhalation noncancer toxicity value available (see Table 4).
[b]The PPRTV assessment for benzo[*e*]pyrene (U.S. EPA, 2021b) discusses hepatotoxicity studies as well as immunotoxicity, cardiovascular toxicity, and retinol cell toxicity studies; however, as a result of the limitations of the available oral and inhalation toxicity data for benzo[*e*]pyrene, the U.S. EPA did not directly derive toxicity values. Instead, screening values were derived in Appendix A of the U.S. EPA PPRTV assessment document, using an alternative analogue approach.

EC = equivalent carbon; H = human data; I = animal inhalation studies; NA = not applicable; O = animal oral studies; PAH = polycyclic aromatic hydrocarbons; PPRTV = Provisional Peer-Reviewed Toxicity Value; U.S. EPA = U.S. Environmental Protection Agency.

To evaluate consistency in endpoint-specific potencies across members of the fraction, the dose-response data from animal studies that met selection criteria were extracted (from IRIS, PPRTV assessment documents, and primary and secondary literature sources) and presented in exposure-response arrays by health outcome and exposure route (see Appendix C). Based on review of the available data presented in Appendix C, 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).

4. TOXICOKINETIC CONSIDERATIONS

The toxicokinetic properties of PAHs have been extensively reviewed (U.S. EPA, 2017a; IARC, 2010; ATSDR, 2005). In general, these compounds are well absorbed following inhalation, oral, and dermal exposure. The lipophilicity of PAHs facilitates absorption; however, compounds with lower molecular weight (i.e., two or three rings vs. five or six rings) are more rapidly and extensively absorbed (IARC, 2010). PAHs are widely distributed with some accumulation in adipose tissues. Oxidative metabolism by cytochrome P450 (CYP450) isozymes occurs rapidly, and is followed by conjugation with sulfate, glutathione (GSH), or glucuronic acid and excretion in urine and feces. Oxidative metabolites of PAHs include epoxides, phenols, dihydrodiols, phenol dihydrodiols, dihydrodiol epoxides, quinones, and tetrols.

1,1-Biphenyl is also rapidly and readily absorbed following oral exposure (U.S. EPA, 2013). Animal studies suggest a potential for absorption by inhalation as 1,1-biphenyl dust or vapors; however, the rate and extent of absorption following inhalation are not known (U.S. EPA, 2013). Absorption by the dermal route is also suggested, although data are limited to an in vitro study of percutaneous absorption (U.S. EPA, 2013). 1,1-Biphenyl is widely distributed in tissues with no indication of preferential accumulation or storage (U.S. EPA, 2013). It is rapidly metabolized by CYP450 isozymes to hydroxylated metabolites, which are conjugated with sulphate or glucuronic acid. 1,1-Biphenyl is rapidly eliminated from the body, primarily as conjugated hydroxylated metabolites in the urine.

1,2,4-Triethylbenzene is expected to form a γ-diketone metabolite (1,2,4-triacetyl-benzene) due to the ortho position of the ethyl moieties on the benzene ring (Tshala-Katumbay et al., 2006; Gagnaire et al., 1993). Its isomer, 1,3,5-triethylbenzene, is not expected to form a γ-diketone due to the meta position of the ethyl moieties.

5. MECHANISTIC CONSIDERATIONS

Reactive oxidative metabolites of PAHs (e.g., benzo[*a*]pyrene diol epoxide [BPDE], 1,2-naphthoquinone) may bind covalently to proteins and nucleic acids, resulting in the cellular toxicity responsible for some noncancer health effects (IARC, 2010; ATSDR, 2005). Using naphthalene as an example, formation of cataracts following exposure is attributed to metabolism of naphthene dihydrodiol into 1,2-naphthoquinone in the lens of the eye (U.S. EPA, 1998). Additionally, GSH depletion and covalent protein binding have been implicated in the nasal and pulmonary toxicity produced by naphthalene due to formation of epoxide intermediates, naphthoquinones, and free radical reactive intermediates (U.S. EPA, 1998). GSH depletion is also associated with oxidative stress and the formation of reactive oxygen species. Oxidative stress has been suggested as a possible mechanism for several health effects of PAHs, including developmental and neurodevelopmental effects, male and female reproductive effects, immunotoxicity, and neurotoxicity (Agarwal et al., 2017; U.S. EPA, 2017a; Crepeaux et al., 2012; Suresh et al., 2009). PAH binding to, and activation of, the aryl hydrocarbon receptor has been shown to affect cellular growth and differentiation and has been postulated as a possible mechanism for the developmental, neurodevelopmental, immunotoxic, and neurotoxic effects of PAHs (U.S. EPA, 2017a). Studies provide support for several other PAH mechanisms, including deoxyribonucleic acid (DNA) damage of somatic and/or germ cell nucleic acids, stimulation of apoptosis, altered neurotransmitter levels, and changes in the balance of reproductive hormones (U.S. EPA, 2017a).

The urinary bladder toxicity observed in rats following exposure to 1,1-biphenyl is believed to be related to the formation of calculi (U.S. EPA, 2013). The liver toxicity of 1,1-biphenyl may be related to activation of peroxisome proliferation-activated receptors (PPARs), and the reduction in body weight may be a result of an inhibition of cellular respiration (U.S. EPA, 2013).

Formation of a γ-diketone metabolite (1,2,4-triacetylbenzene) is the proposed mechanism for peripheral neuropathy associated with exposure to 1,2,4-triethylbenzene (Tshala-Katumbay et al., 2006). While formation of 1,2,4-triactylbenzene has not been demonstrated, it is expected based on ortho arrangement of ethyl moieties (Tshala-Katumbay et al., 2006; Gagnaire et al., 1993). There are well-established data indicating that γ-diketone metabolites of 1,2-diethylbenzene and *n*-hexane (1,2-diacetylbenzene and 2,5-hexanedione, respectively) are associated with peripheral neuropathy (Mckee et al., 2015; OECD, 2007; U.S. EPA, 2005). In support of a role for γ-diketone metabolites in peripheral neuropathy, peripheral nerve damage is not observed following oral exposure to the isomer, 1,3,5-triethylbenzene, which does not have the potential to form a γ-diketone metabolite due to meta arrangement of ethyl moieties (Tshala-Katumbay et al., 2006; Gagnaire et al., 1993).

6. DERIVATION OF PROVISIONAL VALUES

6.1. DERIVATION OF ORAL REFERENCE DOSES

Tables 6 and 7 summarize the subchronic and chronic reference values for constituent compounds, respectively, with points of departure (PODs), uncertainty factors, critical endpoints, and confidence ratings.

Table 6. 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**	**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 (2017a)
Benzo[*e*]pyrene (C20 [EC27.80])	0.092	BMDL	1,000	UF_A, UF_D, UF_H	*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-Methyl-naphthalene (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 (2007a)
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 (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 (2009a)

Table 6. 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 (2007b)
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 (2012)

[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 7. 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**	**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 (2017a)**
Benzo[*e*]pyrene (C20 [EC27.80])	0.092	BMDL	1,000	UF_A, UF_D, UF_H	*0.00009*[d]	NA	Based on benzo[*a*]pyrene as an analogue; neurobehavioral changes (developmental)	Rat, gavage, PNDs 5−11	U.S. EPA (2021b) (in review)
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 (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	Mureta et al. (1997) as cited in U.S. EPA (2003)
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	Mureta 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 males F344 rats (urinary)	Rat, diet, 104 wk	Umeda et al. (2002) as cited in U.S. EPA (2013)
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 7. 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	U.S. EPA (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, 2017a).
[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; p-RfD = provisional reference dose; PND = postnatal day; POD = point of departure; PPRTV = provisional peer-reviewed toxicity value; 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.

Subchronic provisional reference doses (p-RfDs) and a subchronic RfD are available for 10 compounds in the fraction (see Table 6). It should be noted that the chronic RfD for BaP is based on a developmental exposure, which is also applicable to subchronic exposures; accordingly, the chronic RfD value for BaP is listed in Tables 4 and 6 as a proxy for subchronic exposure. As a result of the limitations of the available oral toxicity data for BeP, the U.S. EPA did not directly derive a subchronic p-RfD. Instead, a screening subchronic p-RfD is derived in the U.S. EPA PPRTV assessment document, using an alternative analogue approach based on the RfD for BaP (U.S. EPA, 2017a). The critical endpoints for the other subchronic p-RfDs are clinical signs of toxicity and decreased body-weight gain (naphthalene), lung toxicity (2-methylnaphthalene), developmental effects (1,1-biphenyl), liver effects (acenaphthene, fluorene), and kidney toxicity (pyrene, fluoranthene). The subchronic p-RfD for anthracene is based on a lack of effects.

There are 11 available chronic p-RfDs or RfDs for constituent compounds (see Table 7). The critical endpoints for these chronic RfDs are decreased body weight (naphthalene), lung toxicity (1-methylnaphthalene, 2-methylnaphthalene), kidney toxicity (1,1-biphenyl, pyrene, fluoranthene), liver effects (acenaphthene, fluoranthene), hematological effects (fluorene, fluoranthene), and developmental neurotoxicity (BaP, BeP). The chronic RfD for anthracene is based on a lack of effects.

As suggested by the disparity in critical endpoints and values of RfDs for fraction members and discussed in Section 3 (and Appendix C), the available oral toxicity data for aromatic high carbon range compounds do not show much consistency across fraction members in terms of similarity in critical or sensitive effects and potencies. There is no basis to identify a surrogate mixture or compound that is representative of the effects and potency of the fraction as a whole. Therefore, the compounds that resulted in the lowest RfDs were considered as the basis for indicator chemical selection (see Section 2.3).

6.1.1. Oral Noncancer Assessment Using the Indicator Chemical Method for the Aromatic High Carbon Range Fraction

The lowest oral subchronic and chronic RfD among the compounds in this fraction that are not screening values is the chronic RfD for BaP (see Tables 6 and 7); 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. Accordingly, the chronic RfD for BaP is listed in Table 6 as an available subchronic oral toxicity value for constituents in the aromatic high carbon range fraction. Subchronic and chronic toxicity values for several other PAHs in this fraction 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 may induce altered reproductive tract development (Kim et al., 2011), neurodevelopmental effects (Crepeaux et al., 2014, 2013, 2012), transgenerational changes in immune function (Chu et al.,

2013), 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 protective against 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 derivation in U.S. EPA (2017a).

The IRIS review of BaP (U.S. EPA, 2017b) cited Chen et al. (2012) as the principal study for the chronic RfD. The supplemental information for the toxicological review of BaP (U.S. EPA, 2017b) provided the following summary.

> *Chen et al. (2012) treated male and female neonatal Sprague-Dawley rats (10/sex/group) with benzo[a]pyrene (unspecified purity) dissolved in peanut oil by gavage daily on PNDs 5−11, at doses of 0.02, 0.2, or 2 mg/kg in 3 mL vehicle/kg body weight, determined individually based upon daily measurements. This time period was described as representing the brain growth spurt in rodents, analogous to brain developmental occurring from the third trimester to 2 years of age in human infants. Breeding was performed by pairs of 9-week-old rats, with delivery designated as PND 0. Litters were culled to eight pups/dam (four males and four females, when possible) and randomly redistributed at PND 1 among the nursing dams; dams themselves were rotated every 2−3 days to control for caretaking differences, and cage-side observations of maternal behavior were made daily. One male and female from each litter were assigned per treatment group, and the following physical maturation landmarks were assessed daily in all treatment groups until weaning at PND 21: incisor eruption, eye opening, development of fur, testis decent, and vaginal opening.*
>
> *Neonatal sensory and motor developmental tests were administered to pups during the preweaning period at PNDs 12, 14, 16, and 18, and were behavioral tests administered to rats as adolescents (PNDs 35 and 36) or as adults (PNDs 70 and 71): each rat was only tested during one developmental period. All dosing was performed from 1300 to 1600 hours, and behavioral testing was during the "dark" period from 1900 to 2300 hours, although tests were performed in a lighted environment. Pups were observed individually and weighed daily, the order of testing litters was randomized each day, and all observations were recorded by investigators blinded to group treatment.*
>
> *Sensory and motor developmental tests, including the surface righting reflex test, negative geotaxis test, and cliff aversion test, were performed only once, while the forelimb grip strength test was assessed during three 60-second trials on PND 12. Rat movements during the open-field test were recorded by camera, and two blinded investigators scored movement and rearing separately during a 5-minute evaluation period. Blinded investigators directly observed video monitoring of rat movements during the elevated plus maze, and after a 5-minute free exploration period, recorded number of entries into the closed and open arms, time spent in the open arms, and latency to the first arm entry. Assessment of the Morris water maze was slightly different, in that the rats were habituated to the testing pool by a 60-second swim without a platform on the day prior to testing. The rats were then tested during a 60-second swim with a hidden*

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

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

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

The elevated plus maze performance was only evaluated in adolescent and adult rats. Unlike the previous tests, 3-way ANOVA revealed a statistically significant interaction between neonatal benzo[a]pyrene treatment and sex, so male and female performance was analyzed independently. No significant differences in PND 35 males were observed, and the only significant observation in PND 35 females was increased time spent in the open maze arms by the 2 mg/kg-day treatment group. Significantly decreased latency time to first open arm entry was observed in PND 70 males and females in both 0.2 and 2 mg/kg-day treatment groups; these groups also spent significantly more time in open maze arms, along with the 0.02 mg/kg-day female group. At PND 70, the 2 mg/kg-day males, along with the 0.2 and 2 mg/kg-day females, entered more frequently into open arms and less frequently into closed arms than the vehicle controls. In the Morris water maze, escape latency (time to reach the platform during each of the four testing days) was consistently increased in the 2 mg/kg-day treatment

group of both sexes, in both adolescent and adult animals. These increases were statistically significant in both males and females treated with 2 mg/kg-day benzo[a]pyrene at both PNDs 39 and 74, and were also significantly elevated in 0.2 mg/kg-day animals of both sexes at PND 74. Likewise, performance during the 5th test day, in the absence of the escape platform, was significantly adversely affected by both metrics (decreased time spent in the target quadrant and decreased number of attempts to cross the platform location) in 2 mg/kg-day rats of both sexes at both PNDs 40 and 75. PND 75 females treated with 0.2 mg/kg-day benzo[a]pyrene also showed significant decreases in both performance metrics, while PND 75 0.2 mg/kg-day males only demonstrated significant differences in "time spent in target quadrant." Swim speed was also assessed, but there were no differences among any treatment group at either age evaluated.

6.1.2. Alternative Oral Noncancer Assessment Using the Hazard Index Method for the Aromatic Medium Carbon Range Fraction

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 existing analytical data be calculated and an HI for the mixture be developed using the calculated HQs.

For subchronic oral exposures, the subchronic RfDs or p-RfDs as shown in Table 6 can be used as the denominator in the HQ equations. 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 (see Table 6).

For chronic oral exposures, the chronic RfDs or p-RfDs as shown in Table 7 can be used as the denominator in the HQ equations. 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 (see Table 7).

6.2. DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

The available subchronic and chronic RfC values, with PODs, uncertainty factors, endpoints, and confidence ratings, are presented in Table 8. As shown in the table, there are two subchronic screening p-RfCs (1,1-biphenyl and BeP), one subchronic RfC (BaP), two chronic screening p-RfCs (1,1-biphenyl and BeP), and two chronic p-RfC or RfC values (naphthalene and BaP). Critical effects for the aforementioned RfCs include liver and kidney toxicity (1,1-biphenyl), nasal lesions (naphthalene), and developmental toxicity (BaP and BeP).

Table 8. Available RfC Values for Aromatic High Carbon Range Fraction (C10−C32, EC11−EC35)[a]

Indicator Chemical or Components	POD (mg/m^3)	POD Type (HEC)	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 (2017a)**
Benzo[*e*]pyrene (C20 [EC27.80]	0.0046	LOAEL	3,000	UF_A, UF_D, UF_H, 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	Low-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 (2017a)**

Table 8. Available RfC Values for Aromatic High Carbon Range Fraction (C10−C32, EC11−EC35)[a]

Indicator Chemical or Components	POD (mg/m^3)	POD Type (HEC)	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_D, UF_H, 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 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; U.S. EPA = U.S. Environmental Protection Agency.

As suggested by the disparity in critical endpoints and values of RfCs for fraction members and discussed in the following section, as well as in Appendix C, the available inhalation toxicity data for aromatic high carbon range compounds do not show much consistency across fraction members in terms of toxicological effects or potencies. Additionally, inhalation data are limited to four members of the fraction and one PAH mixture. There is no basis to identify a surrogate mixture or compound that is representative of the effects and potency of the fraction as a whole. Therefore, the compounds that resulted in the lowest RfCs were considered as the basis for indicator chemical selection (see Section 3).

6.2.1. Inhalation Noncancer Assessment the Indicator Chemical Method for the Aromatic High Carbon Range Fraction

The lowest RfC among the compounds in this fraction that is not a screening value is the chronic RfC for BaP (see Table 8); 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. Although a subchronic toxicity value is not available for BaP, the chronic RfC is based on a developmental exposure endpoint, so the RfC value is applicable to subchronic exposures as well. The few available 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, a mixtures study suggests that neurodevelopmental effects may occur at exposures lower than levels at which BaP induces toxicity (Slotkin et al., 2017), suggesting that use of BaP values for the whole fraction may be more appropriate than implied by comparisons limited to compounds with toxicity values. At this time, the database for members of this fraction and relevant mixtures that elicit neurodevelopmental effects is not comprehensive. Thus, BaP is considered an appropriate indicator because it has the lowest RfC among fraction members and the most comprehensive database. In addition, because neurodevelopmental effects are the critical effect for oral exposures to BaP, there is evidence that BaP can affect neurodevelopmental outcomes. 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 derivation in U.S. EPA (2017a).

The IRIS review of BaP (U.S. EPA, 2017a) cited Archibong et al. (2002) as the principal study for the chronic RfC. The supplemental information for the toxicological review of BaP (U.S. EPA, 2017b) provided the following summary.

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

showed a trimodal distribution (average of cumulative mass, diameter) <95%, 15.85 μm; 89%, <10 μm; 55%, <2.5 μm; and 38%, <1 μm (Inyang et al., 2003). Ramesh et al. (2001a) reported that the MMAD (± geometric SD) for the 55% mass fraction with diameters <2.5 μm was 1.7 ± 0.085. Progesterone, estradiol-17β, and prolactin concentrations were determined in plasma collected on GDs 15 and 17. Fetal survival was calculated as the total number of pups divided by the number of all implantation sites determined on GD 8. Individual pup weights and crown-rump length per litter per treatment were determined on PND 4 (PND 0 = day of parturition).

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

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

6.2.2. Alternative Inhalation Noncancer Assessment Using the Hazard Index Method for the Aromatic High Carbon Range Fraction

If the available analytical chemistry data quantify the concentrations of 1,1-biphenyl, naphthalene, BaP, or BeP 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-RfC for 1,1-biphenyl (0.004 mg/m^3), the p-RfC for 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 chronic RfCs or p-RfCs as shown in Table 8 can be used in the denominator of the HQ equations. 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.

6.3. SUMMARY OF NONCANCER PROVISIONAL REFERENCE VALUES

Table 9 summarizes the noncancer health reference values for indicator chemicals used when available analytical data and exposure estimates are limited to either air concentrations of, or oral exposure rates associated with, the whole fraction. When analytical results, air concentrations, or exposure rate measures for individual compounds with reference values are available, then the hazards associated with these compounds are assessed separately, using the HI approach and reference values reported in Tables 6, 7, and 8. The mass of those compounds is then subtracted from the total mass of the fraction, and the risks associated with the remaining mass are assessed using the values in Table 9.

Table 9. Summary of Noncancer Reference Estimates for Aromatic High Carbon Range (C10−C32, EC11−EC35) Fraction of TPHs

Toxicity Type (units); Indicator Chemical	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Reference
Subchronic p-RfD (mg/kg-d); Benzo[*a*]pyrene	Rat/M, F	Neuro-development	3×10^{-4}	$BMDL_{1SD}$	0.092	300	Chen et al. (2012) as cited in U.S. EPA (2017a)
Chronic p-RfD (mg/kg-d); Benzo[*a*]pyrene	Rat/M, F	Neuro-development	3×10^{-4}	$BMDL_{1SD}$	0.092	300	Chen et al. (2012) as cited in U.S. EPA (2017a)
Subchronic p-RfC (mg/m^3) Benzo[*a*]pyrene	Rat/M, F	Decreased embryo/fetal survival	2×10^{-6}	LOAEL (HEC)	0.0046	3,000	Archibong et al. (2002) as cited in U.S. EPA (2017a)

Table 9. Summary of Noncancer Reference Estimates for Aromatic High Carbon Range (C10−C32, EC11−EC35) Fraction of TPHs

Toxicity Type (units); Indicator Chemical	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Reference
Chronic p-RfC (mg/m^3) Benzo[*a*]pyrene	Rat/M, F	Decreased embryo/fetal survival	2×10^{-6}	LOAEL (HEC)	0.0046	3,000	Archibong et al. (2002) as cited in U.S. EPA (2017a)

$BMDL_{1SD}$ = lower confidence limit on benchmark dose using benchmark response of 1 standard deviation change from control mean; C = carbon; EC = equivalent carbon; F = female(s); HEC = human equivalent concentration; M = male(s); POD = point of departure; p-RfC = provisional inhalation reference concentration; p-RfD = provisional oral reference dose; TPH = total petroleum hydrocarbon; UF_C = composite uncertainty factor.

APPENDIX A. LITERATURE SEARCH AND SCREENING

Literature searches were conducted in February 2018 and updated in August 2021 for studies relevant to the derivation of provisional toxicity values for 44 constituents of the aromatic high carbon range fraction of total petroleum hydrocarbons (TPHs). This included the U.S. Environmental Protection Agency (U.S. EPA) initial list of 41 relevant chemicals and 6 additional chemicals identified in the search of the Provisional Peer-Reviewed Toxicity Value (PPRTV) database (total 47) less benzo[*a*]pyrene (BaP) and naphthalene that had chronic and subchronic health risk values on the Integrated Risk Information System (IRIS) and benzo[*e*]pyrene (BeP) that had PPRTV health risk values (see Table 3). Database searches for PubMed and Web of Science were conducted by an information scientist. Initial searches were date limited from 2007 to 2018. The records were stored using the U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. The PubMed database was searched using the HERO interface. The updated search was conducted similarly using the same search strings in PubMed and Web of Science from February 2018 through August 2021. There was an additional search of Agency for Toxic Substances and Disease Registry (ATSDR) and U.S. EPA documents for health risk values for fraction members.

The results of the PubMed searches were screened (title and abstract) for relevance using the Population, Exposure, Comparator, and Outcome (PECO) criteria outline in Table A-1. Full-text screening for relevance to hazard identification was performed using the refined PECO criteria shown in Table A-2.

Table A-1. PECO Criteria for Screening of TPH Constituent Literature Search Results

PECO Element	Inclusion Criteria
Population	Humans (any population) or laboratory mammals (any life stage)
Exposure	**Human**: Exposure to the subject material alone or as the primary component of a mixture, known or presumed to occur by oral, inhalation, and/or dermal routes. **Animal**: In vivo, exposure to the subject material alone, by oral or inhalation (including instillation) routes, for all durations of exposures (durations <28 days will be captured as supporting information), including any duration during gestation. Other routes of exposure will be captured as supporting information.
Comparison	**Human**: Includes any comparison/referent group (no exposure, lower exposure). **Animal**: Includes concurrent negative (untreated, sham-treated, or vehicle) control.
Outcomes	Assesses any cancer or noncancer endpoint in any tissue, organ, or physiological system.

PECO = Population, Exposure, Comparator, and Outcome; TPH = total petroleum hydrocarbon.

Table A-2. PECO Criteria for Relevance to Hazard Identification

PECO Element	Inclusion Criteria
Population	Humans (any population) or laboratory mammals (any life stage)
Exposure	**Human**: Exposure to the subject material alone or as the primary component of a mixture, known or presumed to occur by oral or inhalation routes. **Animal**: In vivo, exposure to the subject material alone, by oral or inhalation routes, for durations ≥28 days[a] or any duration during gestation.
Comparison	**Human**: Includes any comparison/referent group (no exposure, lower exposure). **Animal**: Includes concurrent negative (untreated, sham-treated, or vehicle) control.
Outcomes	Assesses any noncancer health outcome in any tissue, organ, or physiological system.

[a]It is noted that the PPRTV program often considers studies of shorter duration. However, given the database and the described relative potency of benzo[*a*]pyrene (which was selected as the indicator chemical), it is unlikely that a more sensitive endpoint than those captured in studies ≥28 days in duration will be identified in data from acute studies.

PECO = Population, Exposure, Comparator, and Outcome; PPRTV = Provisional Peer-Reviewed Toxicity Value.

APPENDIX B. COMPOSITION OF MIXTURES RELEVANT TO THE AROMATIC HIGH CARBON RANGE FRACTION

Table B-1 lists information on the 21-PAH mixture composition for the Weyand et al. (2004) oral carcinogenicity study. The composition of the 16-PAH mixture in the Crepeaux et al. (2014, 2013, 2012) oral neurodevelopmental toxicity studies is shown in Table B-2. Information on the composition of the 9-PAH mixture in the Yan et al. (2014) and Chu et al. (2013) inhalation developmental studies is provided in Table B-3.

Table B-1. Composition of PAH Mixture Tested in Dietary Carcinogenesis Study (Limited Noncancer Endpoints)[a]

Chemical	C	EC	Level in Diet (mg/kg food)	PAH Mix		PAH Mix with Benzo[*c*]fluorene	
				Dose (µg/mouse/d)	mg/Mouse over 260 d	Dose (µg/mouse/d)	mg/Mouse over 260 d
Indan	9	9.74	1.23	2.6	0.7	2.8	0.7
Naphthalene	10	11.57	80.8	170	43.7	186	48.7
2-Methylnaphthalene	11	12.72	26.8	56.2	14.5	61.5	16.1
1-Methylnaphthalene	11	12.77	14.2	29.7	7.7	32.5	8.5
Acenaphthylene	12	14.82	14.3	30	7.7	32.8	8.6
Acenaphthene	12	14.76	3.18	6.7	1.7	7.3	1.9
Dibenzofuran	12	13.24	4.53	9.5	2.4	10.4	2.7
Fluorene	13	15.68	11.9	25	6.5	27.4	7.2
Phenanthrene	14	18.37	25.3	53	13.7	58.1	15.2
Anthracene	14	18.43	7.25	15.2	3.9	16.7	4.4
Fluoranthene	16	21.11	15.9	33.4	8.6	36.6	9.6
Pyrene	16	22.45	18.1	37.9	9.8	41.5	10.9
Benz[*a*]anthracene	18	25.27	8.35	17.5	4.5	19.2	5
Chrysene	18	26.13	7.4	15.5	4	17	4.5
Benzo[*b*]fluoranthene	20	25.04	7.23	15.2	3.9	16.6	4.4
Benzo[*k*]fluoranthene	20	28.70	2.53	5.3	1.4	5.8	1.5
Benzo[*a*]pyrene	20	29.95	6.9	14.5	3.7	15.9	4.2
Indeno[1,2,3-*cd*]pyrene	22	32.62	4.98	10.4	2.7	11.4	3
Dibenz[*a*,*h*]anthracene	22	32.45	0.93	1.9	0.5	2.1	0.6
Benzo[*ghi*]perylene	22	30.37	5.73	12	3.1	13.2	3.5
Benzo[*c*]fluorene	17	21.45	5.6	–	–	13.6	3.6
Sum				561.5	144.7	628.4	164.8

[a]Weyand et al. (2004).

C = carbon; EC = equivalent carbon; PAH = polycyclic aromatic hydrocarbon.

Table B-2. Composition of 16-PAH Mixture Tested in Oral Neurodevelopmental Studies[a]

CASRN	Name	Rings	C	EC	Percent in 16-PAH Mixture (%)	PAH Dose in Low-Dose Mixture (mg/kg-d)	PAH Dose in High-Dose Mixture (mg/kg-d)
91-20-3	Naphthalene	1	10	11.57	17	0.00034	0.034
208-96-8	Acenaphthylene	2	12	14.82	1.5	0.00003	0.003
83-32-9	Acenaphthene	2	12	14.76	10	0.0002	0.02
86-73-7	Fluorene	2	13	15.68	2.5	0.00005	0.005
85-01-8	Phenanthrene	3	14	18.37	25	0.0005	0.05
120-12-7	Anthracene	3	14	18.43	3.5	0.00007	0.007
129-00-0	Pyrene	4	16	22.45	8.5	0.00017	0.017
206-44-0	Fluoranthene	3	16	21.11	11.5	0.00023	0.023
218-01-9	Chrysene	4	18	26.13	4	0.00008	0.008
56-55-3	Benzo[*a*]anthracene	4	18	25.27	2	0.00004	0.004
205-99-2	Benzo[*b*]fluoranthene	4	20	25.04	2.5	0.00005	0.005
207-08-9	Benzo[*k*]fluoranthene	4	20	28.70	2	0.00004	0.004
50-32-8	Benzo[*a*]pyrene	4	20	29.95	2.5	0.00005	0.005
193-39-5	Indeno(1,2,3-*c*,*d*)pyrene	5	22	32.62	6	0.00012	0.012
53-70-3	Dibenzo[*a*,*h*]anthracene	5	22	32.45	0.5	0.00001	0.001
191-24-2	Benzo[*ghi*]perylene	6	22	30.37	1	0.00002	0.002
Sum/mixture dose						0.002	0.2

[a]Crepeaux et al. (2014, 2013, 2012).

C = carbon; EC = equivalent carbon; PAH = polycyclic aromatic hydrocarbon.

Table B-3. Composition of PAH Aerosol Mixture Tested in Inhalation Developmental Studies[a]

CASRN	Name	Rings	C	EC	Percent in Mixture (%)	Mean Concentration (ng/m^3)	Mean Concentration (mg/m^3)
129-00-0	Pyrene	4	16	20.8	3.99	0.27	0.00027
218-01-9	Chrysene	4	18	26.13	5.13	0.42	0.00042
56-55-3	Benzo[*a*]anthracene	4	18	26.37	7.62	0.59	0.00059
205-99-2	Benzo[*b*]fluoranthene	4	20	30.14	1.79	0.15	0.00015
207-08-9	Benzo[*k*]fluoranthene	4	20	30.14	13.02	1.12	0.00112
50-32-8	Benzo[*a*]pyrene	4	20	31.34	4.82	0.35	0.00035
193-39-5	Indeno(1,2,3-*c*,*d*)pyrene	5	22	33.51	0.89	0.06	0.00006
53-70-3	Dibenzo[*a*,*h*]anthracene	5	22	33.92	7.42	0.64	0.00064
191-24-2	Benzo(*ghi*)perylene	6	22	34	54.59	3.69	0.00369
Sum/mixture concentration						7.29	0.00729

[a]Yan et al. (2014); Chu et al. (2013).

C = carbon; EC = equivalent carbon; PAH = polycyclic aromatic hydrocarbon.

APPENDIX C. POTENTIALLY RELEVANT NONCANCER EVIDENCE

In order to assess consistency in effects and potency across the components of the fraction, experimental data from compound-specific Integrated Risk Information System (IRIS) and Provisional Peer-Reviewed Toxicity Value (PPRTV) assessment documents and primary data sources (identified from literature searches) were used to create exposure-response arrays. Data were extracted only from studies meeting existing IRIS and PPRTV program standards that provided dose-response data enabling the identification of no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs). Target organ-specific NOAELs and LOAELs were determined using the following methodology.

1. Whenever possible, NOAELs and LOAELs were identified from existing IRIS or PPRTV assessments. For chemicals in which both types of assessments were available, preference was given to IRIS (in accordance with the U.S. Environmental Protection Agency [U.S. EPA] Office of Superfund Remediation and Technology Innovation [OSRTI] hierarchy of human health toxicity values for Superfund assessments). In general, these assessments explicitly identified NOAEL and LOAEL values only for the most sensitive target of toxicity.

2. All other target-organ-specific effect levels (i.e., for targets other than the most sensitive target identified in IRIS or PPRTV assessments, and all targets evaluated in newly identified studies) were determined using professional judgment, taking into consideration factors such as statistical significance (at a p-value < 0.05), biological significance (e.g., a greater than 10% increase in liver weight), magnitude and direction of change, and study quality. In the case of chemicals with existing IRIS or PPRTV assessments, NOAELs and LOAELs could often be identified from existing study summaries.

Dose-response data were presented in exposure-response arrays by health outcome and exposure route. From left to right, compounds exhibiting an effect typically are shown before those not exhibiting an effect, to enable identification of patterns. For compounds that do not exhibit an effect, NOAELs in the arrays are ordered by equivalent carbon (EC) number (low to high from left to right), with mixtures shown last. Both administered doses and exposure concentrations reported in the arrays and in the text reflect time-weighted average (TWA) exposures to facilitate comparisons across studies and compounds. Consistency across the fraction was evaluated by assessing if comparable outcomes were observed for members of the fraction, and if these effects were observed at similar dose levels.

Unless otherwise specified, the term “significant,” used throughout this appendix, refers to statistical significance at a p-value of <0.05.

BODY-WEIGHT EFFECTS

Decreased body-weight gain was the critical effect in the study used to derive the chronic reference dose (RfD) for naphthalene (U.S. EPA, 1998). No human studies examining body-weight effects of aromatic high carbon range compounds were identified in the sources reviewed. As shown in Table 5, animal studies that examined body-weight gain as an endpoint are available for nearly all of the compounds and mixtures with toxicity data; exceptions are benzo[*e*]pyrene [BeP], dibenzo[*def,p*]chrysene, and the 16- and 9-polycyclic aromatic hydrocarbon (PAH) mixtures. In this section, body-weight decreases of at least 10% relative to controls in adult animals are considered LOAELs, and smaller changes are not. For studies that reported body-weight gain but did not report absolute body weights, and for studies of maternal weight gain during gestation, statistically significant changes from control are described.

Animal Studies

Figures C-1, C-2, and C-3 show the effects of orally-administered aromatic high carbon range compounds on body weight following subchronic exposure, body weight following chronic exposure, and maternal body weight after gestational exposure, respectively. Data are available for 14 compounds, including compounds with carbon (C) numbers C10−C20. Body-weight decreases were observed after exposure to several compounds across the fraction, including naphthalene, 1,1-biphenyl, 1,2,4-triethylbenzene, fluorene, fluoranthene, and benzo[*a*]pyrene (BaP) (U.S. EPA, 2017a, b, 2013, 2012, 2011a; Tshala-Katumbay et al., 2006; U.S. EPA, 1998, 1990d). The lowest reported LOAELs (by compound) ranged from 0.7 mg/kg-day (BaP) to 1,500 mg/kg-day (fluoranthene) in subchronic studies (see Figure C-1). Body-weight data for chronic exposures were limited, with significant body-weight reductions reported for 1,1-biphenyl at a wide range of LOAELs (7−378 mg/kg-day in rats, ≥291 mg/kg-day in mice) (U.S. EPA, 2013) and for BaP at a LOAEL of 21 mg/kg-day in rats (U.S. EPA, 2017a, b). No body-weight effects were reported after chronic exposure for the remaining tested compounds (see Figure C-2). In gestational studies, the lowest reported LOAELs, for reduced maternal body weight or body-weight gain, were 150 mg/kg-day for naphthalene and 1,000 mg/kg-day for 1,1-biphenyl. No body-weight effects were reported after gestational exposure for the remaining tested compounds (see Figure C-3).

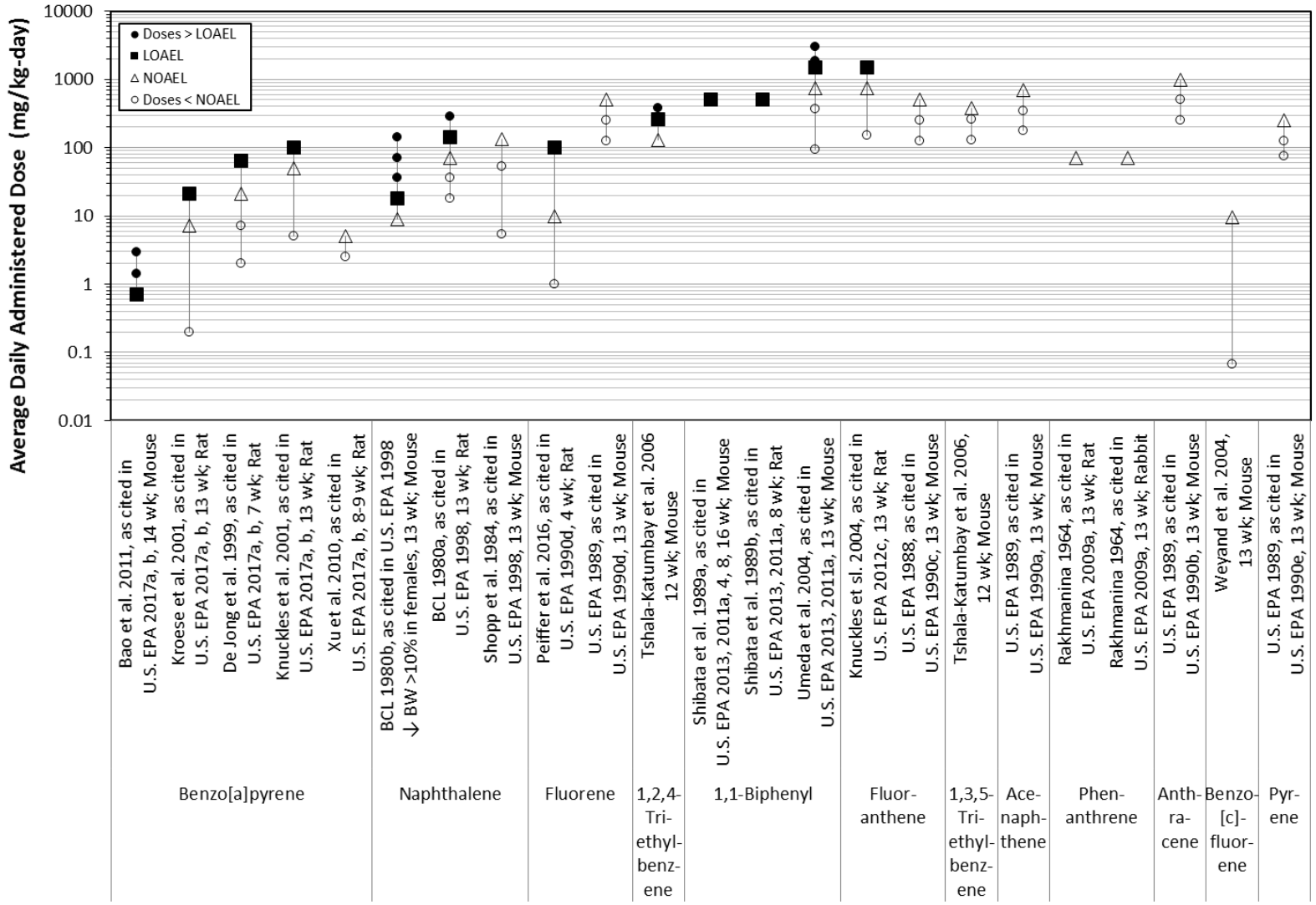


Figure C-1. Body-Weight Effects in Animals after Subchronic (4–16 Weeks) Oral Exposure to Aromatic High Carbon Range Compounds

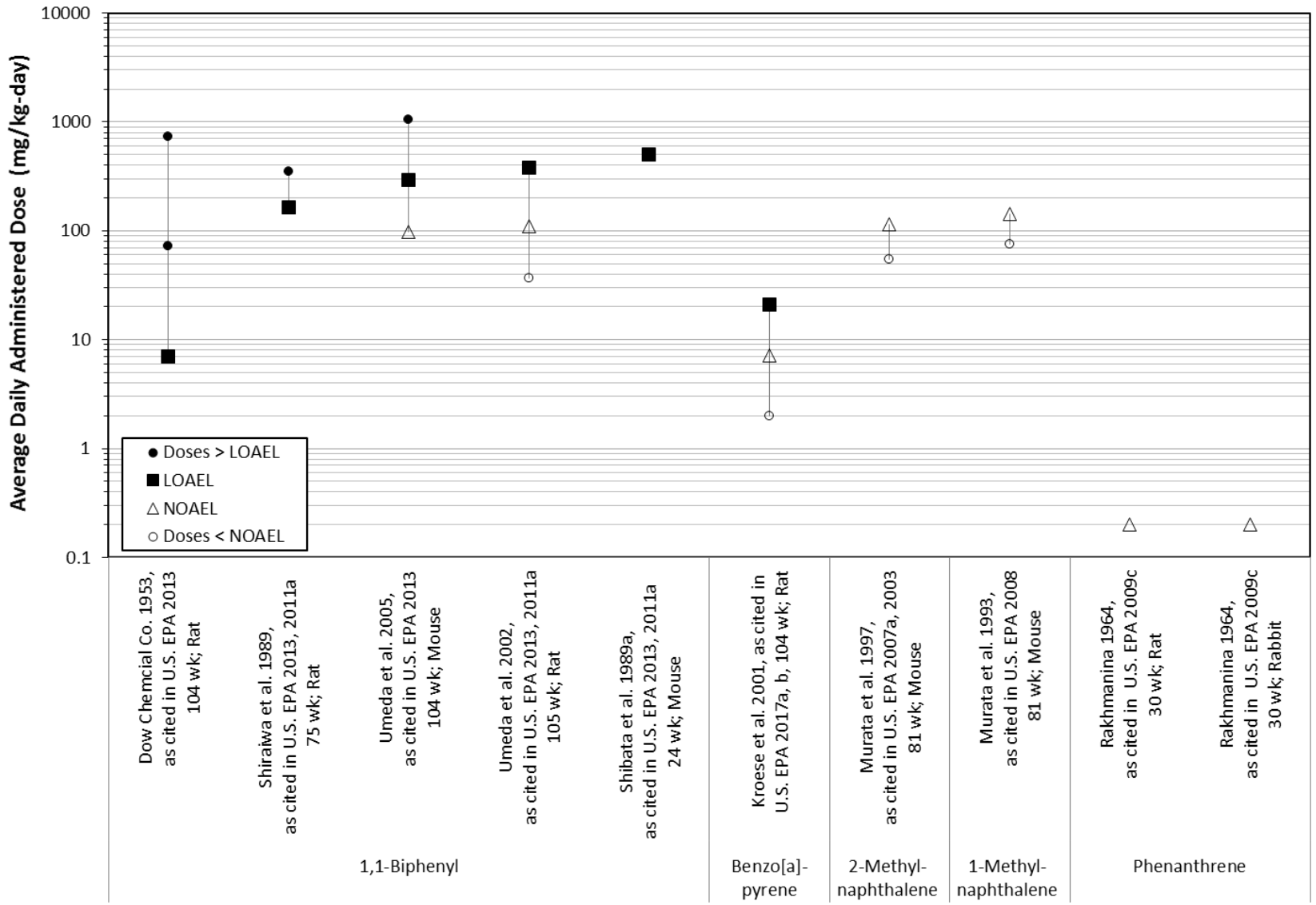


Figure C-2. Body-Weight Effects in Animals after Chronic (≥24 Week) Oral Exposure to Aromatic High Carbon Range Compounds

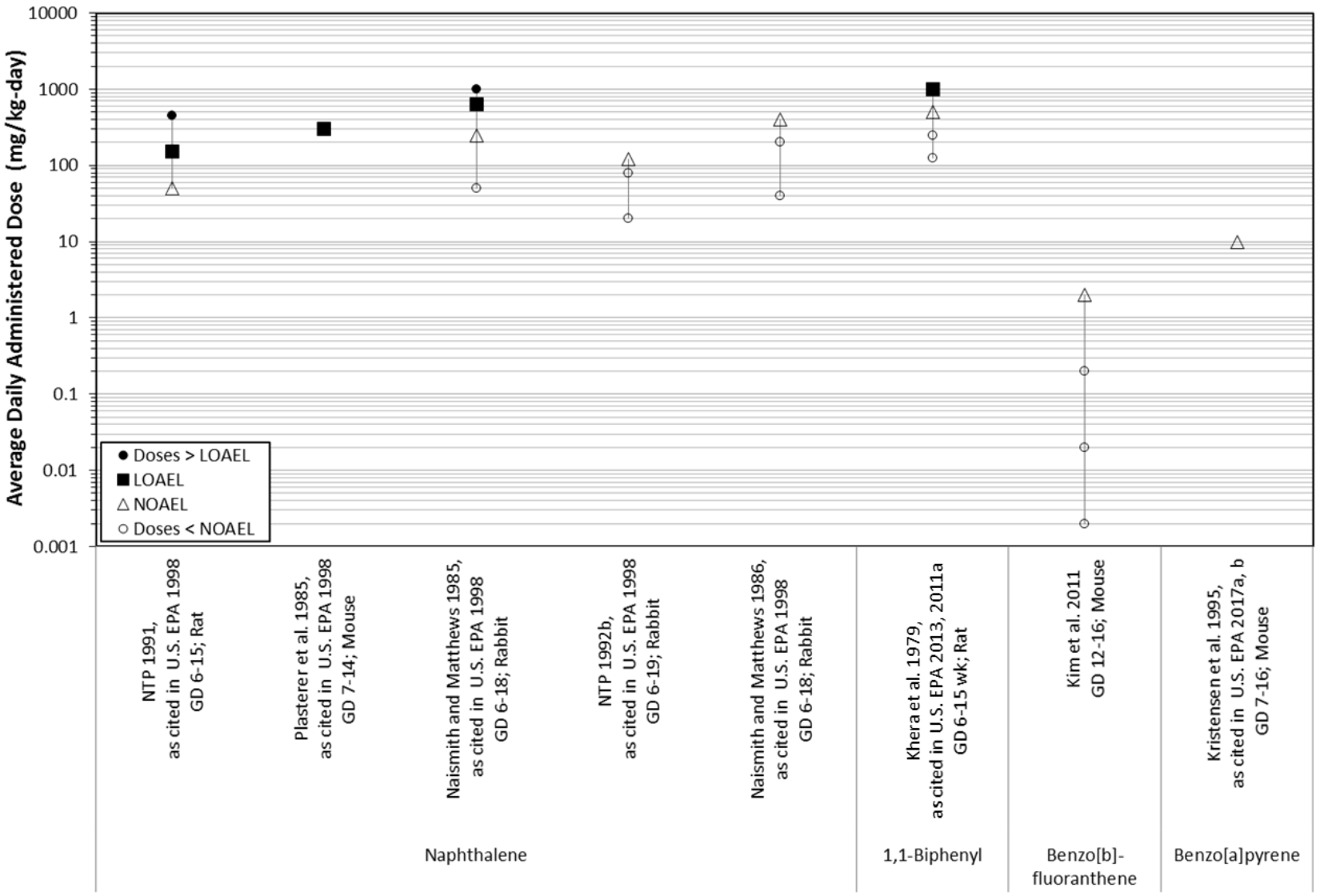


Figure C-3. Maternal Body-Weight Effects in Animals after Gestational Oral Exposure to Aromatic High Carbon Range Compounds

Data for body-weight effects following oral exposure to mixtures are available from one study (not included in the body-weight exposure-response graphs). In this study, no body-weight effects were noted in mice exposed to a 21-PAH mixture with or without benzo[*c*]fluorene in the diet for 37 weeks at doses of approximately 15−17 mg/kg-day (Weyand et al., 2004).

Body-weight data following inhalation exposure were only available for four aromatic high carbon range compounds with carbon numbers C10−C20: naphthalene, 1,1-biphenyl, 2-methylnaphthalene, and BaP. An exposure-response graph to compare potencies across compounds was not included due to limited data. Decreased body weight was reported in rats exposed to 1,1-biphenyl at 60 mg/m^3, a concentration associated with 50% mortality. Mice and rabbits exposed to similar concentrations did not show body-weight effects (or changes in survival) (U.S. EPA, 2013). No body-weight effects were reported following inhalation exposure to other tested compounds (U.S. EPA, 2017a, b; Dodd et al., 2012; Swiercz et al., 2011; ATSDR, 2005; U.S. EPA, 1998).

Summary of Potentially Relevant Evidence

No human data are available for body-weight effects. Compounds across the aromatic high carbon range fraction have been shown to reduce body weights in rats, mice, and rabbits following oral exposure. Compounds associated with body-weight effects following oral route exposures include carbon numbers C10 (naphthalene) to C20 (BaP), with naphthalene having the lowest LOAEL following gestational exposure, BaP having the lowest LOAEL following subchronic exposure, and 1,1-biphenyl (C12) having the lowest LOAEL following chronic exposure. Compounds not associated with body-weight effects also spanned the high carbon range, including carbon numbers C11 (1,3,5-triethylbenzene) to C20 (benzo[*b*]fluoranthene). Taken together, these data suggest that oral exposure to many aromatic high carbon range fraction compounds can cause decreases in body weight, but no apparent pattern of sensitivity is observed based on number of carbons or ring structure. Available inhalation data do not report body-weight effects following inhalation exposure to naphthalene, 1,1-biphenyl, 2-methylnaphthalene, or BaP at nonlethal concentrations.

HEMATOLOGICAL EFFECTS

Decreased red blood cells (RBCs), hemoglobin (Hb), and packed cell volume (PCV) were the critical effects in the study used to derive the chronic reference dose (RfD) for fluorene (U.S. EPA, 1997, 1990d). Hematological alterations (decreased PCV) were also considered cocritical effects in the study used to derive the chronic RfD for fluoranthene (U.S. EPA, 1990c). Human data pertaining to hematological effects of aromatic high carbon range fraction members are limited primarily to case reports of naphthalene exposure. As shown in Table 5, data on hematological effects in animals were located for 10 members of the fraction.

Human Studies

Hemolytic anemia has been reported in adults, children, and neonates exposed to naphthalene by ingestion, inhalation, and dermal contact with clothes and bedding impregnated with naphthalene from moth balls (ATSDR, 2005; U.S. EPA, 1998). It has also been reported in newborns exposed transplacentally during pregnancy. Blood samples from patients with anemia exhibited reduced Hb, hematocrit (Hct), and RBC values and increased reticulocytes, Heinz bodies, serum bilirubin, and fragmented RBCs. Hemolytic anemia was accompanied by jaundice, cyanosis, and kernicterus with neurological signs in severe cases (U.S. EPA, 1998). Individuals with a deficiency in the enzyme, glucose-6-phosphate dehydrogenase (G6PDH), are particularly

susceptible to naphthalene-induced hemolytic anemia (ATSDR, 2005; U.S. EPA, 1998). No data are available regarding potential hematological effects in humans for other members of the fraction.

Animal Studies

Hemolytic anemia was reported in one dog given a single oral dose of 1,525 mg/kg naphthalene in food and in another given 263 mg/kg-day naphthalene in food for 7 days (ATSDR, 2005). These data provide limited evidence of hemolytic anemia in dogs following acute or short-term exposure to naphthalene at high doses. Studies in rats and mice did not find evidence of hemolytic anemia following acute naphthalene exposure (ATSDR, 2005). Figure C-4 shows the effects of orally-administered naphthalene and other aromatic high carbon range compounds on hematological parameters in subchronic and chronic animal studies (studies available only in rodents). Data are available for 10 compounds, including compounds with carbon numbers C10−C20. Hematological alterations were seen with several compounds across the fraction following subchronic oral exposure, including decreases in RBC, Hct/PCV, and/or Hb (BaP, fluorene, fluoranthene) and inconsistent alterations in white blood cell (WBC) populations (naphthalene, fluoranthene, acenaphthene) (U.S. EPA, 2017a, b, 2012, 1998, 1990a, c, d). The lowest LOAELs (by compound) for RBC effects ranged from 7.1 to 250 mg/kg-day, and the lowest LOAELs for WBC effects ranged from 143 to 1,500 mg/kg-day. No hematological alterations were observed following subchronic oral exposure to pyrene or anthracene (NOAELs of 250 and 1,000 mg/kg-day, respectively) (U.S. EPA, 1990b, e). Chronic oral data are limited to three compounds (1-methylnaphthalene, 2-methylnaphthalene, 1,1-biphenyl), none of which showed hematological effects (see Figure C-4) (U.S. EPA, 2013; ATSDR, 2005).

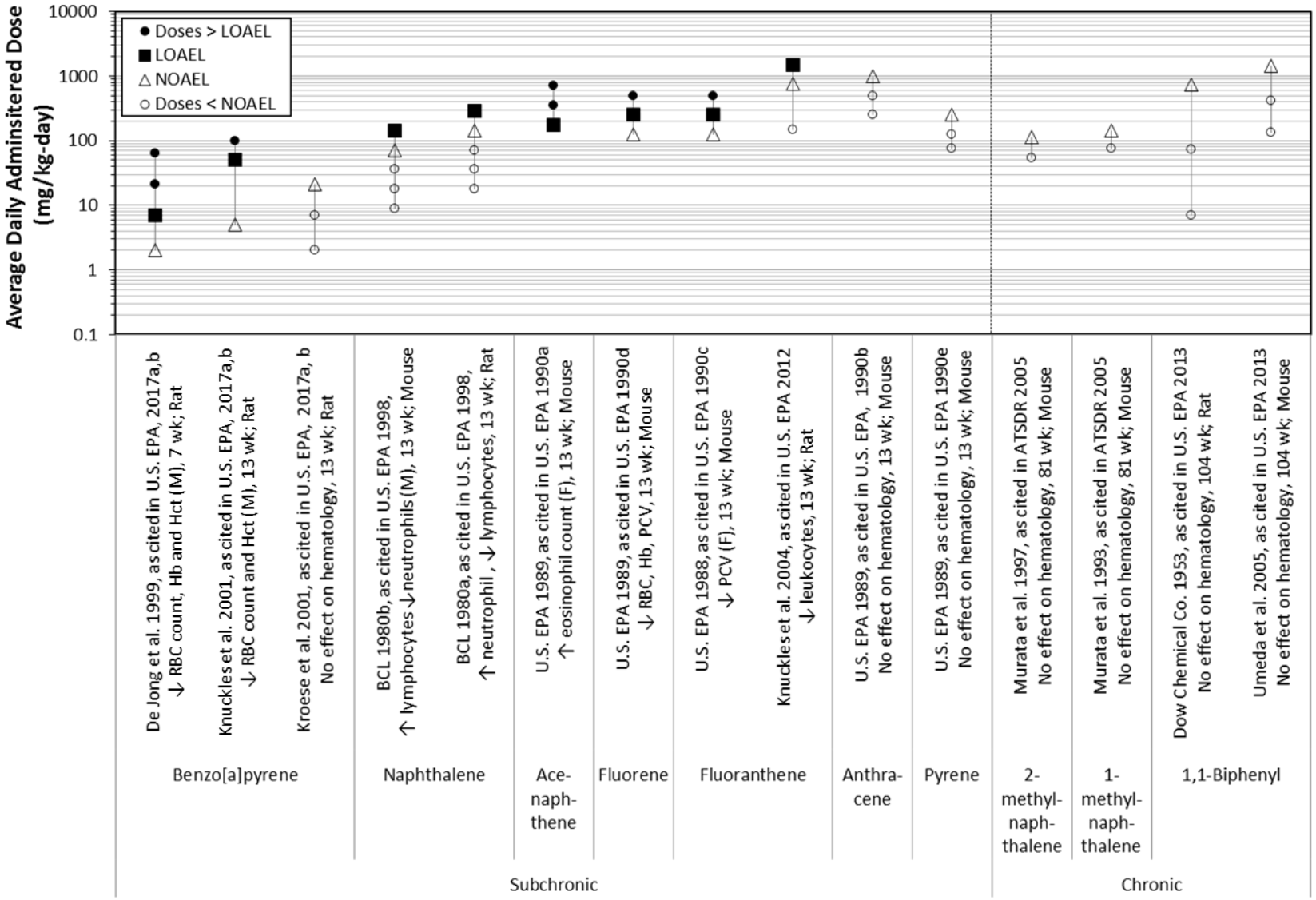


Figure C-4. Hematological Effects in Animals after Oral Exposure to Aromatic High Carbon Range Compounds

Data pertaining to the effects of inhalation exposure to aromatic high carbon range compounds on hematological parameters are limited to naphthalene and 2-methylnaphthalene. An exposure-response graph to compare potencies across compounds was not included due to the limited data. In contrast to effects seen after oral exposure to fraction components, stimulation of the hematopoietic system was observed following inhalation exposure to 2-methylnaphthalene at concentrations ranging from 0.4 to 8.9 mg/m^3 for 4 weeks (Swiercz et al., 2011). Observed effects included exposure-related trends for increased RBC counts, Hct, and Hb in male rats, as well as increased reticulocyte abundance in male and female rats. No exposure-related changes in hematological parameters were observed in mice following exposure to naphthalene at 28 mg/m^3 for 2 weeks (ATSDR, 2005; U.S. EPA, 1998).

Summary of Potentially Relevant Evidence

Available human data indicate that acute exposures to high levels of naphthalene via oral, inhalation, or dermal routes may cause hemolytic anemia, particularly in individuals with G6PDH enzyme deficiency. Available animal data indicate that dogs, but not rodents, may also be susceptible to hemolytic anemia following acute oral exposure to naphthalene. Data in laboratory animals indicate that anemia (decreased RBC count, Hct/PCV, and/or Hb) may occur following subchronic oral exposure to compounds from across the high fraction, including BaP, fluorene, and fluoranthene (C13−C20). Data regarding potential alterations in WBC parameters following oral exposure are inconsistent between and within studied fraction members (see Figure C-4). Too few studies are available to evaluate effects and potencies in animals after inhalation exposure. Taken together, the data indicate that oral exposure to some aromatic high carbon range fraction compounds may result in anemia, and effects may be severe in humans following acute exposure to high levels of naphthalene via any route.

NEUROLOGICAL EFFECTS

Clinical signs of toxicity in pregnant dams, including central nervous system (CNS) depression, are the critical effects for the intermediate minimal risk level (MRL) for naphthalene (ATSDR, 2005). Neurodevelopmental effects are the critical effect for the chronic RfD for BaP; however, these effects are discussed below in the developmental section. Neurological effects in humans have been studied in coke oven workers exposed to complex PAH mixtures and workers exposed to 1,1-biphenyl during production of 1,1-biphenyl-impregnated fruit wrapping paper. As shown in Table 5, data on neurological effects in animals were identified for 12 members of the fraction; however, the studies varied widely with respect to the nature of the neurological endpoints evaluated.

Human Studies

Neurobehavioral examinations of coke oven workers exposed to complex PAH mixtures demonstrated impairments in short-term memory and attention and deficits in sensorimotor coordination, and some effects were directly correlated with measured air levels of BaP (U.S. EPA, 2017a, b). Occupational workers exposed to 1,1-biphenyl in Finland had abnormal electroencephalography (EEG), nerve conduction velocity, and electromyographic (EMG) test results. A study of similarly exposed workers in Sweden did not demonstrate neurological test abnormalities; however, an increase in the relative risk of Parkinson's disease was reported (U.S. EPA, 2013).

Animal Studies

Figure C-5 shows the effects of subchronic oral exposure to aromatic high carbon range compounds on neurological parameters. Subchronic data are available for eight compounds, including compounds with carbon numbers C10−C20. Neurobehavioral alterations and/or clinical signs of neurotoxicity were observed with several compounds across the fraction, including BaP (impaired learning and memory, decreased activity), naphthalene (clinical signs, including CNS depression), fluorene (impaired learning, clinical signs), and 1,2,4-triethylbenzene (impaired gait, muscular weakness) (U.S. EPA, 2017a, b; Peiffer et al., 2016; Tshala-Katumbay et al., 2006; U.S. EPA, 1998, 1990d). The lowest LOAELs (by compound) ranged from 2 to 114 mg/kg-day. Peripheral nerve damage was associated with observed impaired gait and muscular weakness in mice following exposure to 1,2,4-triethylbenzene at ≥129 mg/kg-day (Tshala-Katumbay et al., 2006). Impaired sensory and motor nerve conduction were also observed in rats following subchronic oral exposure to 1,2,4-triethylbenzene at ≥114 mg/kg-day (Gagnaire et al., 1993). However, no changes in peripheral nerve conduction or histology were observed in rats or mice similarly exposed to 1,3,5-triethylbenzene at doses up to 257 or 386 mg/kg-day, respectively (Tshala-Katumbay et al., 2006; Gagnaire et al., 1993). Histopathological findings in the peripheral nervous system (PNS) were not observed following subchronic oral exposure to fluoranthene or acenaphthene at doses of 500 and 700 mg/kg-day, respectively (U.S. EPA, 1990a, c). No changes in CNS histology were observed in animals following subchronic oral exposure to any tested compound (see Figure C-5). Decreased brain weight was observed following subchronic oral exposure to naphthalene at 133 mg/kg-day (U.S. EPA, 1998), but not following subchronic exposure to acenaphthene, anthracene, or fluorene (Peiffer et al., 2016; U.S. EPA, 1990a, b).

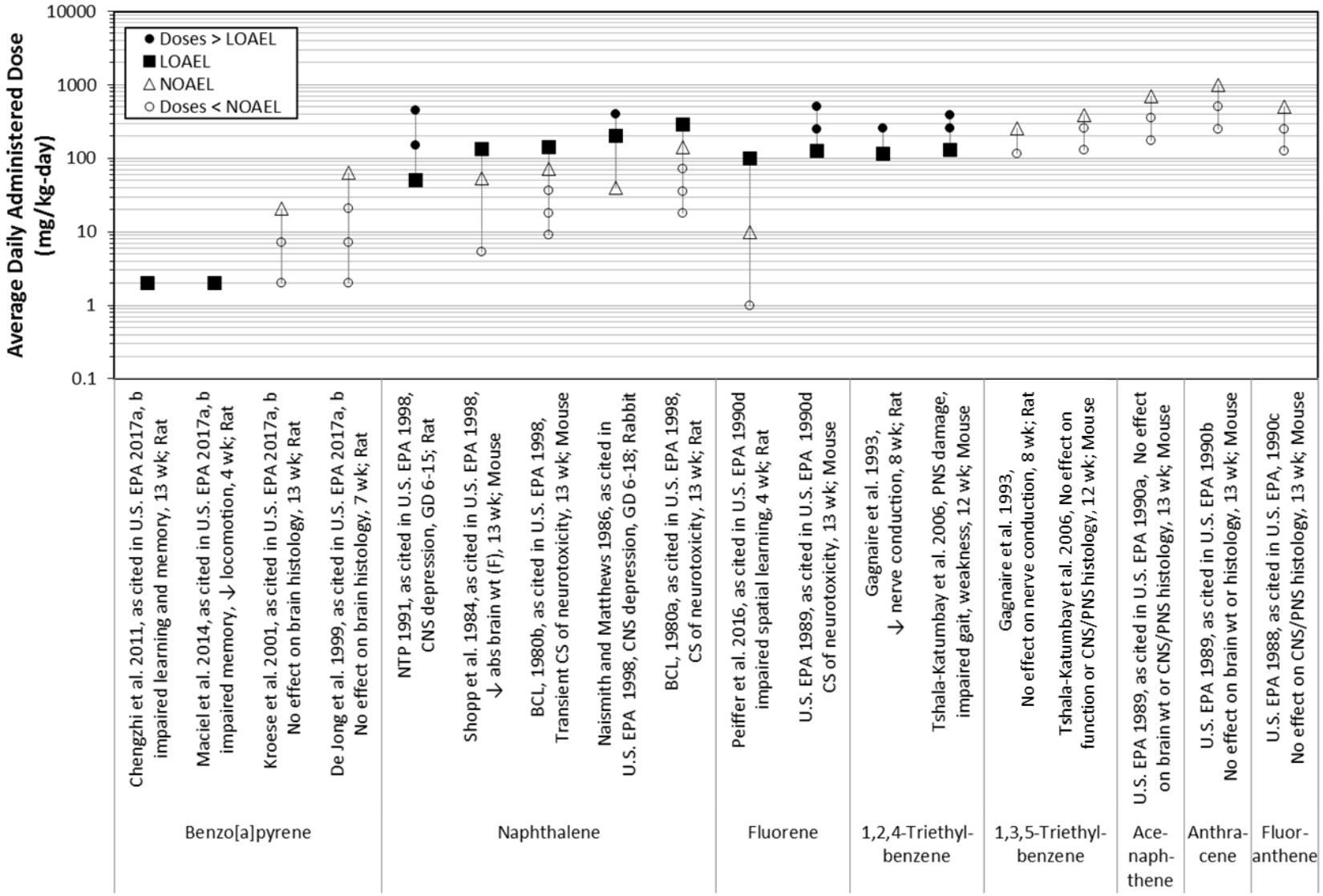


Figure C-5. Neurological Effects in Animals after Subchronic Oral Exposure to Aromatic High Carbon Range Compounds

No adverse neurological effects were observed in a limited number of chronic oral studies; therefore, chronic data are not included in Figure C-5. No changes in brain weight or histology were observed following chronic exposure to 1,1-biphenyl at doses up to 1,420 mg/kg-day, 1-methylnaphthalene at doses up to 144 mg/kg-day, or 2-methylnaphthalene at doses up to 114 mg/kg-day (U.S. EPA, 2013, 2011a, 2008, 2007a, 2003). No changes in PNS histology were observed following chronic exposure to 1,1-biphenyl at doses up to 1,420 mg/kg-day (U.S. EPA, 2013, 2011a). Neurological function was not evaluated in available chronic oral studies.

No data pertaining to neurological function were located following inhalation exposure to aromatic high carbon range compounds. No histopathological changes were observed in the brain following subchronic exposure to 2-methylnaphthalene at concentrations up to 8.9 mg/m^3 or chronic exposure to naphthalene at concentrations up to 56 mg/m^3 (Swiercz et al., 2011; ATSDR, 2005). An exposure-response graph to compare potencies across compounds was not included due to limited data.

Summary of Potentially Relevant Evidence

Human evidence suggests that occupational exposure to PAH mixtures containing members of the aromatic high carbon range fraction, namely BaP, may alter neurobehavior, and occupational exposure to 1,1-biphenyl may damage nerve function. Available animal data show that oral exposure to compounds from across the aromatic high carbon range fraction (C10−C20) can alter neurobehavior in animals, including BaP, naphthalene, fluorene, and 1,2,4-triethylbenzene. Other effects reported in animal studies of one or more compounds include clinical signs of neurotoxicity, peripheral nerve damage, and decreased brain weight. Available data are too limited to assess potential neurological effects in animals following inhalation exposure. Considering human and animal evidence together, the available data indicate that some members of the aromatic high carbon range fraction induce neurological effects. BaP appears to be the most potent neurotoxicant, as the LOAEL for BaP is 1−2 orders of magnitude lower than the lowest LOAELs observed for other compounds see Figure C-5). However, there are a number of compounds within the aromatic high carbon range fraction that have not been evaluated for sensitive measures of neurological function, particularly 1,1-biphenyl. Additionally, no NOAEL values for neurofunctional endpoints were identified for BaP (however, there are BaP studies that did not report neurological effects at higher doses) or 1,2,4-triethylbenzene.

HEPATIC EFFECTS

Hepatic effects are the critical endpoints for the subchronic p-RfD and chronic RfD for acenaphthene (U.S. EPA, 2011b) and the intermediate MRL for fluorene (ATSDR, 1995), and cocritical effects for the chronic RfD for fluoranthene (U.S. EPA, 1990c), and the subchronic provisional reference concentration (p-RfC) and chronic p-RfC for 1,1-biphenyl (U.S. EPA, 2011a). Critical hepatic effects of exposure included increased liver weight and hepatocellular hypertrophy for acenaphthene, increased liver weight for fluorene, and liver congestion and edema for 1,1-biphenyl. Human data pertaining to the hepatotoxicity of aromatic high carbon range fraction members are limited to a single case study of hepatotoxicity following occupational exposure to 1,1-biphenyl. As shown in Table 5, data on hepatic effects in animals were located for 11 members of the fraction. In general, the hepatic endpoints evaluated in the studies were liver weight and histology, with most studies also measuring clinical chemistry.

Human Studies

A case report of a female worker exposed to 1,1-biphenyl indicated the presence of chronic hepatitis. The diagnosis was suggested by the presence of hepatomegaly and altered clinical chemistry findings and was confirmed by liver biopsy. Neutrophilic leukocytosis was also reported, suggesting an immunological or inflammatory response to liver injury. Serum enzymes returned to normal following cessation of exposure to 1,1-biphenyl (U.S. EPA, 2013).

Animal Studies

Figures C-6 and C-7 show the effects of orally-administered aromatic high carbon range compounds on liver weight and histology, respectively. Data are available for 11 compounds, including compounds with carbon numbers C10−C20[4]. Hepatic alterations were observed with several compounds across the fraction, including naphthalene, 1,1-biphenyl, acenaphthene, fluorene, fluoranthene, and BaP (U.S. EPA, 2017a, b; Peiffer et al., 2016; U.S. EPA, 2013, 2012, 2011b, 1998, 1990c, d). The most sensitive and commonly observed effect following subchronic exposure was increased liver weight, with the lowest LOAELs (by compound) ranging from 7.1 to 2,989 mg/kg-day for all compounds listed above except naphthalene, which caused decreased liver weight at 133 mg/kg-day (see Figure C-6). No liver-weight effects were observed following subchronic exposure to anthracene at doses up to 1,000 mg/kg-day (U.S. EPA, 1990b). Liver-weight data for chronic oral exposure are limited to 1,1-biphenyl, 1-methylnaphthalene, and 2-methylnaphthalene. Increased liver weight was observed following chronic exposure to 1,1-biphenyl at 732 mg/kg-day (U.S. EPA, 2013), but not following chronic oral exposure to 1- or 2-methylnapthanene at doses up to 114−144 mg/kg-day (U.S. EPA, 2008, 2007a).

[4]Based on the U.S. EPA PPRTV for BeP, no short-term, subchronic, chronic, or reproductive and developmental toxicity studies of BeP in humans or animals exposed by oral or inhalation routes were adequate for the derivation of a toxicity value. The toxicity values for BeP are based on a read-across approach that used BaP as a surrogate.

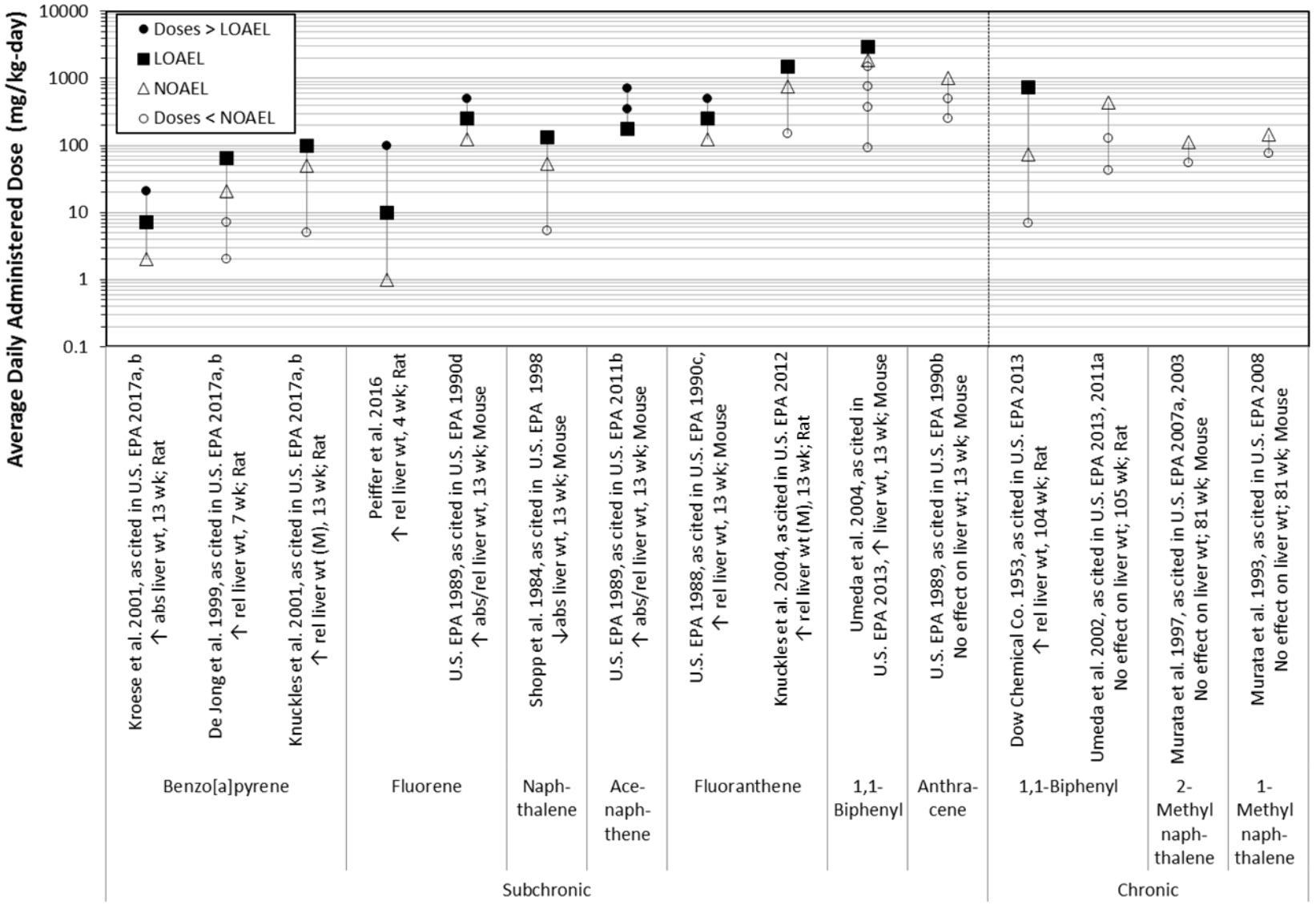


Figure C-6. Liver-Weight Effects in Animals after Oral Exposure to Aromatic High Carbon Range Compounds

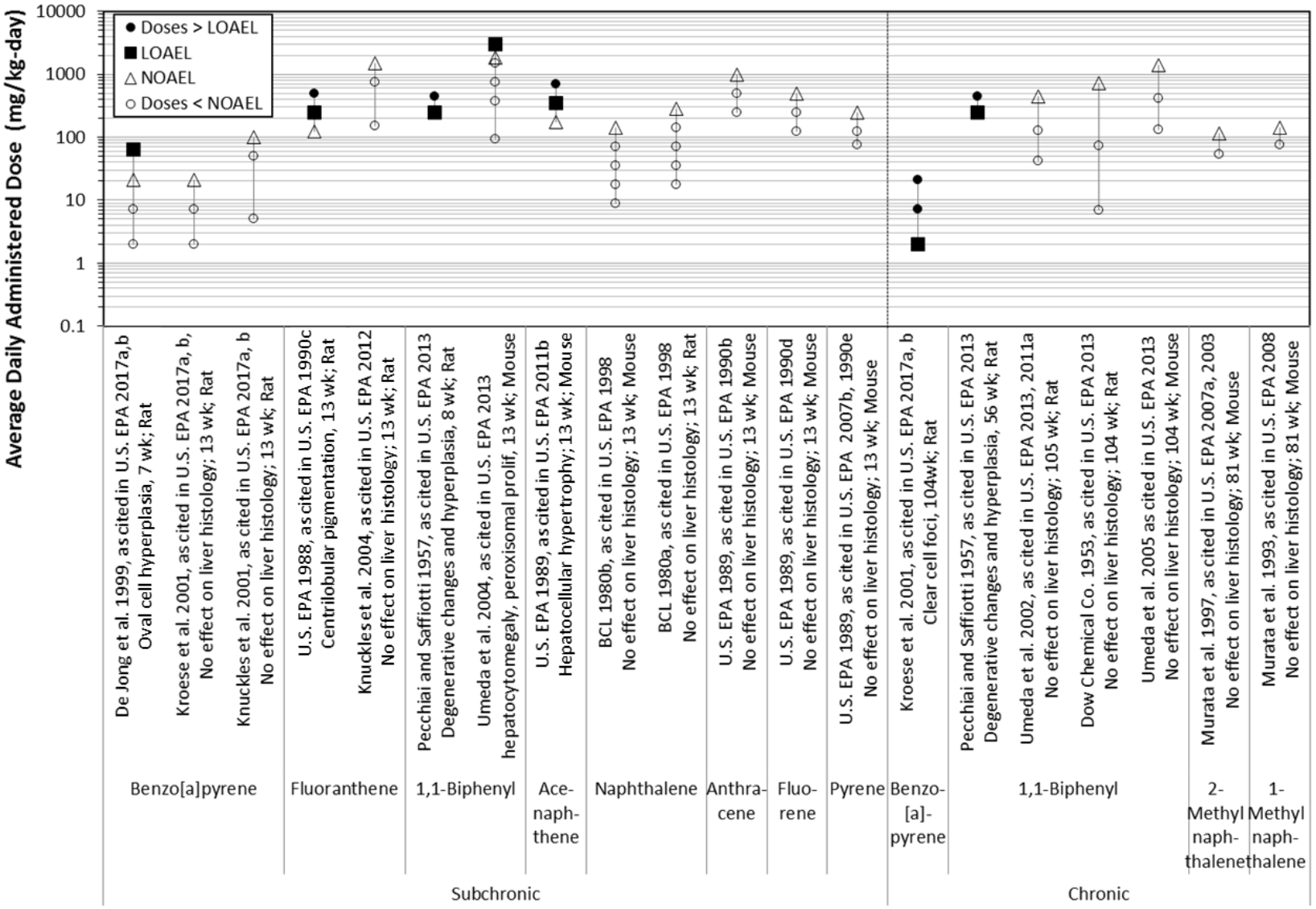


Figure C-7. Liver Histology Effects in Animals after Oral Exposure to Aromatic High Carbon Range Compounds

Histopathological lesions were reported following oral exposure to BaP, fluoranthene, 1,1-biphenyl, and acenaphthene, but findings were generally proliferative effects associated with enzyme induction and were often inconsistent between studies for the same compound. Oval cell hyperplasia was reported in rats following exposure to BaP for 7 weeks at 64 mg/kg-day, but no effects were reported following 13-week exposure to BaP doses up to 100 mg/kg-day (U.S. EPA, 2017a, b). Following chronic exposure to BaP, clear cell foci were observed at ≥2 mg/kg-day (U.S. EPA, 2017a, b). For 1,1-biphenyl, degenerative changes and hepatic hyperplasia were reported in rats at doses ≥250 mg/kg-day for 8 or 56 weeks and hepatocellular hypertrophy and peroxisomal proliferation were observed in mice exposed at 2,989 mg/kg-day for 13 weeks, but no treatment-related liver lesions were observed after exposure for 104 weeks at doses up to 732 and 1,420 mg/kg-day in rats and mice, respectively (U.S. EPA, 2013). Hepatocellular hypertrophy was also reported following exposure to acenaphthene at ≥350 mg/kg-day for 13 weeks (U.S. EPA, 2011b). For fluoranthene, centrilobular pigmentation was reported in mice exposed at ≥250 mg/kg-day for 13 weeks, but not in similarly exposed rats at doses up to 1,500 mg/kg-day (U.S. EPA, 2012, 1990c). No histopathological hepatic lesions were noted following exposure to naphthalene, 1-methylnaphthalene, 2-methylnaphthalene, pyrene, fluorene, or anthracene (see Figure C-7).

Increased plasma aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) were observed in mice (but not rats) exposed to 1,1-biphenyl or fluoranthene at oral doses ≥414 mg/kg-day (U.S. EPA, 2013, 1990c), and increased total cholesterol was observed in mice exposed to acenaphthene at doses ≥350 mg/kg-day (U.S. EPA, 2011b). No significant alterations in hepatic serum chemistry were observed following subchronic exposure to BaP, naphthalene, pyrene, fluorene, or anthracene, or chronic exposure to 1-methylnaphthalene or 2-methylnaphthalene (U.S. EPA, 2017a, b, 2007a, b, 2003, 1998, 1990b, d, e). An exposure-response graph to compare potencies across compounds was not included due to lack of exposure-related effects in the majority of tested compounds.

Figure C-8 shows the effects of inhalation exposure to aromatic high carbon range compounds on hepatic endpoints. Data are available only for naphthalene, 2-methylnaphthalene, and 1,1-biphenyl, which represent compounds with carbon numbers C10−C12. Hepatic alterations were reported following subchronic exposure to 2-methylnaphthalene at ≥1.8 mg/m^3 (decreased liver weight, altered serum chemistry, and bile duct hyperplasia) (Swiercz et al., 2011) and 1,1-biphenyl at ≥32.9 mg/m^3, which was the lowest concentration tested (liver congestion and edema) (U.S. EPA, 2013). No histopathological hepatic findings were reported following chronic exposure to naphthalene at concentrations up to 28 and 56 mg/m^3 in mice and rats, respectively (ATSDR, 2005; U.S. EPA, 1998).

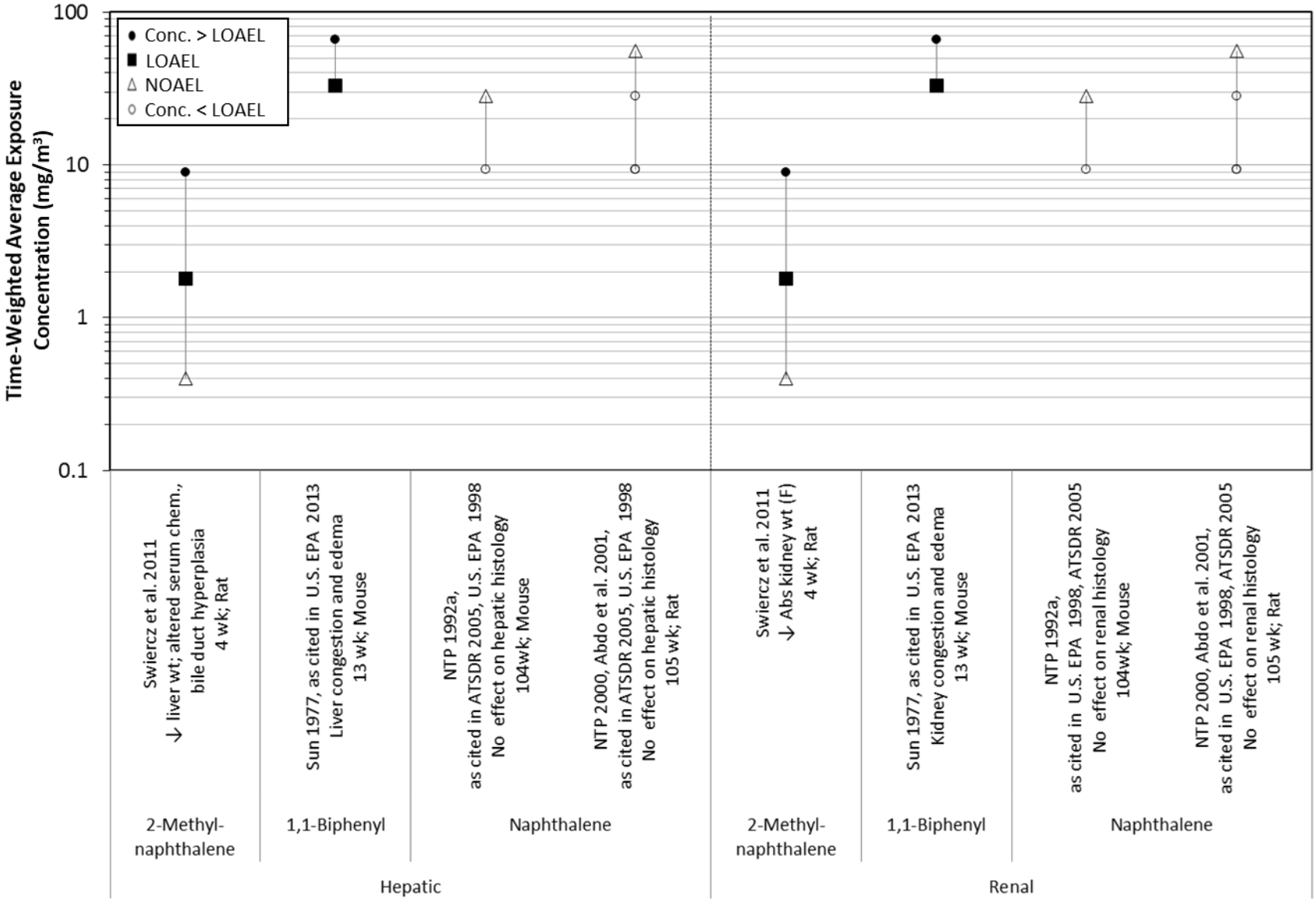


Figure C-8. Liver and Renal Effects in Animals after Inhalation Exposure to Aromatic High Carbon Range Compounds

Summary of Potentially Relevant Evidence

Human data are inadequate to assess potential hepatotoxic effects of aromatic high carbon range compounds. In animals, hepatic effects were primarily elevated liver weights following oral exposure to compounds from across the aromatic high carbon range fraction (C11−C20), with inconsistent evidence of histopathological damage for some compounds at higher doses (generally proliferative effects). A few compounds showed altered serum chemistry values at high oral doses. In aggregate, the data suggest that many aromatic high carbon range fraction compounds can produce increases in rodent liver weight following oral exposure, which is sometimes accompanied by serum chemistry and/or histological changes. No apparent pattern of sensitivity is observed based on number of carbons or ring structure. Available data are too limited to assess potential hepatic effects in animals following inhalation exposure.

RENAL/BLADDER EFFECTS

Renal effects are the critical endpoints for the subchronic p-RfDs for pyrene and fluoranthene (U.S. EPA, 2012, 2007b) and the chronic RfDs for 1,1-biphenyl and pyrene (U.S. EPA, 2013, 1990e), and cocritical effects for the chronic RfD for fluoranthene (U.S. EPA, 1990c) and the subchronic p-RfC and chronic RfC for 1,1-biphenyl (U.S. EPA, 2011a). Critical renal effects of exposure included renal tubular nephropathy (pyrene, fluoranthene), renal mineralization (1,1-biphenyl), and decreased kidney weights (pyrene). No human studies examining renal or bladder effects of aromatic high carbon range compounds were identified in the sources reviewed. As shown in Table 5, data on renal and/or bladder effects in animals were located for 10 members of the fraction. In general, the renal endpoints evaluated in the studies were kidney weight and histology, with some studies also conducting urine and serum chemistry analyses. A few studies also evaluated histology of the bladder.

Animal Studies

Figures C-9 and C-10 show the effects of orally-administered aromatic high carbon range compounds on renal and bladder endpoints following subchronic or chronic exposure, respectively. Data are available for 10 compounds, including compounds with carbon numbers C10−C20. Renal alterations were observed with several compounds across the fraction, including BaP, pyrene, fluorene, fluoranthene, and 1,1-biphenyl (U.S. EPA, 2017a, b, 2013, 2011a, b, 1990c, d, e). The most sensitive finding following subchronic exposure was altered kidney weight, with decreased kidney weight reported at BaP doses ≥21 mg/kg-day or pyrene doses ≥125 mg/kg-day and increased kidney weight reported at fluorene doses ≥250 mg/kg-day. Nephropathy was observed following subchronic exposure to pyrene at ≥125 mg/kg-day or fluoranthene at ≥250 mg/kg-day.

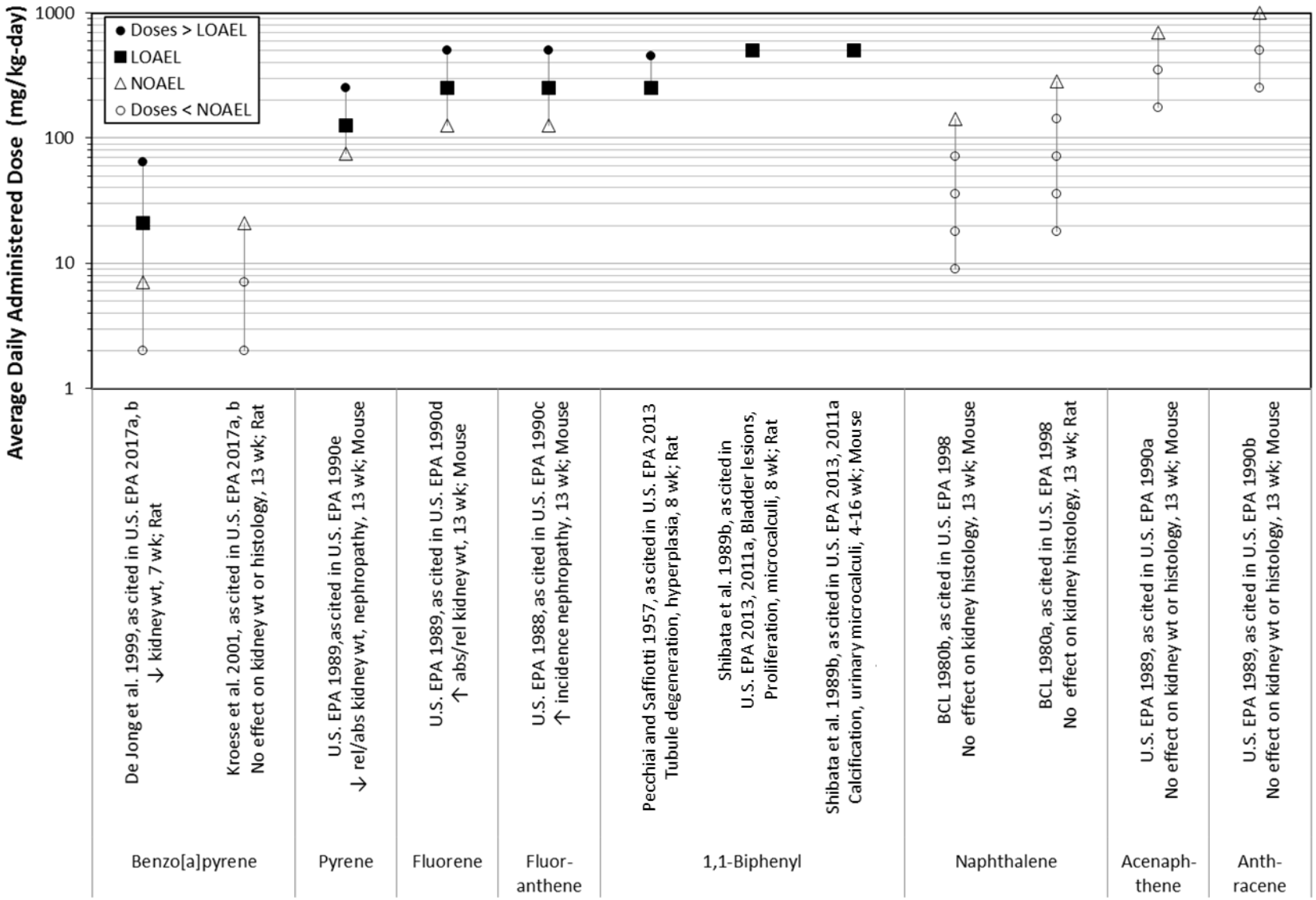


Figure C-9. Renal and Bladder Effects in Animals after Subchronic Oral Exposure to Aromatic High Carbon Range Compounds

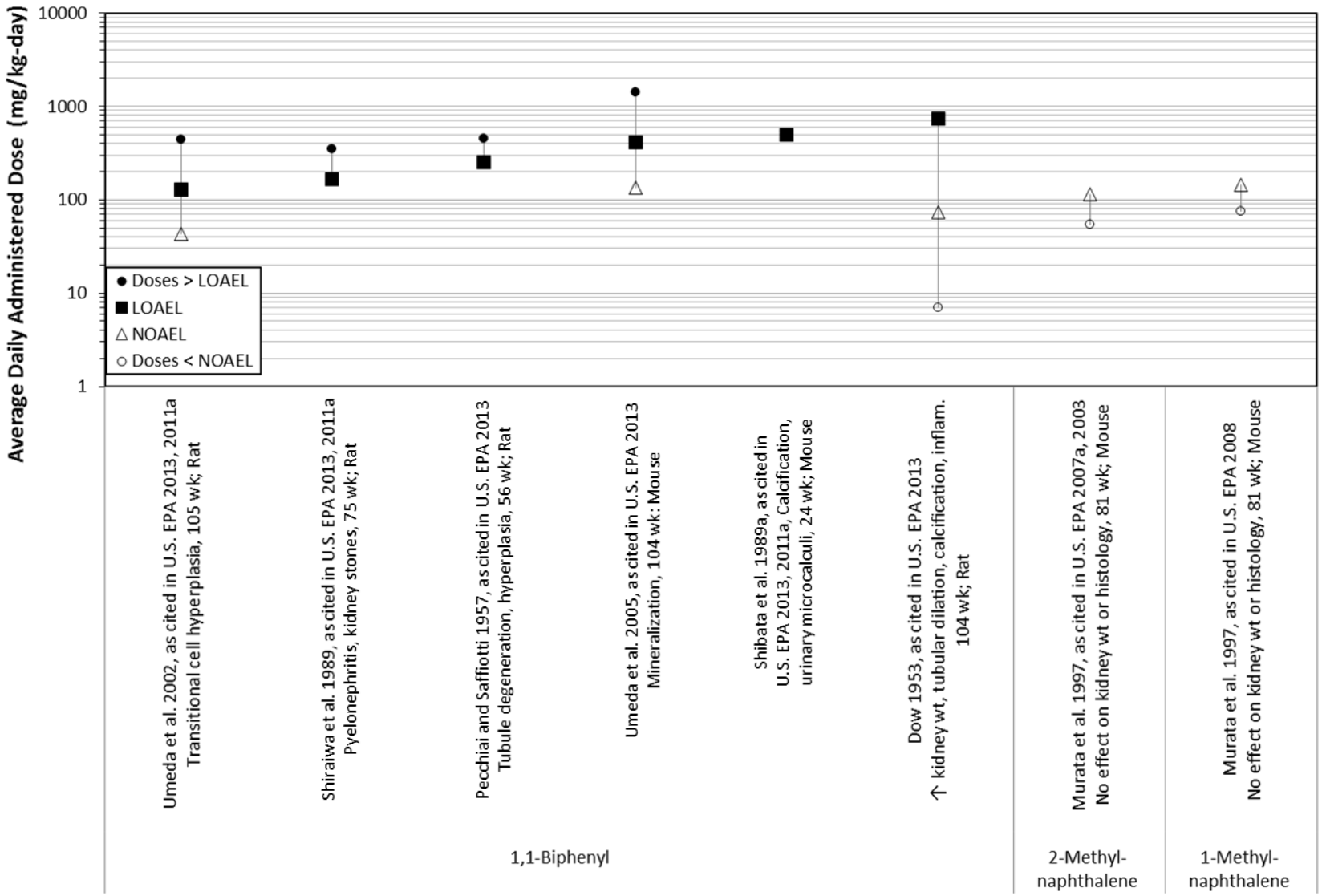


Figure C-10. Renal Effects in Animals after Chronic Oral Exposure to Aromatic High Carbon Range Compounds

Additional renal and bladder effects were only observed following oral exposure to 1,1-biphenyl, including renal tubule degeneration and hyperplasia, focal calcification of the renal medulla, renal mineralization, tubule dilation and inflammation, hyperplastic and metaplastic lesions of the renal pelvis, desquamation of renal pelvis, papillary necrosis, urinary microcalculi, and bladder lesions (hyperplasia, papillomatosis, epithelial proliferation) at subchronic or chronic doses ≥250 mg/kg-day. Additionally, transitional cell hyperplasia in renal pelvis, pyelonephritis, kidney stones, and hemosiderin deposits were reported following chronic exposure to 1,1-biphenyl at LOAELs ranging from 128 to 732 mg/kg-day. Alterations in blood urea nitrogen (BUN) were sporadically reported following exposure to naphthalene, fluoranthene, and fluorene, and were not considered a clear indication of renal effects in the absence of additional renal effects (U.S. EPA, 2012, 1998, 1990d). No clearly adverse renal effects were observed following subchronic exposure to naphthalene, acenaphthene, or anthracene (see Figure C-9) (U.S. EPA, 1998, 1990a, b) or chronic oral exposure to 1- or 2-methylnapthalene (see Figure C-10) (U.S. EPA, 2008, 2007a, 2003).

Refer to Figure C-8 for the reported effects on renal endpoints following inhalation exposures to individual aromatic high carbon range compounds. Data are available only for naphthalene, 2-methylnaphthalene, and 1,1-biphenyl, which represent compounds with carbon numbers C10−C12. Decreased kidney weight was reported in rats exposed to 2-methylnaphthalene at ≥1.8 mg/m^3 for 4 weeks (Swiercz et al., 2011) and kidney congestion and edema were observed in mice exposed to 1,1-biphenyl at ≥32.9 mg/m^3 for 13 weeks (U.S. EPA, 2013). No exposure-related changes in renal histology were observed in rats or mice exposed to naphthalene at 56 or 28 mg/m^3, respectively, for 2 years (ATSDR, 2005; U.S. EPA, 1998).

Summary of Potentially Relevant Evidence

No human data are available. In animals, renal effects appear to be limited to organ weight changes and exacerbation of age-related nephropathy after exposure to high oral doses for compounds from across the aromatic high carbon range fraction (C11−C20), with the exception of 1,1-biphenyl (C12). Oral exposure to high doses of 1,1-biphenyl is associated with histopathological changes in both the kidney and bladder. Available data indicate that renal damage can also occur following inhalation exposure to 1,1-biphenyl. Data for other compounds are too limited to assess potential renal effects in animals following inhalation exposure. Taken together, the kidney and bladder appear to be a target of 1,1-biphenyl toxicity. Other high aromatic carbon range compounds may alter kidney weight and increase age-related nephropathy following oral exposure.

RESPIRATORY

Pulmonary alveolar proteinosis is the critical endpoint for the subchronic p-RfD and chronic RfD for 2-methylnaphthalene, as well as the screening chronic p-RfD for 1-methylnaphthene (U.S. EPA, 2008, 2007a, 2003) (see Tables 6 and 7). Nasal lesions are the critical endpoint for the chronic RfC (see Table 8) and inhalation MRL[5] for naphthalene

[5]The ATSDR chronic inhalation MRL for naphthalene is based on the 105-week study in Fischer 344 rats (NTP, 2000). The study reported inflammation of the nose (including, olfactory epithelium, atypical hyperplasia, atrophy, degeneration); nasal respiratory epithelium (including hyperplasia, squamous metaplasia, and degeneration); and Bowman's glands hyperplasia observed in the 10 PPM dose group. The chronic MRL of 0.0007 ppm was based on a human equivalent concentration LOAEL of 0.2 ppm, which was divided by an uncertainty factor of 300 (10 for

(ATSDR, 2005; U.S. EPA, 1998). No human studies examining respiratory effects of aromatic high carbon range compounds were identified in the sources reviewed. As shown in Table 5, data on respiratory effects in animals were located for 10 members of the fraction. In general, the respiratory endpoints evaluated in the studies were lung weight and histology, with a few studies evaluating the entire respiratory tract (including nasal tissue).

Animal Studies

Respiratory data following oral exposure are available for 10 compounds, including compounds with carbon numbers C10−C20. Respiratory findings were limited to pulmonary alveolar proteinosis alterations in mice following oral exposure to 1- or 2-methylnaphthalene at doses ≥50 or 72 mg/kg-day, respectively, for 81 weeks (no NOAEL was identified) (U.S. EPA, 2008, 2007a, 2003). However, pulmonary findings following oral exposure to 1- or 2-methylnapthalene were likely confounded by unquantified volatilization of these compounds from the feedstock (U.S. EPA, 2008, 2007a, 2003). No effect was observed on lung weight and/or histology following oral exposure to BaP, naphthalene, pyrene, fluoranthene, fluorene, 1,1-biphenyl, acenaphthene, or anthracene (U.S. EPA, 2017a, b, 2013, 2011a, 2007b, 1998, 1990a, b, c, d, e). Additionally, no histopathological changes were found in the upper respiratory tract following exposure to naphthalene or acenaphthene (U.S. EPA, 1998, 1990a). An exposure-response graph to compare potencies across compounds was not included due to lack of exposure-related effects in the majority of tested compounds.

Figure C-11 shows the effects of inhalation exposure to aromatic high carbon range compounds on respiratory endpoints. Data are available for naphthalene, 2-methylnaphthalene, and 1,1-biphenyl only, representing compounds with carbon numbers C10−C12. Respiratory effects were reported for all three compounds (U.S. EPA, 2013; Dodd et al., 2012; Swiercz et al., 2011; U.S. EPA, 2011b; ATSDR, 2005; U.S. EPA, 1998). The predominant respiratory effect associated with naphthalene exposure was nasal lesions following subchronic exposure to ≥0.9 mg/m^3 in rats or chronic exposure to ≥9.3 mg/m^3 (lowest concentration tested) in rats and mice. Lung inflammation was also observed in mice after chronic exposure to ≥9.3 mg/m^3. Less severe nasal effects, characterized as nasal or upper respiratory irritation, were observed in rats and mice following subchronic exposure to 1,1-biphenyl at ≥1 mg/m^3. Tracheal hyperplasia and inflammation, as well as lung congestion and edema, were observed in mice after subchronic exposure to higher concentrations of 1,1-biphenyl (≥32.9 mg/m^3). However, no evidence of respiratory tract irritation was observed in rabbits after subchronic exposure to concentrations up to 60 mg/m^3. Lung lesions (increased goblet cells, interstitial infiltration, hyperplasia of peribronchial tissue) were the primary respiratory effect in rats exposed to 2-methylnapthalene at ≥1.8 mg/m^3 for 4 weeks (Swiercz et al., 2011).

using the LOAEL, 3 for extrapolating from rodents to humans using an interspecies dosimetric adjustment, and 10 for human interindividual variability).

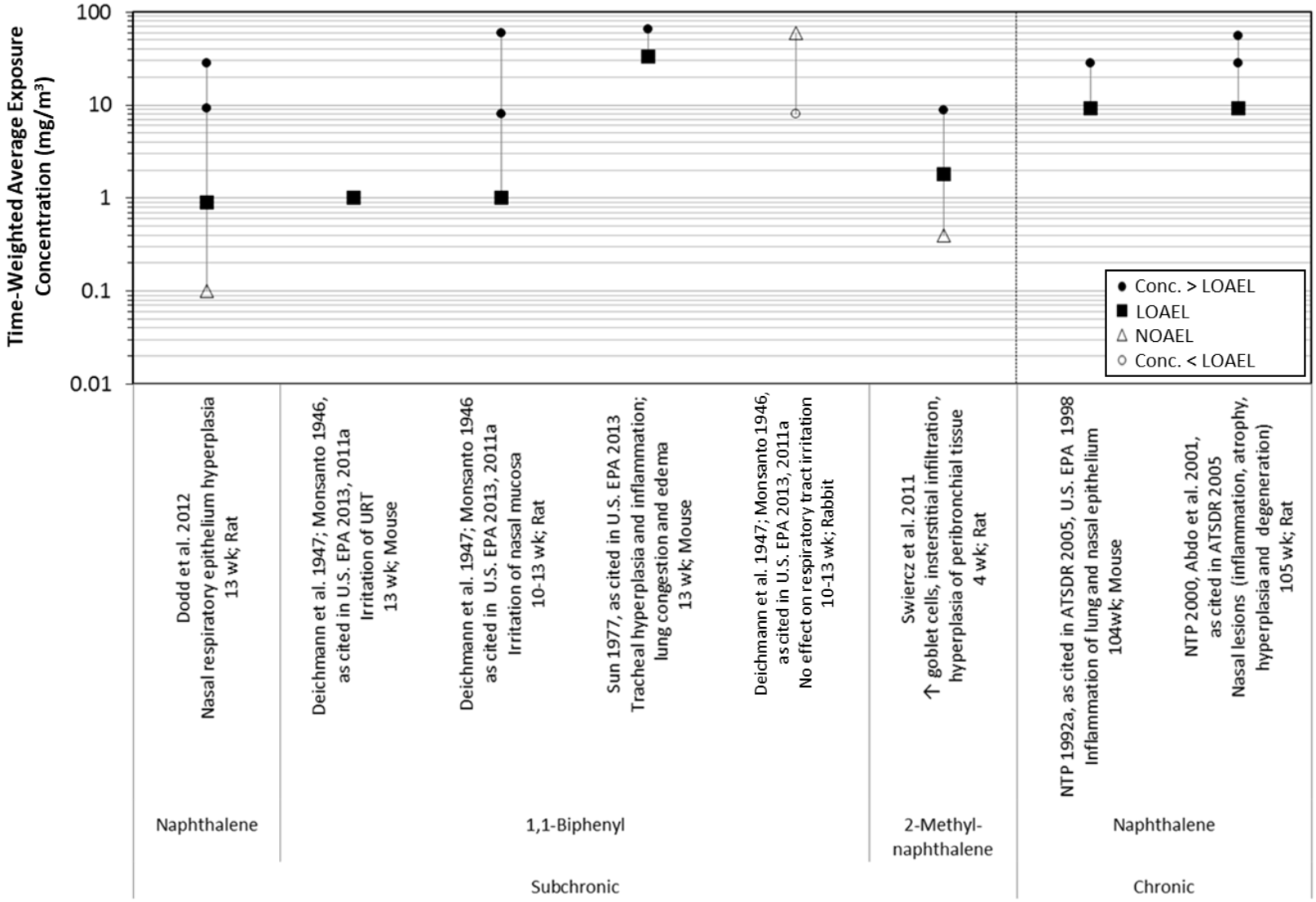


Figure C-11. Respiratory Effects in Animals after Inhalation Exposure to Aromatic High Carbon Range Compounds

Summary of Potentially Relevant Evidence

There were no relevant human data identified. Available animal data indicate that the respiratory tract is only a target of toxicity following oral exposure for methylated naphthalene compounds, 1- and 2-methylnaphthalene. For these two compounds, pulmonary alveolar proteinosis was observed at doses ≥72 or 50 mg/kg-day, respectively. Eight other compounds from across the fraction (C10−C20) did not show respiratory tract damage following oral exposure.

Inhalation data are limited but indicate that the lung is also a target of 2-methylnaphthalene following subchronic inhalation exposure; there are no data for 1-methylnapthalene. Subchronic inhalation studies also indicate that exposure to concentrations of naphthalene ≥0.9 mg/m^3 results in damage to the nasal epithelium; concentrations of 1,1-biphenyl reportedly can result in irritation and irritation of the upper respiratory tract as well as lung congestion and edema. Taken together, data indicate that the respiratory tract (particularly nasal tissue) is a target of at least some aromatic high carbon range compounds following inhalation exposure; however, inhalation data are limited to compounds with carbon numbers ranging from C10 to C12 only. Other than the methylated naphthalene compounds, the respiratory system does not appear to be a target of oral toxicity for aromatic high carbon range compounds.

GASTROINTESTINAL EFFECTS

No reference values for aromatic high carbon range compounds are based on gastrointestinal (GI) effects; however, the point of departure (POD) of 0.663 mg/kg-day based on GI effects reported for benzo[*c*]fluorene (which does not have any reference values) is lower than the currently available subchronic PODs for all fraction members except BaP (see Table 6). Available human studies are limited to reports of side effects in patients taking laxatives containing anthracene (U.S. EPA, 2009a). As shown in Table 5, data on GI effects in animals were located for 10 members of the fraction and a 21-PAH mixture. In general, the GI endpoints evaluated in the studies were GI histology, with a few studies evaluating stomach weight.

Human Studies

Melanosis or hyperpigmentation of the lining of the colon and rectum was reported in patients taking anthracene-based laxatives for treatment of constipation (U.S. EPA, 2009a).

Animal Studies

Figure C-12 shows the effects of orally-administered aromatic high carbon range compounds on GI endpoints. Data are available for nine compounds, including compounds with carbon numbers C10−C20. GI effects, specifically forestomach lesions, were observed following oral exposure to benzo[*c*]fluorene, BaP, and 1,1-biphenyl (U.S. EPA, 2017a, b, 2013; Weyand et al., 2004). Squamous hyperplasia was observed after subchronic exposure to benzo[*c*]fluorene at dietary doses ≥0.663 mg/kg-day (Weyand et al., 2004). Basal cell hyperplasia was observed after exposure to BaP at subchronic gavage doses ≥21 mg/kg-day and chronic gavage doses ≥2 mg/kg-day, but not after subchronic dietary doses up to 100 mg/kg-day (U.S. EPA, 2017a, b). For 1,1-biphenyl, epithelial hyperkeratinization was observed in rats after dietary exposure to doses ≥250 mg/kg-day for 8 or 56 weeks in one study, but not after chronic dietary exposure to doses up to 732 mg/kg-day in rats or 1,420 mg/kg-day in mice in three additional studies (U.S. EPA, 2013). No effects on GI histology were observed following subchronic gavage exposure to naphthalene, pyrene, fluoranthene, fluorene, acenaphthene, or anthracene (see Figure C-12).

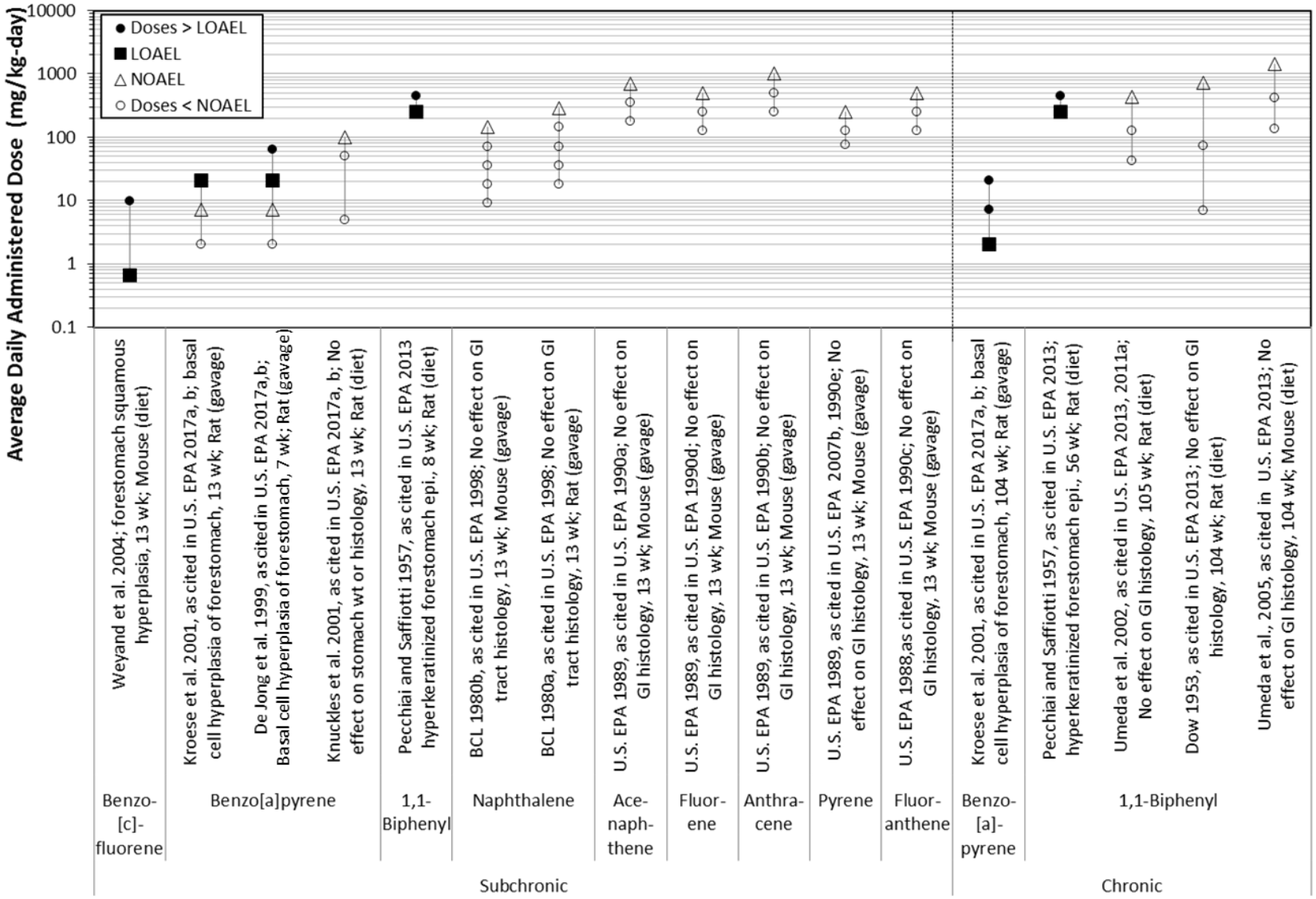


Figure C-12. Gastrointestinal Effects in Animals after Oral Exposure to Aromatic High Carbon Range Compounds

Data for GI effects following oral exposure to mixtures are available from one study (not included in Figure C-12). In this study, squamous hyperplasia of the forestomach was noted in mice exposed to a 21-PAH mixture with or without benzo[*c*]fluorene in the diet for 37 weeks at doses of approximately 15−17 mg/kg-day (Weyand et al., 2004).

The potential effects of inhalation exposure to aromatic high carbon range compounds on the GI system were only evaluated for naphthalene and 2-methylnaphthalene (Swiercz et al., 2011; ATSDR, 2005). No changes were observed in GI histology following subchronic exposure to 2-methylnapthalene at concentrations up to 8.9 mg/m^2 or chronic exposure to naphthalene at concentrations up to 56 mg/m^3. An exposure-response graph to compare potencies across compounds was not included due to limited data.

Summary of Potentially Relevant Evidence

Available human data are insufficient to assess potential GI effects following exposure to aromatic high carbon range compounds. Animal data report damage to the forestomach following exposure to three compounds from across the aromatic high carbon range fraction (C12−C20). Forestomach lesions were observed following subchronic exposure to benzo[*c*]fluorene at dietary doses ≥0.663 mg/kg-day (lowest dose tested, only available study), subchronic BaP at gavage doses ≥21 mg/kg-day, but not dietary doses up to 100 mg/kg-day, chronic BaP at gavage doses ≥2 mg/kg-day (no chronic dietary studies identified for BaP), and subchronic or chronic exposure to 1,1-biphenyl at doses ≥250 mg/kg-day in one of four available dietary studies (no gavage studies identified for 1,1-biphenyl). There was no evidence for GI lesions from six other compounds following subchronic exposure via gavage (C10−C16). Taken together, these data indicate that some aromatic high carbon range fraction compounds may cause hyperplastic lesions in the GI tract following oral exposure. Data are too limited to assess potential GI effects in animals following inhalation exposure.

REPRODUCTIVE EFFECTS

No existing health reference values for aromatic high carbon range compounds are based on reproductive effects; however, available data from workers occupationally exposed to PAH mixtures indicates that the male and female reproductive systems may be a target of some members of this fraction. Human studies with data on PAH mixtures, often with a focus on BaP, include both occupational and smoking exposure studies. As shown in Table 5, data on reproductive endpoints in animals were located for 10 members of the fraction. However, data on reproductive function were only located for two members; the remaining studies evaluated reproductive organ weight and/or histology but did not assess reproductive function or capacity.

Human Studies

Exposure to PAH mixtures has been associated with effects on male and female reproductive function (U.S. EPA, 2017a, b). Decreased sperm quality has been demonstrated in cigarette smokers, coke oven workers, and other men occupationally exposed to PAHs (U.S. EPA, 2017a, b). A study in coke oven workers reported oligospermia and an increase in the proportion of morphologically abnormal sperm (U.S. EPA, 2017a, b). Associations were also reported between exposure to PAHs (occupational exposure and smoking), PAH-adduct formation, and increased deoxyribonucleic acid (DNA) fragmentation in sperm (U.S. EPA, 2017a, b). A relationship was observed between the level of benzo[*a*]pyrene diol epoxide (BPDE)-DNA adducts in sperm and altered motility and morphology in patients at fertility clinics (U.S. EPA, 2017a, b). Higher levels of PAH-DNA adducts in sperm and higher urinary

levels of PAHs were also associated with infertility (U.S. EPA, 2017a, b). The fertilizing capacity of sperm and the implantation rates of embryos were reduced in cigarette smokers (U.S. EPA, 2017a, b).

Reproductive effects related to ovulation, pregnancy, and spontaneous abortion have been reported in women who smoked cigarettes (U.S. EPA, 2017a, b). In utero exposure to maternal tobacco smoke may also affect the future fertility of female offspring (U.S. EPA, 2017a, b). Associations were reported between follicular fluid BaP levels and reduced conception and maternal blood BaP-DNA adduct levels and risk of miscarriage (U.S. EPA, 2017a, b). The level of BaP in placental tissue was significantly increased in women that experienced preterm birth (<36 weeks, *n* = 29) compared to women with full-term delivery (>36 weeks, *n* = 55) (Agarwal et al., 2017).

Animal Studies

Oral and inhalation data on reproductive function are only available for a limited number of aromatic high carbon range fraction compounds. Therefore, exposure-response graphs were not generated to compare potencies across compounds for reproductive data.

Reproductive function studies following oral exposure were only available for two compounds: 1,1-biphenyl and BaP (U.S. EPA, 2017a, b, 2013, 2011a). Decreased fertility and litter size were observed in F_0 and F_1 parental rats exposed to 1,1-biphenyl in a multigenerational study at dietary doses of 887−1,006 mg/kg-day, but not ≤101 mg/kg-day. In one-generation studies in rats, no effects on reproductive performance were reported at doses up to 525 mg/kg-day; however, endpoints evaluated were very limited and considered insufficient for a full evaluation of reproductive performance. For BaP, male mice exposed to ≥1 mg/kg-day had low sperm counts, and sperm had decreased ability to penetrate ova in vitro; however, reproductive performance in vivo was not evaluated. Other reproductive studies reported sperm effects in male rats and mice following exposure to BaP at doses ≥0.01 mg/kg-day. Additional effects reported at ≥5 mg/kg-day include decreased testosterone levels, decreased testicular testosterone production, decreased sperm motility, increased percentage of abnormal sperm, and histopathological changes in the testes. In females, adverse effects were noted in rats (decreased ovary weight, decreased estradiol, decreased primordial follicles, and prolonged estrous cycle) and mice (increased cervical epithelial inflammation and hyperplasia) at doses ≥2.5 and 0.7 mg/kg-day, respectively.

Ten compounds from across the fraction (C10−C20) have data on reproductive organ weight and/or histology from subchronic or chronic assays that did not assess reproductive function or specialized reproductive endpoints (e.g., sperm parameters). One study reported significant decreases in ovary weight in mice exposed to acenaphthene at doses ≥175 mg/kg-day for 13 weeks (U.S. EPA, 2011b, 1990a). No exposure-related changes in reproductive organ weight were observed following oral exposure to naphthalene, fluoranthene, anthracene, 1,1-biphenyl, or BaP (U.S. EPA, 2013, 2011a; ATSDR, 2005; U.S. EPA, 1998, 1990b, c). No effects on reproductive organ histology were reported following subchronic or chronic exposure to 1-methylnaphthalene, 2-methylnaphthalene, pyrene, naphthalene, 1,1-biphenyl, fluorene, fluoranthene, acenaphthene, anthracene, or BaP (U.S. EPA, 2013, 2011a, b, 2008, 2007a, b; ATSDR, 2005; U.S. EPA, 2003, 1998, 1990a, b, c, d, e).

Inhalation data on the potential for altered reproductive function following exposure to aromatic high carbon range fraction compounds are limited to BaP (U.S. EPA, 2017a, b). Decreased ovulation rate was observed in female rats exposed to concentrations ≥0.008 mg/m^3 for 2 weeks prior to mating (lowest concentration tested), with decreased ovarian weights observed at ≥0.013 mg/m^3 and decreased pups/litter and embryo/fetal survival at 0.02 mg/m^3. In another study, various effects were noted in male rats exposed to 0.013 mg/m^3 (only concentration tested), including altered serum hormone levels (increased luteinizing hormone, decreased testosterone), decreased seminiferous tubule diameter and length, and sperm alterations (decreased motility and count, and increased percent of abnormal sperm).

Available inhalation data for other compounds in the fraction are limited to naphthalene and 2-methylnaphthalene (Swiercz et al., 2011; ATSDR, 2005). There was no evidence of histopathological changes in reproductive organs following chronic exposure to naphthalene at concentrations up to 56 mg/m^3 and a lack of exposure-related changes in testes weight following subchronic exposure to 2-methylnaphthalene or naphthalene at concentrations up to 8.9 or 28 mg/m^3, respectively.

Summary of Potentially Relevant Evidence

Human data suggest that PAH mixtures, including compounds from the aromatic high carbon range fraction, may affect the male and female reproductive systems. Limited data from two compounds in animals, BaP and 1,1-biphenyl, support that fertility may be reduced following exposure to some compounds from the aromatic high carbon range fraction. However, the lack of data from other compounds regarding reproductive function precludes the ability to assess potential reproductive effects across the fraction in animals following oral or inhalation exposure.

DEVELOPMENTAL EFFECTS

Developmental toxicity is the critical effect for the subchronic p-RfD for 1,1-biphenyl (U.S. EPA, 2011a) and the subchronic and chronic RfDs and RfCs for BaP[6] (U.S. EPA, 2017a, b). Observed developmental effects include increased incidence of skeletal anomalies following oral exposure to 1,1-biphenyl, neurodevelopmental effects following oral exposure to BaP, and decreased embryo/fetal survival following inhalation exposure to BaP. Several human cohort studies evaluated potential associations between PAH exposure and altered offspring growth or neurodevelopment; many of these studies focused on BaP. As shown in Table 5, data on developmental endpoints in animals were located for five compounds and two mixtures from this fraction. Endpoints evaluated include standard teratology and offspring growth and survival studies, as well as special developmental studies (neurological, reproductive, and cardiac function).

Human Studies

Several cohort studies have evaluated the potential association between exposure to PAH mixtures and offspring growth (U.S. EPA, 2017a, b). In Chinese women, elevated levels of benzo[*a*]pyrene diolepoxide-DNA (BPDE-DNA) adducts in cord blood were associated with reduced offspring weight at 18, 24, and 30 months of age, but not at birth (U.S. EPA, 2017a, b).

[6]The chronic RfD for BaP is based on a developmental exposure; therefore, it is also applicable to subchronic exposures. Subchronic and chronic screening p-RfD values for BeP were also based on developmental effects because BaP was used as an analogue.

In a U.S. cohort, reduced birth weight was associated with a doubling of cord blood BPDE-adducts combined with exposure to environmental tobacco smoke (no effect of either parameter alone) (U.S. EPA, 2017a, b). In a Spanish study, dietary BaP intake, determined by questionnaire, was associated with reduced birth weight, birth length, and small for gestational age (SGA) infants born to mothers with low vitamin C intake only (U.S. EPA, 2017a, b). Similar findings were reported in a larger cohort from Norway, which demonstrated an association between reported dietary BaP intake and reduced birth weight and birth length of offspring from all women, regardless of vitamin C intake. The magnitude of the association was increased for women consuming less than the recommended intake of vitamin C (U.S. EPA, 2017a, b). A case-control study of fetal death prior to 14 weeks of gestation in China showed a significant association between the level of maternal blood BPDE-DNA adducts and increased risk of fetal death; however, no association was observed between fetal tissue BPDE-DNA adduct levels and risk of fetal death (U.S. EPA, 2017a, b).

Several cohort studies have also evaluated the potential relationships between PAH exposure and neurodevelopmental effects occurring at birth and during childhood (U.S. EPA, 2017a, b). A birth cohort study from China showed evidence of associations between cord blood BPDE-adducts and reduced head circumference at birth, altered motor behavior and coordination at age 2 years, and reduced intelligence quotient scores at age 5 years (U.S. EPA, 2017a, b). Interactions with the effects of environmental tobacco smoke were noted. A birth cohort study conducted in New York City showed a similar association between cord blood BPDE-adducts and reduced head circumference at birth and also symptoms of anxiety/depression and attention problems at ages 6−7 years (U.S. EPA, 2017a, b). An magnetic resonance imaging (MRI) study of 8−12-year-old children in Spain showed an association between indoor and outdoor air levels of BaP and a decrease in the caudate nucleus volume of the basal ganglia (Mortamais et al., 2017). Neurobehavioral testing did not reveal significant changes in attention-deficit/ hyperactivity disorder (ADHD) symptoms in this study.

Animal Studies

Figures C-13 and C-14 show the effects of orally-administered aromatic high carbon range compounds on standard developmental endpoints (teratology and growth) and specialized developmental endpoints (neurodevelopment, reproductive development, cardiac function), respectively. Data for these endpoints are available for four compounds, including compounds with carbon numbers C10−C20. Developmental effects were reported for all tested compounds. Effects associated with gestational exposure to benzo[*b*]fluoranthene included impaired male reproductive development at ≥0.002 mg/kg-day (lowest dose tested) and decreased pup weight at 0.02 mg/kg-day (Kim et al., 2011). Effects associated with exposure to BaP included neurodevelopmental effects (altered behavior, impaired learning, altered cortical activity) following gestational exposure to doses ≥0.2 mg/kg-day, altered cardiovascular function in offspring following gestational exposure to doses ≥0.6 mg/kg-day, decreased pup body weight following early postnatal exposure to doses ≥2 mg/kg-day or gestational doses ≥10 mg/kg-day, and altered reproductive development and decreased F_1 fertility in males and females at ≥10 mg/kg-day (U.S. EPA, 2017a, b).

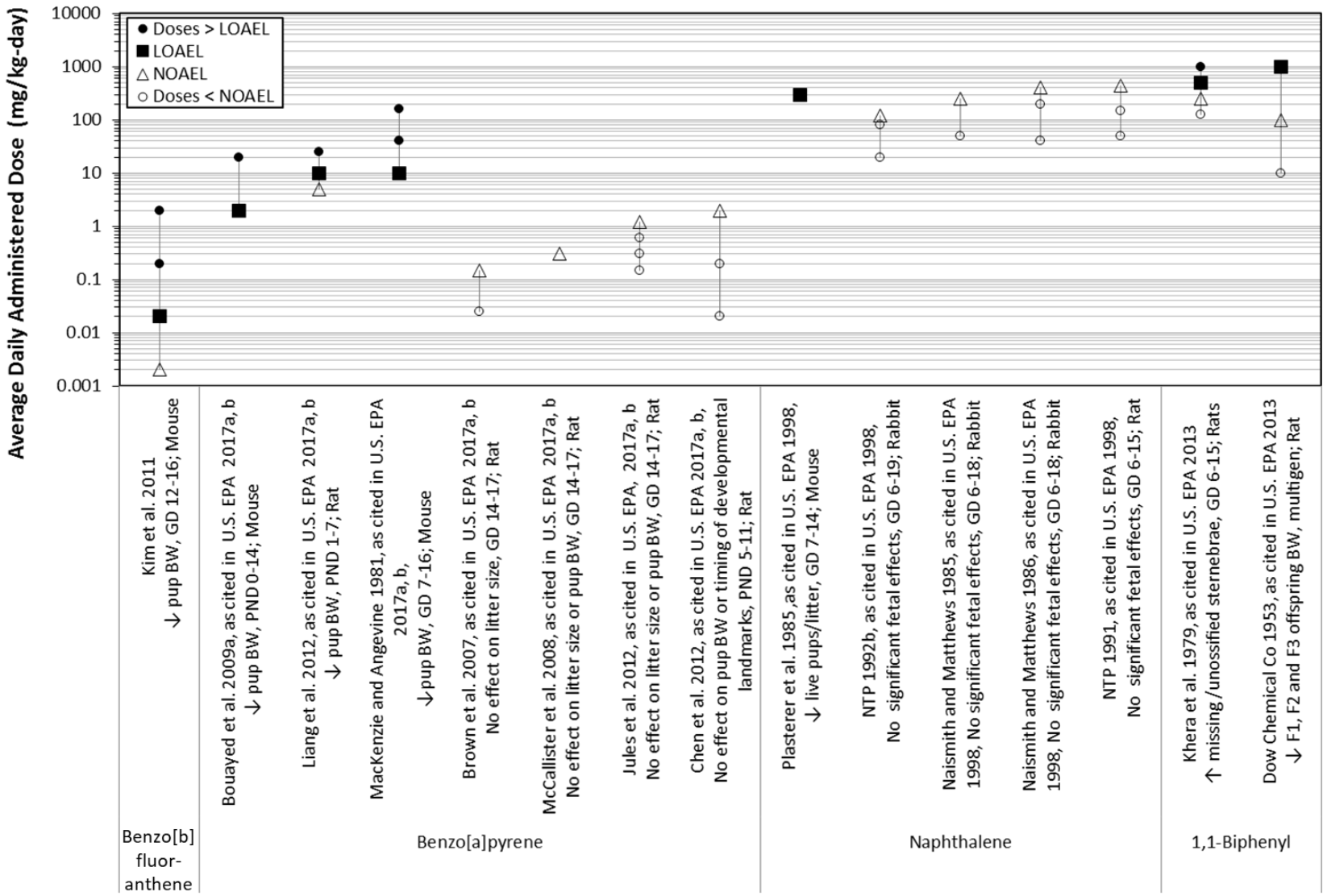


Figure C-13. Teratology and Offspring Growth Effects in Animals after Oral Exposure to Aromatic High Carbon Range Compounds

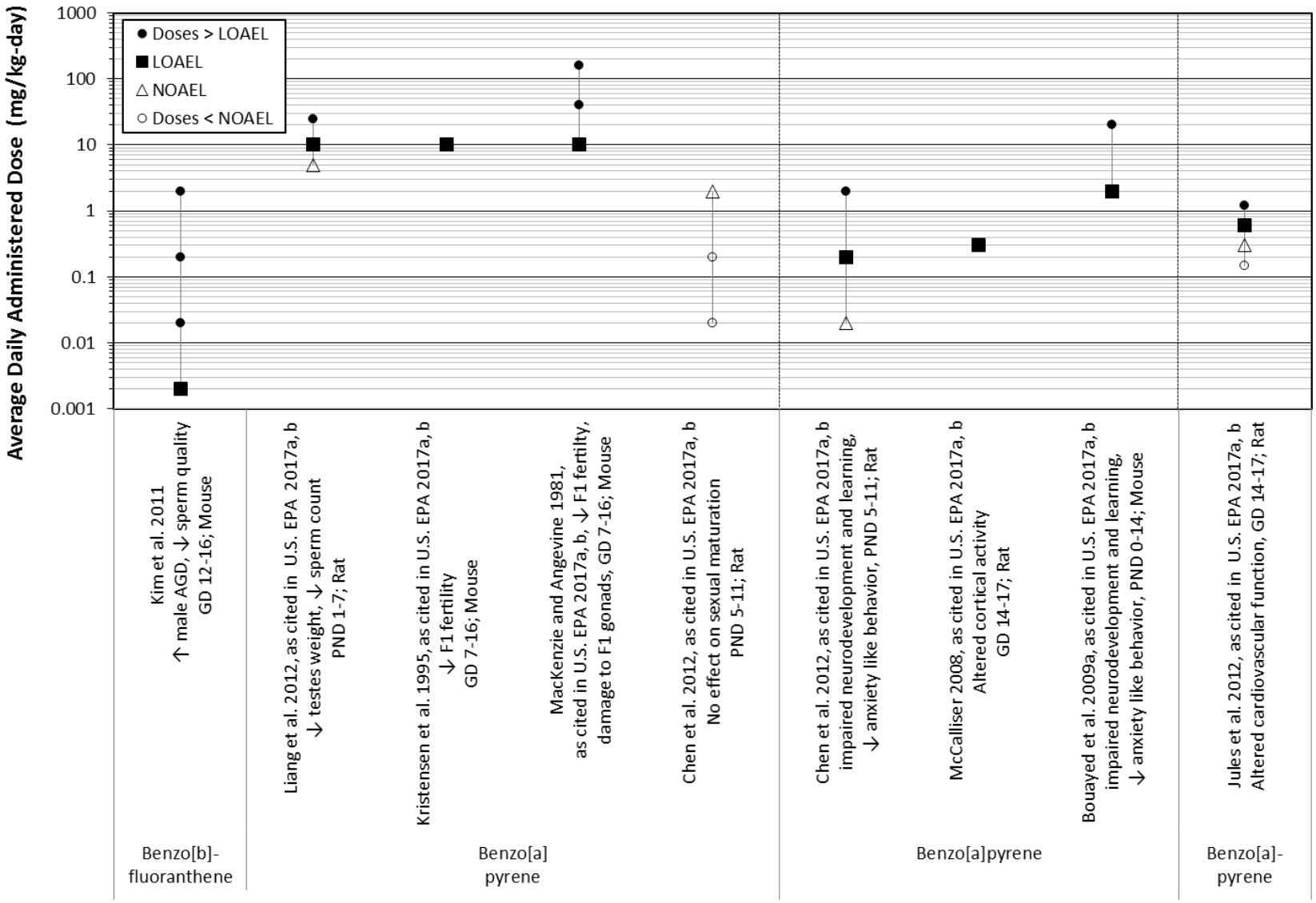


Figure C-14. Specialized Developmental Endpoints in Animals after Oral Exposure to Aromatic High Carbon Range Compounds

Effects associated with naphthalene and 1,1-biphenyl occurred at much higher doses; however, no special developmental studies (e.g., neurodevelopmental) were identified. A decrease in the number of live pups was observed in mice following gestational exposure to naphthalene at 300 mg/kg-day; similar effects were not seen in similarly exposed rats or rabbits (U.S. EPA, 1998). For 1,1-biphenyl, effects included increased incidence of missing or unossified sternebrae after gestational exposure to doses ≥500 mg/kg-day and decreased F_1, F_2, and F_3 pup weights in a multigenerational study with exposure to 1,006 mg/kg-day (U.S. EPA, 2013).

Neurodevelopmental data are also available in rats following exposure to a mixture of 16 PAHs during gestation or gestation and lactation, which contained 2.5% BaP (Crepeaux et al., 2014, 2013, 2012); this study is not included in Figure C-14. Complete mixture composition is presented in Appendix B, Table B-2. Adverse effects (delayed eye or ear opening, impaired neuromuscular coordination, increased activity, increased anxiety-like behavior) were observed at mixture doses ≥0.002 mg/kg-day, which delivered a BaP dose of 0.00005 mg/kg-day.

The potential effects of inhalation exposure to aromatic high carbon range compounds on the developing organism were only evaluated for BaP and a 9-PAH mixture (predominantly pyrene, composition shown in Appendix B, Table B-3); therefore, an exposure-response graph comparing potencies across compounds was not included. Adverse developmental effects were noted in all three available BaP gestational studies, including decreased embryo survival, decreased number of implantations, and decreased pups/litter at concentrations ≥0.0042 mg/m^3 (U.S. EPA, 2017a, b). Electrophysiological changes in the hippocampus were also observed in offspring following maternal exposure to BaP at 0.02 mg/m^3 during gestation (only tested concentration). Standard developmental endpoints were not evaluated for the 9-PAH mixture; instead, endpoints in offspring included adiposity and immune function in offspring (Yan et al., 2014; Chu et al., 2013). Observed findings included increased airway reactivity in ovalbumin-sensitized mice following early postnatal exposure (Chu et al., 2013) and elevated body weight and fat mass in F_1 and F_2 offspring (Yan et al., 2014). The study authors reported a nominal exposure concentration of 7.29 ng/m^3 (7.29×10^{-6} mg/m^3) for the mixture exposure level. However, the measured concentration of pyrene (as a marker of mixture exposure) in the exposure chamber averaged 23 ng/m^3 (range 7.38−40 ng/m^3); the control exposure chamber averaged 3 ng/m^3 pyrene, with a range of 0−9 ng/m^3. Based on the reported proportion of pyrene in the mixture (52.59%), the 23 ng/m^3 average for pyrene corresponds to an approximate average mixture concentration of 44 ng/m^3 (4.4×10^{-5} mg/m^3). This exposure concentration is well below the developmental LOAEL for BaP (0.0042 mg/m^3).

Summary of Potentially Relevant Evidence

Human data suggest that PAH mixtures, including compounds from the aromatic high carbon range fraction, may adversely affect offspring growth and neurodevelopment. Limited data from three compounds in animals, benzo[*b*]fluoranthene, BaP, and 1,1-biphenyl, show that offspring growth may be affected following exposure to some compounds from the aromatic high carbon range fraction. Data on neurodevelopment in animals are limited to BaP (and mixtures containing BaP) but indicate that adverse neurological effects can occur following early life exposure at low doses. Limited animal data from benzo[*b*]fluoranthene, BaP, and mixtures also indicate that the developing reproductive, immune, and cardiovascular systems may be targets of toxicity for this fraction. However, the lack of developmental data from other

compounds, particularly specialized developmental data, precludes a comparison of developmental effects and potencies across the fraction.

OTHER EFFECTS

Human Studies

Cataract formation was reported in 8 of 21 workers exposed to naphthalene for >5 years in a dye-producing plant. Bilateral cataracts were also reported in a case study of a pharmacist who ingested 5 g of naphthalene (ATSDR, 2005; U.S. EPA, 1998).

Studies in coke oven workers have suggested that PAHs may impair the immune system (U.S. EPA, 2017a, b). Affected immune parameters include reductions in serum immunoglobulin M (IgM) and/or immunoglobulin A (IgA) titers, elevated immunoglobulin G (IgG) and immunoglobulin E (IgE) levels, and reduced T-cell mitogenic and proliferative responses (U.S. EPA, 2017a, b). Elevated levels of the urinary metabolites of naphthalene, phenanthrene, and pyrene were associated with hypersensitivity in 5- and 9-year-old children, as measured by serum levels of cockroach-specific IgE (an indicator of hypersensitivity) (U.S. EPA, 2017a, b). Blood phenanthrene levels were elevated in children (1−14 years old) diagnosed with bronchial asthma in a hospital-based, case-control study in India (Suresh et al., 2009).

Occupational exposure to PAH mixtures and cigarette smoke have been associated with cardiovascular effects including atherosclerosis and ischemic heart disease (U.S. EPA, 2017a, b). Mortality from cardiovascular disease and risk of ischemic heart disease were elevated in workers at a coke oven plant and an aluminum smelter, respectively (U.S. EPA, 2017a, b). Urinary metabolites of phenanthrene, BaP, and benzo[*a*]anthracene were positively correlated with diastolic blood pressure in chimney sweeps in Sweden (Alhamdow et al., 2017). Serum markers of cardiovascular disease risk were also elevated in these workers (increased homocysteine, cholesterol, and high-density lipoproteins). Two cross-sectional studies of the U.S. population used National Health and Nutrition Examination Survey (NHANES) data to evaluate potential associations between urinary PAH metabolites and risk factors of cardiovascular disease (Ranjbar et al., 2015; Clark et al., 2012). Clark et al. (2012) did not demonstrate a relationship between urinary concentrations of naphthalene, fluorene, phenanthrene, or pyrene metabolites (NHANES 2001−2004 data set) and serum biomarkers of cardiovascular disease (fibrinogen, homocysteine, and WBC count) (Clark et al., 2012). Ranjbar et al. (2015) showed positive associations between the urinary concentrations of some PAH metabolites (NHANES 2001−2008 data set) and hypertension (naphthalene and phenanthrene), obesity (phenanthrene), metabolic syndrome risk factors including cholesterol, triglycerides, blood pressure, and glucose abnormalities (naphthalene, fluorene, and phenanthrene), and type 2 diabetes (naphthalene, phenanthrene, and pyrene).

Animal Studies

As observed in human studies, cataract formation is a well-documented effect in laboratory animals following exposure to high oral doses of naphthalene, generally at doses ≥1,000 mg/kg-day (U.S. EPA, 1998).

The immune system has been identified as a potential target of BaP toxicity in animals exposed by multiple routes (U.S. EPA, 2017a, b). Changes in thymus weight and histology and alterations in the spleen (e.g., decreased B cell percentages) have been reported at oral doses ≥7.1 mg/kg-day, with decreased immune responses in a modified local lymph node assay at

13 mg/kg-day. Immune function was also impaired following subcutaneous doses ≥5 mg/kg-day. Developmental immunotoxicity studies reported impaired immune responses following in utero exposure via intraperitoneal (i.p.) injection. Inhalation data for immune endpoints were not available for BaP. Data regarding immune function for other members of the fraction are limited to naphthalene, which did not show any exposure-related changes in a battery of immunological assays following oral exposure to doses up to 133 mg/kg-day for 90 days (U.S. EPA, 1998).

Several studies have reported oral transplacental carcinogenesis following gestational exposure to dibenzo[*def,p*]chrysene in mice (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). In these studies, dibenzo[*def,p*]chrysene was administered during gestation, resulting in the induction of fatal T-cell acute lymphoblastic leukemia/ lymphoma in offspring; pups typically died from this or other tumors within a year. Those that survived frequently developed lung, liver, or ovarian tumors. Because of the fatal nature of the neoplasia in offspring, and the fact that they result from gestational exposure, these studies can be considered to straddle the line between cancer and developmental toxicity outcomes. None of the studies identified a dose that did not influence offspring tumor incidence, with doses ≥1 mg/kg administered once yielding increased lung tumor incidences. Pup mortality due to T-cell acute lymphoblastic leukemia/lymphoma was increased at doses ≥6.5 mg/kg.

APPENDIX D. REFERENCES

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