

FINAL
9-30-2009

Provisional Peer-Reviewed Toxicity Values for Complex
Mixtures of Aliphatic and Aromatic Hydrocarbons
(CASRN Various)

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Commonly Used Abbreviations

BMD	Benchmark Dose
HI	Hazard Index
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
LOAEL _{ADJ}	LOAEL adjusted to continuous exposure duration
LOAEL _{HEC}	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
NOAEL _{ADJ}	NOAEL adjusted to continuous exposure duration
NOAEL _{HEC}	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
p-sRfC	provisional subchronic reference concentration
p-sRfD	provisional subchronic reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
RPF	Relative Potency Factor
UF	uncertainty factor
UF _A	animal to human uncertainty factor
UF _C	composite uncertainty factor
UF _D	incomplete to complete database uncertainty factor
UF _H	interhuman uncertainty factor
UF _L	LOAEL to NOAEL uncertainty factor
UF _S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR COMPLEX MIXTURES OF ALIPHATIC AND AROMATIC HYDROCARBONS (CASRN Various)

Executive Summary

This Provisional Peer-Reviewed Toxicity Value (PPRTV) document supports a fraction-based approach to risk assessment for complex mixtures of aliphatic and aromatic hydrocarbons. The approach takes into account previous efforts, most notably those of the Massachusetts Department of Environmental Protection (MADEP) and the Total Petroleum Hydrocarbon Criteria Working Group (TPHCWG). These organizations use a fraction-based approach that defines petroleum hydrocarbon fractions on the basis of expected transport in the environment and analytical methods that may be applied to identify and quantify petroleum hydrocarbon environmental contamination. Toxicity values are selected or derived and used as surrogates to represent the toxicity of these fractions; then, health risk information for the complex mixture is developed using chemical mixture risk assessment methods where dose-addition or response-addition is assumed across or within the fractions, as appropriate. For similar use by U.S. EPA, this PPRTV document presents toxicity values for aliphatic and aromatic hydrocarbon fractions—including subchronic and chronic reference doses (RfDs) and reference concentrations (RfCs), cancer weight-of-evidence (WOE) assessments, oral slope factors (OSF) and inhalation unit risks (IUR). These values have been obtained from the U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) (U.S. EPA, 2009o), U.S. EPA Health Effects Assessment Summary Table (HEAST) (U.S. EPA, 1997), and existing PPRTVs, or were derived using updated U.S. EPA methods to provide new provisional assessments (U.S. EPA, 2009a-i) when needed and supported by the data.

In the U.S. EPA's approach, the potential health risk of each of the six aliphatic or aromatic hydrocarbon fractions is represented in one of three ways:

- 1) Surrogate Method: the toxicity value for a surrogate (similar) aliphatic or aromatic hydrocarbon mixture or compound is integrated with the exposure data for the entire mass of the fraction;
- 2) Component Method: the toxicity values for well-studied individual chemicals that make up a large portion of the fraction are combined with their respective exposure estimates using a components-based method under an assumption of dose- or response-addition; or
- 3) Hybrid Method: a combination of 1) and 2) above is used for the same fraction and the results are combined under an assumption of dose- or response-addition.

Table 1 summarizes the U.S. EPA approach and illustrates how these three methods are applied to the six hydrocarbon fractions. In the first column of Table 1, the hydrocarbon mixtures are first classified into Aliphatics and Aromatics; each of these two major fractions is further separated into low-, medium-, and high-carbon range fractions in the second column. The fractions are defined by the number of carbon atoms (C) in the compounds of the fraction and, also, by the compounds' equivalent carbon (EC) number index, which is related to their transport in the environment. The surrogate chemicals or mixtures selected to represent the toxicity of these fractions are shown in the third column. The components method may involve all of the compounds in the fraction, as is done for the low-carbon-range aromatics, or may involve only the compounds known to have certain toxicological properties, as is done for the carcinogenicity of the high-carbon-range aromatics. A combination of surrogate and component methods may be used for the mid-carbon-range aromatics, if naphthalene and

2-methylnaphthalene are evaluated as target analytes, as occurs in Massachusetts (MADEP, 2003). The remaining columns of Table 1 show the availability of noncancer and cancer toxicity values for use in this approach and, when available, indicates which table in this PPRTV document contains that information.

Table 1. Aliphatic and Aromatic Fractionation and the Availability of Toxicity Values in this PPRTV Document for Surrogate Chemicals or Mixtures						
Primary Fractions	Secondary Fractions	Surrogates and/or Components	Oral Toxicity Value(s)	Inhalation Toxicity Value(s)	Cancer Oral Slope Factor or RPF	Cancer Inhalation Unit Risk
Aliphatics	Low carbon range (C5–C8; EC5–EC8)	Commercial hexane or <i>n</i> -hexane (surrogates)	Table 7	Table 8	No Value	Table 9
	Medium carbon range (C9–C18; EC > 8–EC16)	Mid range aliphatic hydrocarbon streams (surrogate)	Table 7	Table 8	No Value	Table 9
	High carbon range (C19–C32; EC > 16–EC35)	White mineral oil (surrogate)	Table 7	No Value(s)	No Value	No Value
Aromatics	Low carbon range (C6–C8; EC6–EC < 9)	Benzene, ethylbenzene, xylenes, and toluene (components)	Table 7	Table 8	Table 9	Table 9
	Medium carbon range (C9–C16; EC9–EC < 22)	High-flash aromatic naphtha (surrogate); naphthalene and 2-methylnaphthalene (components)	Table 7	Table 8	No Value	No Value
	High carbon range (C17–C32; EC22–EC35)	Fluoranthene (surrogate); benzo[a]pyrene and six other Group B2 PAHs (components)	Table 7	No Value(s)	Table 9	No Value

To estimate total health risk or hazard for the entire hydrocarbon mixture, the estimates for all six of the aromatic and aliphatic fractions are summed using an appropriate additivity method. Figures 1 and 2 provide a graphic illustration of how cancer and noncancer risk assessments are carried out, respectively. The illustrated noncancer assessment (Figure 1) is performed at a screening level, consistent with Superfund practice and guidance (1989a). Use of surrogate mixture data and component-based methods is consistent with the U.S. EPA's supplemental mixtures guidance (U.S. EPA, 2000). The application of appropriate additivity methods for mixture components, also consistent with U.S. EPA (1986, 1989a, 1993, 2000) mixtures guidance and methodology, is recommended to estimate the potential total risk within and across fractions. These methods include the hazard index (HI) for noncarcinogenic effects, the relative potency factor (RPF) method for the carcinogenic effects of the high carbon aromatic fraction, and response addition for carcinogenic effects. By applying additivity concepts to the risk evaluation of these complex mixtures, the U.S. EPA is applying a straightforward approach that incorporates a number of simplifying assumptions. Because assumptions for complex chemical mixtures are often difficult to substantiate, this U.S. EPA

approach can be considered as a default approach that can be used to evaluate potential health risks from exposures to aliphatic and aromatic hydrocarbon mixtures when whole mixture toxicity data for a specific site are not available.

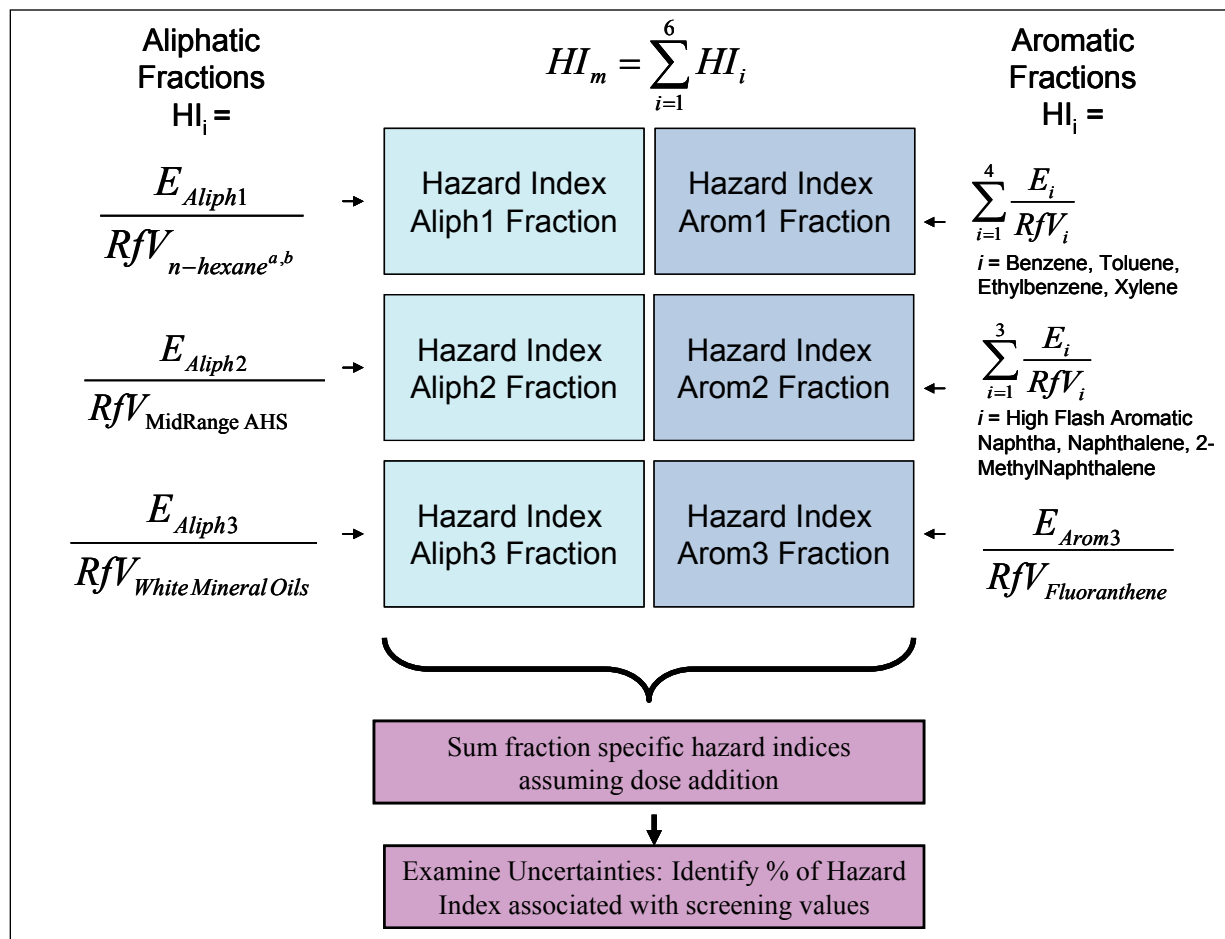


Figure 1. Fraction-based Noncancer Risk Assessment for Complex Mixtures of Aliphatic and Aromatic Hydrocarbons

^aFor inhalation, use commercial hexane, if *n*-hexane present at ≤53% of fraction

^bFor inhalation, use *n*-hexane, if present at >53% of fraction

Where:

- HI_m = Screening Hazard Index for the Whole Mixture
- HI_i = Hazard Index Calculated for the *i*th Fraction
- E_i = Daily Oral or Inhalation Intake of the *i*th Chemical or Fraction (mg/kg-day or mg/m³, respectively)
- RfV = Reference Value: Oral Reference Dose or Inhalation Reference Concentration (RfC) (mg/kg-day or mg/m³, respectively)
- AHS = Aliphatic Hydrocarbon Streams

Finally, when evaluating risk through the application of these additivity methods, the U.S. EPA suggests that risk assessors carefully identify the underlying assumptions of the risk estimate and describe the sources of support for these. The U.S. EPA also suggests that risk assessors carefully identify sources of uncertainty in their estimates. For the hydrocarbon fractions these assumptions include: the surrogate mixture or component(s) represent the toxicity of the entire fraction; independence of toxic action exists when adding carcinogenic risks within and across fractions under response addition; there is common toxicity within and across fractions for dose-addition-based methods (i.e., HI, RPF); and, synergistic or potentiating toxicological interactions among chemicals are not likely to happen at low environmental contamination levels. An important source of uncertainty is the quality of the underlying toxicity data used to develop either a provisional or screening RfD or a provisional or screening cancer slope factor. To convey the difference in quality in the mixture risk assessment, the U.S. EPA suggests the risk assessors identify the percentage of the estimated risk or of the hazard index that is associated with screening toxicity estimates (i.e., screening cancer slope factors or screening RfDs) and the percentage based on provisional estimates (i.e., provisional cancer slope factors or provisional RfDs). Such examinations of mixture risk estimates are consistent with mixture risk assessment practices (U.S. EPA, 2000; Rice et al., 2005).

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

- 1) U.S. EPA's Integrated Risk Information System (IRIS).
- 2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
- 3) Other (peer-reviewed) toxicity values, including
 - ▶ Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
 - ▶ California Environmental Protection Agency (CalEPA) values, and
 - ▶ EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

Background

Contamination of the environment by aliphatic and aromatic hydrocarbons is widespread. The initial contaminating materials range from crude oil to a wide variety of fuels and lubricating oils. These hydrocarbon products are complex mixtures containing hundreds to thousands of hydrocarbon compounds—including aliphatic compounds (straight-chain, branched-chain, and cyclic alkanes and alkenes) and aromatic compounds (benzene and alkyl benzenes, polycyclic aromatic hydrocarbons [PAHs]). In addition, some of these products contain nonhydrocarbon additives or contaminants.

Once released to the environment, the composition of a hydrocarbon product will change due to weathering (i.e., differential fate and transport of its components). Partitioning of the mixture will occur, such that the more soluble and/or volatile compounds will migrate to other locations and environmental media, leaving the relatively nonmobile components (the weathered product) at the original location. Thus, the actual aliphatic and aromatic hydrocarbon mixture to which a receptor population is exposed will vary with location, time, and environmental medium.

The assessment of human health risks posed by hydrocarbon-contaminated sites has involved analysis for "total petroleum hydrocarbons" (TPH). TPH is a loosely defined aggregate that depends on the method of analysis as well as the contaminating material; it represents the total mass of hydrocarbons without identifying individual compounds. As TPH is not a

consistent entity, the assessment of health effects and development of toxicity criteria such as oral reference doses (RfDs) and slope factors for the complex mixture as a whole are problematic.

Some toxicity data are available for whole, unweathered hydrocarbon products (e.g., as reviewed by ATSDR [1995] and IARC [2008a]). However, there are limitations to using the whole product data due to composition variability caused by differences in the crude oils from which hydrocarbon products are refined, differences in the refining processes itself, and differences in formulations of the final products. In addition, the identity of the released material may not be known, or more than one product may have been released. Toxicity data for whole hydrocarbon products that are relatively heterogeneous are not necessarily applicable to the weathered materials or transport fractions to which exposure actually occurs.

The number of individually identified hydrocarbon components of various petroleum-derived fuels and crude oil has been estimated at approximately 250 by the Total Petroleum Hydrocarbon Criteria Working Group (TPHCWG, 1997b, 1999; Weisman, 1998). At the time, toxicity data were available for about 95 of the identified compounds, but only about 25 were found by the TPHCWG (1997b) to have U.S. EPA toxicity values or sufficient data to develop toxicity criteria. Thus, any attempt to assess the health effects of TPH from the individual hydrocarbon components is impractical because many of the known components lack appropriate toxicity data and criteria. In addition, the cost of analyzing individually for all known TPH constituents would be prohibitive.

In recognition of the impact of weathering, the inapplicability of whole product toxicity data to many contamination scenarios, the impracticality of chemically analyzing each constituent separately, and the need for risk-based assessment of hydrocarbons, an approach has been developed to assess aliphatic and aromatic hydrocarbons on the basis of fractions with similar physical and chemical properties. The advantages of this approach are that these fractions can be defined analytically and that constituents of a fraction have similar environmental transport properties. This type of approach appears to have been initiated by the Massachusetts Department of Environmental Protection (MADEP) to assess TPH, and it has served as the starting point for the TPHCWG. These two groups continued to evolve their approaches somewhat independently. Key publications and technical reports describing the MADEP approach include Hutcheson et al. (1996) and MADEP (1994, 1996, 1997, 2001, 2002, 2003, 2008). Key publications describing the TPHCWG approach are TPHCWG (1997a, b, 1998a, b, 1999), Twerdok (1999) and Weisman (1998). The following sections describe the U.S. EPA Approach. Appendix A contains related discussions on the existing approaches established or adopted by MADEP, TPHCWG, the American Society for Testing and Materials (ASTM), and the Agency for Toxic Substances and Disease Registry (ATSDR).

U.S. EPA Approach: An Overview

At the outset, it is important to emphasize that the present U.S. EPA approach represents expert judgment for the purpose of establishing toxicity values, including PPRTVs, and a risk assessment method for evaluating complex mixtures of aliphatic and aromatic hydrocarbons. As further scientific advancements are made on the toxicology and chemical mixture risk assessment methodologies, it is anticipated that these toxicity values and this U.S. EPA approach will be revisited periodically and appropriate adjustments will be made.

A fractional approach, similar to those advanced by the MADEP and TPHCWG (see separate discussions in Appendix A), is adopted by the U.S. EPA in this PPRTV document. In doing so, some modifications have been incorporated. The present PPRTV document is the principal document outlining the approach, the methodology, and the definition of fractions, selection of surrogates or components, and derivation/selection of toxicity values. In addition, there are nine accompanying PPRTV documents for *n*-hexane, benzene, toluene, ethylbenzene, xylenes, commercial or practical grade hexane, midrange aliphatic hydrocarbon streams, white mineral oil, and high-flash aromatic naphtha (U.S. EPA, 2009a–i). These are surrogate chemicals or mixtures selected for the six fractions (see Table 1 and discussion in following paragraphs), and for which complete toxicity and carcinogenicity assessments were not available from IRIS (U.S. EPA, 2009o) or existing PPRTVs.

Thus, collectively, this PPRTV document plus the nine additional PPRTV documents constitute the entire PPRTV effort undertaken by the U.S. EPA specifically for complex mixtures of aliphatic and aromatic hydrocarbons. As shown in Table 1, prior to defining “fractions,” the components are first classified into Aliphatics and Aromatics; each of these two major fractions is further separated into low-, medium-, and high-carbon range fractions. Surrogate chemicals or mixtures are then selected (see section below on method for surrogate compound or mixture selection) from the available toxicity data for each of these fractions. In the U.S. EPA’s approach, the potential health risk of each of the six aliphatic or aromatic hydrocarbon fractions is represented in one of three ways:

- 1) Surrogate Method: the toxicity value for a surrogate (similar) aliphatic or aromatic hydrocarbon mixture or compound is integrated with the exposure data for the entire mass of the fraction;
- 2) Component Method: the toxicity values for well-studied individual chemicals that make up a large portion of the fraction are combined with their respective exposure estimates using a components-based method under an assumption of dose- or response-addition; or
- 3) Hybrid Method: a combination of 1) and 2) above is used for the same fraction and the results are combined under an assumption of dose- or response-addition.

The fractionation scheme described above is consistent with the analytical chemistry performed on the field samples in the laboratory (Hutcheson et al., 1996). Thus, in field offices of the U.S. EPA, it is anticipated that analytical information in conjunction with the “fraction approach” described herein are to be used for risk assessment of complex mixtures of aliphatic and aromatic hydrocarbons on a specific site. In those fractions where components were isolated, these components may be evaluated individually according to a component method (U.S. EPA, 2000). The components either represent that whole fraction (e.g., aromatic low carbon range) or are indicators for the carcinogenicity of that fraction (e.g., aromatic high carbon range).

The rationale for U.S. EPA's adoption of the fractional approach developed by the MADEP and TPHCWG is based on several factors. First, the development of the "fraction approach" by MADEP and TPHCWG represents the collective wisdom and scientific consensus of numerous scientists involved from governmental agencies, professional organizations, academia, and industry. Second, risk assessment of a chemical mixture, particularly one that is changing due to weathering, is a very difficult and complex issue. The "fraction approach" coupled with analytical information on complex mixtures of aliphatic and aromatic hydrocarbons from a given hazardous waste site, represents a reasonable, flexible, and best available methodology for risk assessment. Third, U.S. EPA scientists have employed computational chemistry and statistical methods to assess the fractionation scheme and found supporting evidence for selecting the fractions in this report.

Risk assessment for complex mixtures of aliphatic and aromatic hydrocarbons, using the fraction approach, is consistent with U.S. EPA mixtures guidelines and supplemental guidance (U.S. EPA, 1986, 2000) and with specific guidance for Superfund (e.g., U.S. EPA, 1989a). The basic approach treats fractions as components of the complex mixture and uses additivity methods within and across fractions to conduct the risk assessment. Thus, the risk of exposure to a fraction, or several fractions at any given time is the sum of the risks within and across fractions.

The U.S. EPA (2000) recommends use of dose-addition methods (HI or RPFs) for characterization of potential risk from exposure to a mixture of chemicals that are toxicologically similar¹. Response addition is recommended for mixture components that act on different systems or produce effects that do not influence each other, and, thus, can be assumed to act independently. Summaries of these methods are provided below. For further guidance, details, and discussion, see U.S. EPA (2000) and the other references cited below.

Hazard Index (HI) (U.S. EPA, 2000)

- Assumes a common mode of action and similarly shaped dose-response curves across the components. The common mode of action assumption can be based on the same target organ or similar effect.
- Component exposures (oral intakes or inhalation concentrations) are scaled by a measure of relative potency—typically the RfD for oral doses and the RfC for inhalation exposure.
- The scaled intakes or concentrations are then summed to provide an indicator of risk from exposure to the mixture.
- Exposures should be relatively low so that interaction effects are not expected.
- Used extensively as an indicator of potential noncancer health risk. Method is commonly used in Superfund site assessments (U.S. EPA, 1989a), for which a screening approach is generally used to estimate the HI for all chemicals with pertinent exposure data and toxicity values, regardless of mode of action or target organ. If the resulting HI is greater than unity, additional procedures, including estimating HIs on a subset of components that have a similar mode of action or target organ may be used to further assess the potential hazard (U.S. EPA, 1989a, 2000).

¹U.S. EPA (2000) defines "similar components" as single chemicals that cause the same biologic activity or are expected to cause a type of biologic activity based on chemical structure. Evidence of similarity may include similarly shaped dose-response curves, or parallel log dose-probit response curves for quantal data on the number of animals (people) responding, and the same mechanism of action or toxic endpoint. These components may also be expected to have comparable characteristics for fate, transport, physiologic processes, and toxicity.

Relative Potency Factors (RPFs) (U.S. EPA, 2000)

- Assumes a common mode of action or similar toxicity and similarly shaped dose-response curves across the components at least in exposure levels of interest to the risk assessment. The common mode of action assumption can be met by toxicological similarity but for specific conditions (endpoint, route, duration).
- Used when toxicity data are incomplete for some components.
- Component exposures (oral intakes or inhalation concentrations) are scaled relative to the potency of an index chemical (typically the best-studied component).
- Scaled intakes or concentrations are then summed, and the dose-response curve of the index chemical is used to generate a response (risk) estimate for the mixture.
- Used for carcinogenic PAHs (U.S. EPA, 1993).

Response Addition (U.S. EPA, 2000)

- Assumes toxicological independence of action and is calculated using the law of statistical independence.
- Risk of an effect is estimated for each component using its dose-response curve (in percent responding) at the component's exposure (oral intake or inhalation concentration).
- Risks are summed (simple sum for small number of chemicals or using the independence formula for large number of chemicals) to yield a risk estimate for the mixture.
- Exposures should be relatively low so that interaction effects are not expected.
- Used extensively for cancer risk characterization. Used in Superfund site assessments (U.S. EPA, 1989a).

The overall risk of exposure to complex mixtures of aliphatic and aromatic hydrocarbons is the sum of the risks or HI's from all fractions to which a population is exposed, as shown in Figures 1 and 2, respectively, and discussed in the following paragraphs. The quantitative exposure information for these individual chemicals or fractions/subfractions is based on analytical data from the hazardous waste sites. For the sake of completeness, Figures 1 and 2 show a summation across all six fractions, but, depending on the source of the mixture and weathering and transport, exposure may be limited to only one or a few fractions. Each of the six fractions is represented by (1) an individual surrogate chemical; (2) a surrogate mixture; and/or (3) actual components (e.g., aromatic low carbon range, see Table 1). In the case of (1) and (2), the surrogate chemical or mixture is the entity that meets criteria for similarity with the fraction or its components (as discussed later in this PPRTV), and for which there is sufficient information for derivation of toxicity values. In one instance (i.e., mid carbon range aromatic fraction, see Table 1), a surrogate mixture is selected to represent the remainder of the fraction after the components with different and more potent toxicities (i.e., naphthalene and 2-methylnaphthalene) are assessed individually. Figures 1 and 2 provide a graphic illustration of how cancer and noncancer risk assessments are carried out, respectively. The illustrated noncancer assessment (Figure 1) is performed at a screening level, consistent with Superfund practice and guidance (1989a).

By applying additivity concepts to the risk evaluation of these complex mixtures, the U.S. EPA is applying a straightforward approach that incorporates a number of simplifying assumptions. Because assumptions for complex chemical mixtures are often difficult to substantiate, this U.S. EPA approach can be considered as a default approach that can be used to evaluate potential health risks from exposures to aliphatic and aromatic hydrocarbon mixtures

when whole mixture toxicity data for a specific site are not available. These assumptions include: the surrogate mixture or component(s) represent the toxicity of the entire fraction; independence of toxic action exists when adding carcinogenic risks within and across fractions under response addition; there is common toxicity within and across fractions for dose-addition-based methods (i.e., HI, RPF); and, synergistic or potentiating toxicological interactions among chemicals are not likely to happen at low environmental contamination levels. Discussions are presented in the next section of this document regarding how well each of the surrogate mixtures or component(s) represents the toxicity of its associated fraction; information from these discussions can be used in a risk characterization. Because the composition of hydrocarbon mixtures is complex and varies with time-dependent weathering and transport changes, it will be difficult to provide evidence that the other three assumptions mentioned here are being met for every exposure scenario. For cancer risk estimation, response addition (for most chemicals) and RPFs (for PAHS) are well-established chemical mixture methods. Response addition has been identified as a default method for evaluating carcinogenic risk for mixtures, assuming independence of toxic action, whose result is interpreted as the risk of any cancer regardless of tumor site (U.S. EPA, 1989a, 2000). The RPF method, based on an assumption of dose-addition, has long been used by U.S. EPA to evaluate seven PAHs for carcinogenicity (U.S. EPA, 1993); B[a]P has been used as the surrogate to represent the carcinogenicity of the other PAHs. These methods, shown in Figure 2, are recommended in this document and may be used as defaults within the fraction approach to evaluate potential cancer risks. Application of the HI to the fractions, as shown in Figure 2 may be performed at a screening level, consistent with Superfund practice and guidance (U.S. EPA, 1989a). Although exposures to the surrogate mixtures and components that represent the fractions may produce different toxic effects, it may be argued that a screening level HI is appropriate because it is unknown whether the effects caused by other compounds in the fractions may indeed cause similar toxicity across fractions. Finally, when two or more chemicals at a site are identified as having high exposure concentrations, the toxicology literature should be consulted for evidence of toxicological interactions among these chemicals. If synergism is found for these chemicals, then this should be called out in the risk characterization along with the quantitative risk or hazard estimates. In general, these four assumptions should be evaluated and verified whenever possible and the results articulated as part of the final risk characterization.

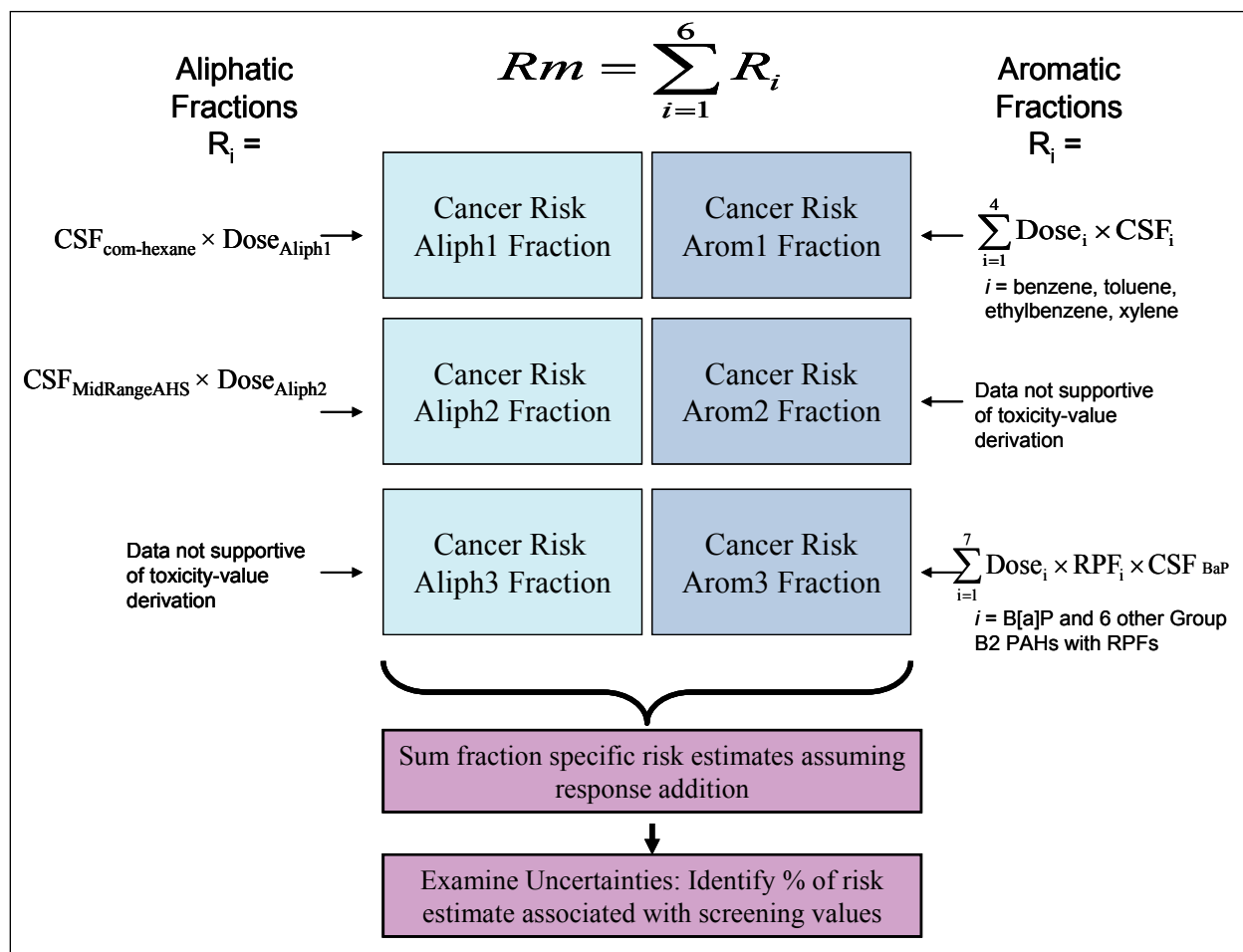


Figure 2. Fraction-based Cancer Risk Assessment for Complex Mixtures of Aliphatic and Aromatic Hydrocarbons

Where:

- R_m = Risk posed by the mixture
- R_i = Risk function associated with the i th fraction
- $Dose_i$ = Oral Exposure Dose or Inhalation Exposure Concentration for the i th fraction (mg/kg-day or mg/m³, respectively)
- CSF_i = Cancer Slope Factor (OSF) or Inhalation Unit Risk (IUR) of surrogate chemical or components in (mg/kg-day)⁻¹ or (μg/m³)⁻¹, respectively
- $Com-hexane$ = commercial hexane
- AHS = Aliphatic Hydrocarbon Streams
- RPF_i = Relative Potency Factor for the i th PAH
- BaP = Benzo(a)pyrene

In addition to describing the underlying assumptions when evaluating risks posed by hydrocarbon mixtures, risk assessors also will consider sources of uncertainty in the assessment. One source of uncertainty pertains to the quality of the data underlying toxicity values. Differences or perceived differences in the quality of the underlying data led the U.S. EPA to categorize some hydrocarbon RfDs and cancer slope factors as provisional values, while others with less information or lower quality information were categorized as screening values, which appear in appendices of the PPRTVs. For example, in some cases, U.S. EPA could not determine whether the relevant toxicity data had undergone independent, external, scientific peer review; in these cases, a screening RfD or screening cancer slope factor was developed (see Table 1). To convey this difference in the quality of the data used in the mixture risk assessment, the U.S. EPA suggests that risk assessors identify the percentage of the estimated risk or of the hazard index that is associated with screening toxicity estimates (i.e., screening cancer slope factors or screening RfDs) and the percentage based on provisional estimates (i.e., provisional cancer slope factors or provisional RfDs). It is likely that there will be less confidence in estimates utilizing a higher percentage of screening RfDs or screening cancer slope factors when compared to those estimates comprised of a lower percentage of screening RfDs or screening cancer slope factors. Such examinations of mixture risk estimates are consistent with mixture risk assessment practices (U.S. EPA, 2000; Rice et al., 2005).

DEFINITION OF FRACTIONS AND DERIVATION/ SELECTION OF TOXICITY VALUES

Rationale and Recommendations for U.S. EPA Approach

The U.S. EPA approach to evaluating complex mixtures of aliphatic and aromatic hydrocarbons is fundamentally a fraction-based approach, building on the contributions of the MADEP and the TPHCWG. Some modifications are recommended in (1) fraction definition, (2) selection of a surrogate compound or mixture, or of a components-based method for the fraction, and (3) selection or derivation of toxicity values based on up-to-date methods and data.

Given the complexity of the problem and the number of individual compounds that are constituents of complex mixtures of aliphatic and aromatic hydrocarbons, a fraction approach is a practical method for assessing the health risks from exposure to these mixtures that accounts for variation in mixture composition across sites. MADEP (2003) establishes hydrocarbon fractions based first on molecular structure (aromatic versus aliphatic), and then, secondly, on number of carbon atoms (C), using toxicologically similar groupings and excluding compounds with less than five carbons because their high volatility precludes chronic exposure from spills/releases. The TPHCWG (1997a) also establishes hydrocarbon fractions based on molecular structure, but, as the second delineator, it uses equivalent carbon (EC) number index. This index is equivalent to the retention time of the compounds on a boiling-point gas chromatography (GC) column (nonpolar capillary column), normalized to the *n*-alkanes. For example, benzene, a C₆ aromatic compound has an EC of 6.5 because its boiling point and GC retention time are approximately halfway between those of *n*-hexane (C₆, EC₆) and *n*-heptane (C₇, EC₇). The assessment of transport fractions, as defined by the TPHCWG (1997a) for TPH, appears particularly useful because these fractions relate to transport in the environment (at least under certain conditions). Their transport can be modeled, and they are consistent with the analytical methods used to quantify and identify hydrocarbons. These fractions are defined by the ranges of their EC number indices, which are related to their transport in the environment.

The following sections of this PPRTV document present the aliphatic and aromatic fractions and discuss the available toxicity assessments for individual compounds and similar mixtures (if any) for each fraction. Both the C and EC ranges of the fractions are noted. In addition, recommendations are presented for a fraction-based assessment of complex mixtures of aliphatic and aromatic hydrocarbons. The recommendations include selection of appropriate surrogates or a components method for each fraction and selection of appropriate toxicity values for those surrogates/components.

The aliphatic hydrocarbon fractions are discussed first. These compounds pose a particular problem because little or no toxicity data are available for most of the individual constituents, and, although data for mixtures corresponding to these fractions have been generated, many of the studies originally were unpublished industry studies. Some of the studies are now available as Toxic Substances Control Act Test Submissions (TSCATS) microfiche, or were provided by MADEP, and a few have been published.

The aromatic hydrocarbon fractions, discussed subsequently, pose less of a problem because of the availability not only of toxicity data, but also, in many cases, of U.S. EPA RfDs and cancer assessments. The definition of the fractions, however, is not as clear.

As a preliminary step in identifying potential surrogate compounds to represent the toxicity of the fractions or identifying compounds useful in a components method, a list of individual hydrocarbons was compiled and additional background searching was performed. The list included all individual hydrocarbons considered previously by the U.S. EPA NCEA's Superfund Technical Support Center in the evaluation of hydrocarbons, as well as all those with toxicity data reviewed by MADEP (2003) or the TPHCWG (1997b). Similarly, a list of mixtures, primarily hydrocarbon streams, was compiled from these sources. Background searching focused on the IRIS database (U.S. EPA, 2009o), the HEAST (U.S. EPA, 1997), ATSDR Toxicological Profiles (ATSDR, 2008), the Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994), and the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). Additionally, CalEPA (2008), the National Toxicology Program (NTP, 2008), the World Health Organization (WHO, 2008), and the International Agency for Research on Cancer (IARC, 2008a, b) were consulted for information. The U.S. EPA's (2007a) High Production Volume (HPV) Challenge Program, and particularly the Petroleum HPV Testing Group (2007) publications, as well as the Organisation for Economic Co-operation and Development (OECD) HPV Programme Screening Information Data Set (SIDS) documents (OECD/SIDS, 2007) were searched for pertinent information. Additional pertinent individual compounds and mixtures encountered during this background search were added to the list for further consideration. On the basis of the information found during background searches, some compounds and mixtures that appeared to be possible candidates for use as surrogates were subjected to preliminary searching in MEDLINE (PUBMED) and TSCATS. If chosen for PPRTV development on the basis of the results of the background searching or the preliminary searching, compounds and mixtures were then subjected to the full suite of searching (through 2009). The search details are described in the front matter of the PPRTV documents (U.S. EPA, 2009a-i). Final lists of candidate toxicity values for consideration as surrogates for the aromatic and aliphatic fractions are compiled in Tables 2-6 of this document; the sources are identified in the left column as IRIS, PPRTV, HEAST, MADEP, TPHCWG, or ATSDR.

Method for Surrogate Compound or Mixture Selection

The criteria used for selecting chemicals or mixtures for potential use as surrogates, or for choosing a components method, are as follows:

- The surrogate mixture or compound had to be a relevant aliphatic or aromatic hydrocarbon or composed exclusively of aliphatic or aromatic hydrocarbons.
- The surrogate mixture or compound had to have either U.S. EPA toxicity values or adequate data for the derivation of toxicity values—particularly subchronic and chronic RfDs and/or RfCs. The ability to support the development of a carcinogenicity assessment was desirable but not required.
- First preference was given to mixtures that are similar² to the fraction in composition, and that have toxicity values or adequate toxicity data to support the derivation of toxicity values.
 - Criteria for similarity of composition included similar C and EC number range, similar aliphatic or aromatic hydrocarbon components, and purity (e.g., lack of contamination of aliphatic mixtures with aromatics and vice versa, and lack of contamination with nonaliphatic or aromatic hydrocarbon compounds).
 - Toxicity considerations include similarity of effect of the surrogate mixture with known toxicities of the individual components of the fraction.
- If suitable mixture data were lacking, the next step was to select from the fraction a representative compound that was known or could be assumed to be similar toxicologically (defined previously), in terms of types of effects in vivo and potency, to the other compounds in the fraction, and that had either suitable toxicity values or adequate toxicity data to support the derivation of toxicity values.
- If the components of the fraction varied highly in type or potency of toxic action, the more toxic component (e.g., *n*-hexane, low carbon range aliphatic fraction) was used as the surrogate when it exceeded the percentage found in the surrogate mixture (e.g., commercial hexane, inhalation assessment) or when other suitable values were not available for the exposure route (oral). Alternatively, the components with different and more potent toxicities (naphthalene and 2-methylnaphthalene) were recommended to be assessed separately, and the remaining mass of the fraction (medium carbon range aromatics) assessed using values for a surrogate mixture (high-flash aromatic naphtha).
- If the toxicities of all the individual compounds were well characterized, toxicity values were available or could be derived for the individual compounds, and these compounds were monitored at sites of aliphatic or aromatic hydrocarbon contamination, then toxicity values were provided for the individual compounds to support a components method wherein the potential risk from exposure to each component is assessed individually (e.g., the low carbon range aromatic fraction), followed by application of appropriate additivity methods.
- For the high carbon range aromatic fraction, a components method was recommended for the carcinogenic (Group B2) PAHs, using an existing method, the RPF method, to assess carcinogenicity.

²Similar mixtures are mixtures that differ slightly, but they are expected to have comparable characteristics for fate, transport, physiologic processes, and toxicity. These mixtures may have the same components but in slightly different proportions, or they have most components in nearly the same proportions with only a few different (more or fewer) components. Similar mixtures cause the same biologic activity or are expected to cause the same type of biologic activity due to chemical composition. Similar mixtures act by the same mechanism of action or affect the same toxic endpoint (U.S. EPA, 2000).

- Uncertainties regarding the suitability of the surrogate compound or mixture to represent the toxicity of the fraction were discussed.

Toxicity Values for Aliphatic Fractions

The aliphatic fractions as defined by MADEP in terms of C range are similar to the fractions as defined by the TPHCWG (1997a, b) in terms of EC range. This provisional assessment adopts these fractions and lists both C and EC ranges.

Low Carbon Range Aliphatic Fraction: C5–C8, EC5–EC8

This fraction includes *n*-pentane, *n*-hexane, cyclohexane, the dimethylbutanes and methylpentanes, cyclopentane, *n*-heptane, *n*-octane, some branched chain alkanes including the trimethylpentanes, cyclohexane, methylcyclopentane, and methylcyclohexane. According to the TPHCWG, this fraction also includes some alkenes, such as 1-hexene. MADEP, however, includes alkenes with aromatics and says they are not present in high concentrations in petroleum products. Previous efforts by MADEP (2003) and TPHCWG (1997b) to identify toxicity data for hydrocarbons in this fraction reported toxicity data for *n*-pentane, 2- and 3-methylpentane, *n*-hexane, methylcyclopentane, cyclohexane, *n*-heptane, methylcyclohexane, 2,2,4-trimethylpentane, and 1-hexene, as well as for two mixtures: commercial hexane and technical-grade heptane (MADEP, 2003; TPHCWG, 1997b).

Commercial hexane generally contains approximately 50–53% *n*-hexane (TPHCWG, 1997b; U.S. EPA, 2005b). The remaining constituents of commercial hexane are the following branched and cyclic C6 aliphatic compounds: 3-methylpentane, methylcyclopentane, 2-methylpentane, cyclohexane, 2,3-dimethylbutane, and <1% of several minor constituents. Technical-grade heptane, in the only toxicity study located for this mixture (Truhaut et al., 1973), contained approximately 52% *n*-heptane, with the remainder of the mixture consisting of the following C6–C8 aliphatic compounds: 2- and 3-methylhexane, 2,3-dimethylpentane, cyclohexane, methylcyclohexane, 2,4-dimethylhexane, and approximately 3% aromatic compounds (benzene and toluene). It did not contain *n*-hexane.

For this low carbon range aliphatic fraction, derivations of toxicity values have been considered by the U.S. EPA, ATSDR, MADEP, and TPHCWG and are summarized in Table 2. RfCs are available for *n*-hexane and cyclohexane, but no RfDs are available on IRIS (U.S. EPA, 2009c). A subchronic provisional RfD (p-RfD) and a subchronic p-RfC have been developed for *n*-hexane (U.S. EPA, 2009c). The only aliphatic hydrocarbon mixture in this fraction range that has sufficient toxicity data for derivation of oral or inhalation toxicity values is commercial hexane. Although the oral data do not support derivation of RfDs, a subchronic p-RfC, a p-RfC, and a cancer assessment, including a screening³ inhalation unit risk, have been developed for commercial hexane (U.S. EPA, 2009f). Updated literature searches were performed for cyclohexane in 2009, but no newer data that would support derivation of oral toxicity values or impact the inhalation RfC were found. *n*-Heptane and methylcyclohexane were the subjects of PPRTV development; the data did not support development of subchronic or chronic RfDs or RfCs for these compounds (U.S. EPA, 2004d, 2005a). Development of a PPRTV for *n*-pentane is in process; information from that PPRTV will be considered for use in evaluating hydrocarbon mixtures when this mixtures PPRTV document is revised.

³ Screening values are developed in the Appendix of a PPRTV. For example, in cases where a high degree of uncertainty exists. Screening values are intended for use in limited circumstances when no Tier 1, 2, or 3 values are available.

Table 2. Toxicity Values for the Low-Carbon Range Aliphatic Fraction: C5–C8, EC5–EC8^a

Source	C	EC	Name	Derived Value		Cancer WOE	OSF (per mg/kg-day)	IUR (per µg/m ³)	Date ^b
				Oral (mg/kg-day)	Inhalation (mg/m ³)				
IRIS and PPRTV Values									
IRIS (U.S. EPA, 2009o)	6	6	<i>n</i> -Hexane	RfD: Inadequate data	RfC: 7×10^{-1} , peripheral neuropathy, Huang et al., 1989	Inadequate data	NA	NA	2005b
	6	6.59	Cyclohexane	RfD: Inadequate data	RfC: 6×10^0 , reduced pup weight, DuPont HLR, 1997	Inadequate data	NA	NA	2003
	7	7	<i>n</i> -Heptane	Not assessed	Not assessed	Group D (not classifiable)	NA	NA	1996
	8	6.98	2,2,4-Trimethylpentane	RfD: Inadequate data	RfC: Inadequate data	Inadequate data	NA	NA	2007
PPRTV (U.S EPA, date in last column)	5	5	<i>n</i> -Pentane						INPROC
	6	6	<i>n</i> -Hexane	sRfD: 3×10^{-1} , reduced nerve conduction velocity (Ono et al., 1981) RfD: Not assessed	sRfC: 2×10^0 , decreased motor nerve conduction velocity, Huang et al., 1989 RfC: Not assessed	Not assessed	Not assessed	Not assessed	2009b
	7	7	<i>n</i> -Heptane	sRfD: Inadequate data RfD: Inadequate data	sRfC: Inadequate data RfC: Inadequate data	Inadequate data	Inadequate data	Inadequate data	2004d
	7	7.22	Methylcyclohexane	sRfD: Inadequate data RfD: Inadequate data	sRfC: Inadequate data RfC: Inadequate data	Cannot be determined-suggestive	NA	NA	2005a
PPRTV (U.S EPA, date in last column)	6	–	Commercial hexane	sRfD: Inadequate data RfD: Inadequate data	sRfC: 27×10^0 , clinical and histopathological signs of neuropathy, IRDC, 1992a,b RfC: 6×10^{-1} , nasal epithelial cell hyperplasia, Biodynamics, 1993a/Daughtrey et al.,1999	Suggestive evidence	Inadequate data	1.9×10^{-7} pituitary adenoma or carcinoma, Biodynamics, 1993b; Daughtrey et al., 1999 (*Screening Value)	2009f

Table 2. Toxicity Values for the Low-Carbon Range Aliphatic Fraction: C5–C8, EC5–EC8^a

Source	C	EC	Name	Derived Value		Cancer WOE	OSF (per mg/kg-day)	IUR (per µg/m ³)	Date ^b
				Oral (mg/kg-day)	Inhalation (mg/m ³)				
Other Peer-Reviewed or Relevant Toxicity Values									
HEAST (U.S. EPA, 1997)	6	6	<i>n</i> -Hexane	sRfD: 6×10^{-1} neuropathy and testicular atrophy, Krasavage et al., 1980 RfD: 6×10^{-2} neuropathy and testicular atrophy, Krasavage et al., 1980	sRfC: 2×10^{-1} adopted RfC on IRIS at the time as sRfC	Not assessed	Not assessed	Not assessed	–
	7	7.22	Methylcyclohexane	Not assessed	sRfC: 3×10^0 , possible male rat hyaline droplet nephropathy, Kinkead et al., 1985 RfC: 3×10^0 , possible male rat hyaline droplet nephropathy, Kinkead et al., 1985	Not assessed	Not assessed	Not assessed	–
MADEP (2003)	6	6	<i>n</i> -Hexane	RfD: 4×10^{-2} , reduced body weight (peripheral neuropathy at high dose), Krasavage et al., 1980	RfC: 2×10^{-1} , neurotoxicity, 1993 IRIS value	Not assessed	Not assessed	Not assessed	–
TPHCWG (1997b)	6	–	Commercial hexane	RfD: 5×10^0 , extrapolated from TPHCWG RfC	1.84×10^1 , neurotoxicity and other systemic and portal of entry effects (several industry studies, mostly referenced to abstracts)	Not assessed	Not assessed	Not assessed	–
ATSDR (date in last column)	6	6	<i>n</i> -Hexane	Intermediate MRL: Inadequate data Chronic MRL: Inadequate data	Intermediate MRL: Inadequate data Chronic MRL: 6×10^{-1} ppm, reduced motor nerve conduction velocity, Sanagi et al., 1980	Not assessed	Not assessed	Not assessed	1999b

^aComplete citations for the principal studies can be found in the source documents (e.g., IRIS [U.S. EPA, 2009o])

^bDate of IRIS assessment (last revision) or of PPRTV or ATSDR toxicological profile; dates for HEAST, MADEP and TPHCWG are provided in far left column of table.

ATSDR = Agency for Toxic Substances and Disease Registry, C = carbon number, EC = equivalent carbon number index, HEAST = Health Effects Assessment summary Table, INPROC = in process, IRIS = Integrated Risk Information System, IUR = inhalation unit risk, MADEP = Massachusetts Department of Environmental Protection, MRL = Minimal Risk Level, NA = Not applicable, OSF = oral slope factor, p- = provisional, PPRTV = Provisional Peer-Reviewed Toxicity Value, PTV = Provisional Toxicity Value (draft), RfC = inhalation reference concentration, sRfC = subchronic RfC, RfD = oral reference dose, sRfD = subchronic RfD, TPHCWG = Total Petroleum Hydrocarbon Criteria Working Group, WOE = weight of evidence

ATSDR has considered *n*-hexane, but it has not developed oral MRLs for this compound (ATSDR, 1999b). The HEAST (U.S. EPA, 1997) lists subchronic and chronic RfDs for *n*-hexane and subchronic and chronic RfCs for methylcyclohexane, but these values are superseded by the more recent PPRTV documents for these chemicals. MADEP (2003) has developed an RfD for *n*-hexane and has adopted the previous IRIS RfC for this compound (the current RfC became available in 2005). The TPHCWG (1997b) has derived an inhalation RfC for commercial hexane using methods inconsistent with current U.S. EPA practice, and they performed a route-to-route extrapolation of this value to derive an RfD.

As per MADEP's (2003) update of its toxicity values and the 2004 PPRTV on *n*-heptane (which also covered technical-grade heptanes; U.S. EPA, 2004d), pertinent data for technical-grade heptane are limited to a single study (i.e., Truhaut et al., 1973) that suggested peripheral neuropathy in rats exposed by inhalation. Information in the study, however, does not support development of toxicity values, and the mixture contained both toluene and benzene, as previously described. Literature searches conducted in 2009 revealed no newer data or any data on an aromatic-free heptane mixture that could be used to develop toxicity values.

Data on the individual aliphatic hydrocarbons of this fraction suggest nervous system effects. While some of the compounds have central nervous system effects, as well as liver and kidney effects, peripheral neuropathy is the critical effect of *n*-hexane, mediated through its metabolite, 2,5-hexandione (a gamma-diketone; U.S. EPA, 2009o). Concern has focused on the potential for some of the other compounds in this fraction to be metabolized to gamma-diketones and, therefore, also cause peripheral neuropathy. As reviewed by MADEP (2003), studies with the putative gamma-diketone metabolites (e.g., 2,5-heptanedione, 3,6-octanedione) of some of the compounds in this fraction have suggested that they may cause peripheral neuropathy, but data showing that exposure to the parent compound may cause peripheral neuropathy are inadequate. For example, neither oral nor inhalation exposure to *n*-heptane caused peripheral neuropathy in rats in studies that specifically investigated this potential outcome (U.S. EPA, 2004d). In a study of the potential peripheral neurotoxicity of *n*-hexane isomers, 2-methylpentane, 3-methylpentane, and methylcyclopentane were administered by gavage to rats in increasing amounts over the course of 8 weeks (Ono et al., 1981). Although *n*-hexane, administered in the same manner, significantly decreased peripheral nerve conduction velocity (motor nerve, mixed nerve-distal portion, and mixed nerve-proximal portion of the tail), the other compounds were less effective or ineffective. The data, however, were reported graphically, no clinical signs of neuropathy were seen for any of the compounds, and histopathological examinations of the peripheral nerves were not conducted. Thus, the effects of these hexane isomers are not readily quantifiable and the clinical significance of the isomer results is unclear. However, Krasavage et al. (1980) also directly showed that none of these compounds produced toxicity to the extent that 2,5-hexandione did. This study showed a correlation between neurotoxicity index and the peak serum concentrations of 2,5-hexandione from several peripheral neurotoxicants including *n*-hexane.

To represent the toxicity of this fraction, the inhalation PPRTVs for commercial hexane (U.S. EPA, 2009f) are recommended, unless *n*-hexane accounts for >53% of the analyzed fraction, in which case the *n*-hexane toxicity values should be used (see Table 2). Use of the mixture data better represents the toxicity of the fraction, although there are uncertainties with this method because it is predominantly a C6 mixture. Exposure to airborne commercial mixtures has been associated in a few studies with neurological effects in workers (e.g.,

Passero et al., 1983), and a subchronic continuous inhalation exposure study of commercial hexane in experimental animals (IRDC, 1992a, b) reported peripheral neuropathy as the critical effect. In contrast, the critical effect for chronic inhalation exposure to this mixture was nasal lesions. While histopathological evaluation of the respiratory tract was performed in the subchronic study, no adverse findings were observed. Therefore, a chronic p-RfC based on nasal and laryngeal lesions is protective for the peripheral neuropathy seen in the subchronic continuous exposure study (IRDC, 1992a, b). Because no oral toxicity values could be derived for commercial hexane, the oral toxicity of the fraction can be assessed using the subchronic p-RfD for *n*-hexane (U.S. EPA, 2009c). The data for commercial hexane are considered adequate to develop a quantitative estimate of cancer risk from inhalation exposure for this fraction. However, because the WOE indicates “*Suggestive Evidence for the Carcinogenic Potential*,” there is some uncertainty associated with the quantification. For these reasons, Appendix A of the commercial hexane PPRTV document contains a screening p-IUR that may be useful in certain instances (i.e., when *n*-hexane accounts for $\leq 53\%$ of this fraction). Please see the that Appendix for details (U.S. EPA, 2009f). Table 2 lists these values and assessments.

Medium Carbon Range Aliphatic Fraction: C9–C18, EC > 8–EC16

This fraction includes *n*-nonane, *n*-decane, and longer chain *n*-alkanes; a few *n*-alkenes (e.g., tridecene); branched chain alkanes and alkenes; and alkyl-substituted cycloalkanes (see comment about alkenes at the beginning of the previous section). Derivations of toxicity values for these compounds are not available from the U.S. EPA’s IRIS or HEAST, or from ATSDR, MADEP, or TPHCWG. PPRTVs for *n*-nonane and *n*-decane are completed; information from those PPRTVs will be considered for use in evaluating hydrocarbon mixtures when this mixtures PPRTV document is revised. Limited toxicity data are available for *n*-undecane (VCCEP, 2004). ATSDR toxicological profiles and inhalation MRLs are available for various jet fuels and kerosene, but these mixtures have a substantial aromatic content and are therefore not suitable to represent the toxicity of this fraction. The toxicity of this fraction may be better represented by dearomatized hydrocarbon streams and solvents that fall within this carbon range and have minimal (<1.0%) aromatic content. Subchronic oral toxicity studies were performed with the mixtures listed in the following bullets (note that the term *n*-paraffins refers to *n*-alkanes, the term isoparaffins refers to branched chain alkanes, and the terms naphthenes and cycloparaffins refer to cyclic alkanes):

- C11–C17 isoparaffin mixture, typical aromatic content <0.05% (Anonymous, 1990);
- C9–C12 isoparaffin/*n*-alkane/naphthene mixture with an aromatic content <0.5% (Anonymous, 1991b);
- C10–C13 isoparaffin/naphthene/*n*-alkane mixture with an aromatic content of 0.1% (Anonymous, 1991a).

Subchronic and 6-month inhalation toxicity studies have been performed with the following mixtures:

- C10–C11 isoparaffin mixture with no aromatic content (Phillips and Egan, 1984a);
- C11–C12 dearomatized white spirit (paraffin/naphthene mixture) with an aromatic content <0.5% (Phillips and Egan, 1984b);
- C range not reported, dearomatized white spirit (content not reported; Lund et al., 1996).

Subchronic toxicity and 2-year toxicity/carcinogenicity studies have been performed with the following mixture:

- C10–C13 Stoddard Solvent IIC (*n*-paraffins, isoparaffins, cycloparaffins) with an aromatic content <1.0% (NTP, 2004).

Complete citations for these studies are provided in U.S. EPA (2009h). Some additional supporting toxicity studies on similar mixtures are available as well.

Table 3 lists the available toxicity information for this fraction. The MADEP (2003) and TPHCWG (1997b) have based their toxicity values for this fraction on some of the studies of aliphatic hydrocarbon streams. Other suitable data have not been located. The mixture data are considered preferable to single component data, as previously discussed. Accordingly, PPRTVs were derived based on the mixture data as part of the effort to provide suitable toxicity values for this fraction (U.S. EPA, 2009h) using current U.S. EPA methods. These PPRTVs, listed in Table 3, are the recommended values for this fraction and include subchronic and chronic p-RfCs and a provisional cancer WOE of “*Suggestive Evidence of Carcinogenic Potential.*” In addition, Table 3 contains several screening values that may be useful in evaluating this fraction, developed in Appendix A of U.S. EPA (2009h). Because the toxicity data based on the three unpublished studies (Anonymous, 1990, 1991a,b) are not peer-reviewed, only screening chronic or subchronic RfDs are available in Table 3. The data are considered adequate to develop a quantitative estimate of cancer risk from inhalation exposure. However, because the WOE indicates “*Suggestive Evidence for the Carcinogenic Potential,*” there is some uncertainty associated with the quantification. Appendix A of the PPRTV document on the Midrange Aliphatic Hydrocarbon Streams contains a screening p-IUR and screening chronic or subchronic RfDs that may be useful in certain instances (U.S. EPA, 2009h). Please see that Appendix for details. The screening IUR is listed in Table 3 (U.S. EPA, 2009h).

Table 3. Toxicity Values for the Medium Carbon Range Aliphatic Fraction: C9–C18, EC > 8–EC16^a

Source	C	EC	Name	Derived Value		Cancer WOE	OSF (per mg/kg-day)	IUR (per µg/m ³)	Date ^b
				Oral (mg/kg-day)	Inhalation (mg/m ³)				
PPRTV Values									
PPRTV (U.S. EPA) date in last column	9	9	<i>n</i> -Nonane						INPROC
	10	10	<i>n</i> -Decane						INPROC
	9–18	8–16	Aliphatic hydrocarbon streams/solvents within the C9–C18 range and containing <0.5% to <1% aromatics	sRfD: 1×10^{-1} , liver, kidney and hematologic effects, Anonymous, 1990, 1991a,b (*Screening Value) RfD: 1×10^{-2} , based on same study as the sRfD (*Screening Value)	sRfC: 1×10^{-1} , nasal goblet cell hypertrophy, NTP, 2004 RfC: 1×10^{-1} , nasal goblet cell hypertrophy and adrenal hyperplasia, NTP, 2004	Suggestive evidence	Inadequate data	4.5×10^{-6} , benign or malignant adrenal pheochromocytoma, NTP, 2004 (*Screening Value)	2009h
Other Peer-Reviewed or Relevant Toxicity Values									
MADEP (2003)	9–18	8–16	Aliphatic hydrocarbon streams within the C9–C18 range and containing <0.5% aromatics	RfD: 1×10^{-1} , liver effects, Anonymous, 1990, 1991a,b	RfC: 2×10^{-1} , neurological effects, Lund et al., 1995	Not assessed	Not assessed	Not assessed	–
TPHCWG (1997b)	9–18	8–16	Aliphatic hydrocarbon streams within the C9–C18 range and containing <0.5% aromatics	RfD: 1×10^{-1} , liver effects, unpublished studies not further referenced	RfC: 1×10^0 , NOAELs, multiple studies	Not assessed	Not assessed	Not assessed	–

^aComplete citations for the principal studies can be found in the source documents (e.g., MADEP, 2003).

^bDate of PPRTV; dates for MADEP and TPHCWG are provided in far left column of table.

*Screening values are developed in the Appendix of a PPRTV. For example, in cases where a high degree of uncertainty exists. Screening Values are intended for use in limited circumstances when no Tier 1, 2, or 3 values are available.

C = carbon number, EC = equivalent carbon number index, INPROC = in process, IUR = inhalation unit risk, MADEP = Massachusetts Department of Environmental Protection, NOAEL = no-observed-adverse-effect level, OSF = oral slope factor, p- = provisional, PPRTV = Provisional Peer-Reviewed Toxicity Value, RfC = inhalation reference concentration, sRfC = subchronic RfC, RfD = oral reference dose, sRfD = subchronic RfD, TPHCWG = Total Petroleum Hydrocarbon Criteria Working Group, WOE = weight of evidence

High Carbon Range Aliphatic Fraction: C19–C32, EC > 16–EC35

This fraction includes longer *n*-alkanes, such as eicosane, and branched and cyclic alkanes. Toxicity values are not available for the individual compounds. A search for toxicity information on eicosane in particular was desirable because MADEP (1994) had suggested it as a reference compound for this fraction, but data supportive of derivation of toxicity values were not located. Food-grade and medicinal-grade mineral oils are pure (aromatic-free) mixtures of aliphatic hydrocarbons that correspond to this carbon range fraction and have data suitable for toxicity-value derivation. Both MADEP (2003) and TPHCWG (1997b) have based RfDs on these data. To support this update of the PPRTV on aliphatic and aromatic hydrocarbons, literature searches on mineral oils were performed and the medical literature on mineral oils was consulted. Oral PPRTVs and a cancer assessment, including a WOE of “*Inadequate Information to Assess the Carcinogenic Potential*” of white mineral oil, were derived (U.S. EPA, 2009i) using current U.S. EPA methods. Table 4 summarizes the resulting values and the previous MADEP and TPHCWG values. The PPRTVs are recommended for assessment of this fraction.

Toxicity Values for Aromatic Fractions**Low Carbon Range Aromatic Fraction: C6–C8, EC6–EC < 9**

This fraction contains aromatic hydrocarbons in the C6-C8 range: benzene, toluene, ethylbenzene, and *o*-, *m*-, and *p*-xylenes (commonly referred to as BTEX). The TPHCWG (1997b) defined this fraction variously as EC > 7–EC8 and EC5–EC8. Benzene was not included in the noncancer assessment because it was a carcinogenic indicator compound. Toluene, ethylbenzene, styrene, and xylene were included, but, with the exception of toluene, the EC values for these C8 compounds are all >8 (and <9), so it appears that the TPHCWG (1997b) was using actual C number rather than EC number. The MADEP recommended that the low-carbon-range aromatics (BTEX [MADEP 1994, 2003] and styrene [MADEP, 2003]) be assessed individually. It is unclear, however, whether styrene is a constituent of petroleum products. For example, styrene is not reported as a constituent of any of the petroleum mixtures including gasoline, kerosene, jet fuels, diesel fuel, fuel oils, lubricating and motor oils, and crude oil in the TPHCWG (1998b) Volume 2. The TPHCWG (1997a) Volume 3 lists styrene as a constituent for only one mixture, diesel, at a very low weight percentage of <0.002%, which may mean that it was detected but was below the quantitation limit. The reference provided for that information is a personal communication prepared for British Petroleum; thus, the information cannot readily be confirmed.

Because U.S. EPA toxicity values and cancer assessments are available for the individual compounds in this fraction, and because the BTEX routinely are monitored at sites of aromatic hydrocarbon contamination, the recommendation for this fraction is to assess the BTEX individually. Consistent with this recommendation, the low carbon range aromatic fraction is defined as a C6–C8 and EC6–EC < 9 fraction so that it includes all of the BTEX. RfDs, RfCs, and cancer assessments are available on IRIS (U.S. EPA, 2009o) for these compounds, and provisional toxicity values were derived for subchronic oral and inhalation exposure (U.S. EPA, 2009a–d) as part of this effort. The HEAST (U.S. EPA, 1997) lists some values or assessments for the compounds, but they are superseded by the newer IRIS and PPRTV assessments. ATSDR has derived MRLs for the BTEX as well, but their methods sometimes differ from U.S. EPA methods and some of their assessments of these compounds are older. Table 5 summarizes these values and the bases for their derivations.

Table 4. Toxicity Values for the High Carbon Range Aliphatic Fraction: C19–C32, EC > 16–EC35^a

Source	C	EC	Name	Derived Value		Cancer WOE	OSF (per mg/kg-day)	IUR (per µg/m ³)	Date ^b
				Oral (mg/kg-day)	Inhalation (mg/m ³)				
PPRTV Values									
PPRTV (U.S. EPA, date in last column)	19–32	>16–35	White mineral oils generally in the C and EC range of interest	sRfD: 3×10^1 lower end of human therapeutic dose range for laxative effects, NASPGHN, 2006 RfD: 3×10^0 , based on same data as the sRfD	sRfC: NA RfC: NA	Inadequate information to assess	Inadequate data	NA	2009i
Other Peer-Reviewed or Relevant Toxicity Values									
MADEP (2003)	19–32	>16–35	White mineral oils generally in the C and EC range of interest	RfD: 2×10^0 , liver granuloma Smith et al., 1996	RfC: Inadequate data, not volatile	Not assessed	Not assessed	Not assessed	–
TPHCWG (1997b)	19–32	>16–35	White mineral oils generally in the C and EC range of interest	RfD: 2×10^0 , liver granuloma, Smith et al., 1996	RfC: Not assessed	Not assessed	Not assessed	Not assessed	–

^aComplete citations for the principal studies can be found in the source documents (e.g., MADEP, 2003).

^bDate of PPRTV; dates for MADEP and TPHCWG are provided in far left column of table.

C = carbon number, EC = equivalent carbon number index, IUR = inhalation unit risk, MADEP = Massachusetts Department of Environmental Protection; NA = Not applicable, OSF = oral slope factor, p- = provisional, PPRTV = Provisional Peer-Reviewed Toxicity Value, PTV = Provisional Toxicity Value (draft); RfC = inhalation reference concentration, sRfC = subchronic RfC, RfD = oral reference dose, sRfD = subchronic RfD, TPHCWG = Total Petroleum Hydrocarbon Criteria Working Group, WOE = weight of evidence

Table 5. Toxicity Values for the Low Carbon Range Aromatic Fraction: C6–C8, EC6–EC < 9^a

Source	C	EC	Name	Derived Value		Cancer WOE	OSF (per mg/kg-day)	IUR (per µg/m ³)	Date ^b
				Oral (mg/kg-day)	Inhalation (mg/m ³)				
IRIS and PPRTV Values									
IRIS (U.S. EPA, 2009o)	6	6.5	Benzene	RfD: 4×10^{-3} , decreased lymphocyte count, Rothman et al., 1996, extrapolated from inhalation	RfC: 3×10^{-2} , decreased lymphocyte count, Rothman et al., 1996	Group A (human carcinogen), known/likely human carcinogen	1.5×10^{-2} to 5.5×10^{-2} , leukemia, several studies, extrapolated from inhalation	2.2×10^{-6} to 7.8×10^{-6} , leukemia, several studies	2003/2000-cancer
	7	7.58	Toluene	RfD: 8×10^{-2} , increased kidney weight, NTP, 1990	RfC: 5×10^0 , neurological effects, multiple studies	Inadequate data	NA	NA	2005
	8	8.5	Ethylbenzene	RfD: 1×10^{-1} , liver and kidney lesions, Wolf et al., 1956	RfC: 1×10^0 , developmental effects, Andrew et al., 1981; Hardin et al., 1981	Group D (not classifiable)	NA	NA	1991
	8	8.6–8.81	Xylenes	RfD: 2×10^{-1} , decreased body weight, increased mortality, NTP, 1986	RfC: 1×10^{-1} , impaired motor coordination, Korsak et al., 1994	Inadequate data	NA	NA	2003
PPRTV (U.S. EPA, date in last column)	6	6.5	Benzene	sRfD: 1×10^{-2} , decreased lymphocyte count, Rothman et al., 1996, extrapolated from inhalation (U.S. EPA, 2009o) RfD: Not assessed	sRfC: 8×10^{-2} , decreased lymphocyte count, Rothman et al., 1996 RfC: Not assessed	Not assessed	Not assessed	Not assessed	2009a
	7	7.58	Toluene	sRfD: 8×10^{-1} , increased kidney weight, NTP, 1990 RfD: Not assessed	sRfC: 5×10^0 , neurological effects, multiple studies, U.S. EPA, 2009o RfC: Not assessed	Not assessed	Not assessed	Not assessed	2009d
	8	8.5	Ethylbenzene	sRfD: 5×10^{-2} , centrilobular hepatocyte hypertrophy, Mellert et al., 2007 RfD: Not assessed	sRfC: 9×10^0 , ototoxicity, Gagnaire et al., 2007 RfC: Not assessed	Not assessed	Not assessed	Not assessed	2009b
	8	8.6–8.81	Xylenes	sRfD: 4×10^{-1} , reduced body weight, Wolfe, 1988 RfD: Not assessed	sRfC: 4×10^{-1} , neurological effects, Korsak et al., 1994 RfC: Not assessed	Not assessed	Not assessed	Not assessed	2009e

Table 5. Toxicity Values for the Low Carbon Range Aromatic Fraction: C6–C8, EC6–EC < 9^a

Source	C	EC	Name	Derived Value		Cancer WOE	OSF (per mg/kg-day)	IUR (per µg/m ³)	Date ^b
				Oral (mg/kg-day)	Inhalation (mg/m ³)				
Other Peer-Reviewed or Relevant Toxicity Values									
HEAST (U.S. EPA, 1997)	6	6.5	Benzene	Not assessed	sRfC: [Comment: Contact Superfund Health Risk Technical Support Center] RfC: Not assessed	Not assessed	Not assessed	2.9 × 10 ⁻² (per mg/kg-day), leukemia	–
	7	7.58	Toluene	sRfD: 2 × 10 ⁰ , altered liver and kidney weight, NTP, 1989 RfD: Not assessed	sRfC: [Comment: Contact the Superfund Health Risk Technical Support Center] RfC: Not assessed	Not assessed	Not assessed	Not assessed	–
	8	8.5	Ethylbenzene	sRfD: [Comment: Contact Superfund Health Risk Technical Support Center] RfD: Not assessed	sRfC: [Comment: Contact Superfund Health Risk Technical Support Center] RfC: Not assessed	Not assessed	Not assessed	Not assessed	–
	8	8.6–8.81	Xylenes	sRfD: [Comment: Contact Superfund Health Risk Technical Support Center] RfD: Not assessed	sRfC: Not assessed RfC: Not assessed	Not assessed	Not assessed	Not assessed	–
ATSDR (date in last column)	6	6.5	Benzene	Intermediate MRL: Inadequate data Chronic MRL: 5 × 10 ⁻⁴ , extrapolated from inhalation	Intermediate MRL: 6 × 10 ⁻³ ppm, delayed splenic lymphocyte reaction to antigens (Rosenthal and Snyder, 1987) RfC: 3 × 10 ⁻³ ppm, decreased B-lymphocyte counts, Lan et al., 2004a,b	Not assessed	Not assessed	Not assessed	2007a
	7	7.58	Toluene	Intermediate MRL: 2 × 10 ⁻² , regional increases in brain monoamine neurotransmitters, Hsieh et al., 1990 Chronic MRL: Inadequate data	Intermediate MRL: Inadequate data; use chronic MRL Chronic MRL: 8 × 10 ⁻² ppm (3 × 10 ⁻¹ mg/m ³), color vision impairment, Zavalic et al., 1998a	Not assessed	Not assessed	Not assessed	2000
	8	8.5	Ethylbenzene	Intermediate MRL: Inadequate data Chronic MRL: Inadequate data	Intermediate MRL: 1 × 10 ⁰ ppm, developmental effects, Andrew et al., 1981 Chronic MRL: Inadequate data	Not assessed	Not assessed	Not assessed	1999c

Table 5. Toxicity Values for the Low Carbon Range Aromatic Fraction: C6–C8, EC6–EC < 9^a

Source	C	EC	Name	Derived Value		Cancer WOE	OSF (per mg/kg-day)	IUR (per µg/m ³)	Date ^b
				Oral (mg/kg-day)	Inhalation (mg/m ³)				
ATSDR (date in last column)	8	8.6–8.81	Xylenes	Intermediate MRL: 4×10^{-1} , neurotoxic effects (NTP, 1986) Chronic MRL: 2×10^{-1} , decreased body weight gain and survival (NTP, 1986)	sRfC: 6×10^{-1} ppm, neurotoxic effects, Korsak et al., 1994 RfC: 5×10^{-2} ppm, respiratory and neurological effects, Uchida et al., 1993	Not assessed	Not assessed	Not assessed	2007b

^aComplete citations for the principal studies can be found in the source documents (e.g., IRIS [U.S. EPA, 2009_o]).

^bDate of IRIS assessment (last revision) or of PPRTV; date for the HEAST is provided in far left column of table.

ATSDR = Agency for Toxic Substances and Disease Registry, C = carbon number, EC = equivalent carbon number index, HEAST = Health Effects Assessment summary Table, IRIS = Integrated Risk Information System, IUR = inhalation unit risk, MRL = Minimal Risk Level, NA = Not applicable, OSF = oral slope factor, PPRTV = Provisional Peer-Reviewed Toxicity Value, PTV = Provisional Toxicity Value (draft), RfC = inhalation reference concentration, sRfC = subchronic RfC, RfD = oral reference dose, sRfD = subchronic RfD, RPF = Relative potency factor, WOE = weight of evidence

The IRIS RfDs, RfCs, and cancer assessments and the PPRTVs (subchronic p-RfDs and subchronic p-RfCs) provided in Table 5 are the recommended values for assessment of the components of this fraction.

Medium Carbon Range Aromatic Fraction: C9–C16, EC9–EC < 22

The MADEP (2003) grouped the entire range of aromatics from C9–C32 into a single fraction for the assessment of oral noncancer toxicity and divided the fraction into C9–C18 and C19–C32 fractions for the assessment of inhalation noncancer toxicity. The TPHCWG (1997a, b) defined their transport fractions by EC number rather than C number, but in selecting and deriving toxicity values, they actually used the C number range of C>8–C16 rather than the EC number range (TPHCWG, 1997b). For the aromatic hydrocarbons, the difference between C and EC can be large (e.g., the C16 compound fluoranthene has an EC of 21.85). An EC range of EC9–EC < 22 is recommended in this document, which corresponds to a C range of about C9–C16, for this medium carbon range aromatic fraction based on environmental transport and toxicological considerations—including volatility and carcinogenicity. This fraction is virtually the same as the fraction defined by the TPHCWG (1997b).

This medium carbon range aromatic fraction includes longer chain and multi-substituted benzenes (e.g., cumene [isopropylbenzene], *n*-propylbenzene, methylethylbenzenes, and trimethylbenzenes), indan, methylindans, naphthalenes, and some lower molecular weight PAHs (e.g., acenaphthylene, acenaphthene, fluorene, phenanthrene, anthracene, and pyrene). As listed in Table 6, toxicity values and cancer assessments are available for some of these individual compounds. IRIS values include RfDs for cumene, naphthalene, 2-methylnaphthalene, 1,1-biphenyl, acenaphthene, fluorene, anthracene, and pyrene, RfCs for cumene and naphthalene and only qualitative cancer assessments for many of these compounds with the exception of an oral slope factor (OSF) for benzo(a)pyrene. Also listed in Table 6 are a mix of provisional toxicity values including values for p-RfDs, subchronic p-RfDs, p-RfCs, subchronic p-RfCs, p-OSFs, screening RPFs, cancer assessments, and screening p-RfDs, subchronic p-RfDs, p-RfCs and subchronic p-RfCs (see entries for *n*-propylbenzene, 1,3,5-trimethylbenzene, 1,2,4-trimethylbenzene, high-flash aromatic naphtha, 2-methylnaphthalene, 1-methylnaphthalene, anthracene, pyrene, and benz(a)anthracene). A PPRTV for 1,2,3-trimethylbenzene is completed (U.S. EPA, 2009k); information from that PPRTV will be considered for use in evaluating hydrocarbon mixtures when this mixtures PPRTV document is revised. Table 6 includes both the medium and high carbon range fractions to facilitate evaluation of the selected C and EC ranges for these two fractions, and because of the overlap between ranges in the MADEP approach and the TPHCWG's classification by C rather than the EC number range.

**Table 6. Toxicity Values for the Medium and High Carbon Range Aromatic Fractions:
C9–C16, EC9–EC < 22 and C17–C32, EC22–EC35^a**

Source	C	EC	Name	Derived Value		Cancer WOE, RPF	OSF (per mg/kg-day)	IUR (per µg/m ³)	Date ^b
				Oral (mg/kg-day)	Inhalation (mg/m ³)				
IRIS and PPRTV Values									
IRIS (U.S. EPA, 2009o), RPF from U.S. EPA (1993)	9	9.13	Cumene (isopropylbenzene)	RfD: 1×10^{-1} , increased kidney weight, Wolf et al., 1956	RfC: 4×10^{-1} , increased kidney and adrenal weights, Cushman et al., 1995	Group D (not classifiable)	NA	NA	1997
	10	11.69	Naphthalene	RfD: 2×10^{-2} , decreased body weight, BCL, 1980	RfC: 3×10^{-3} , nasal lesions, NTP, 1992	Group C (possible human carcinogen)	Inadequate data	Inadequate data	1998
	11	12.84	2-Methylnaphthalene	RfD: 4×10^{-3} , alveolar proteinosis, Morata et al., 1997	Inadequate data	Inadequate data	NA	NA	2003
	12	14.26	1,1-Biphenyl	RfD: 5×10^{-2} , kidney damage, Ambrose et al., 1960	Inadequate Data	Group D (not classifiable)	NA	NA	1989/ 1991
	12	15.06	Acenaphthylene	Not assessed	Not Assessed	Group D (not classifiable)	Inadequate data	Inadequate data	1991
	12	15.5	Acenaphthene	RfD: 6×10^{-2} , hepatotoxicity, U.S. EPA, 1989b	Not Assessed	Not assessed	Not assessed	Not assessed	1994
	13	16.55	Fluorene	RfD: 4×10^{-2} , decreased red blood cells, packed cell volume and Hgb, U.S. EPA, 1989c	Not assessed	Group D (not classifiable)	NA	NA	1990
	14	19.36	Phenanthrene	Not assessed	Not assessed	Group D (not classifiable)	NA	NA	1990
	14	19.43	Anthracene	RfD: 3×10^{-1} , freestanding NOEL, U.S. EPA, 1989d	Not Assessed	Group D (not classifiable)	NA	NA	1993/ 1991

**Table 6. Toxicity Values for the Medium and High Carbon Range Aromatic Fractions:
C9–C16, EC9–EC < 22 and C17–C32, EC22–EC35^a**

Source	C	EC	Name	Derived Value		Cancer WOE, RPF	OSF (per mg/kg-day)	IUR (per µg/m ³)	Date ^b
				Oral (mg/kg-day)	Inhalation (mg/m ³)				
IRIS (U.S. EPA, 2009o), RPF from U.S. EPA (1993)	16	20.8	Pyrene	RfD: 3×10^{-2} , kidney effects, U.S. EPA, 1989e	Not assessed	Group D (not classifiable)	NA	NA	1993/1991
	16	21.85	Fluoranthene	RfD: 4×10^{-2} , kidney, liver, hematologic and clinical effects, U.S. EPA, 1988	Not assessed	Group D (not classifiable)	NA	NA	1993/1990
	18	26.37	Benz(a)anthracene	Not assessed	Not assessed	Group B2 (probable human carcinogen), RPF=0.1	Not assessed	Not assessed	1994
	18	27.41	Chrysene	Not assessed	Not assessed	Group B2 (probable human carcinogen), RPF=0.001	Inadequate data	Inadequate data	1994
IRIS (U.S. EPA, 2009o), RPF from U.S. EPA (1993)	20	30.14	Benzo(b)fluoranthene	Not assessed	Not assessed	Group B2 (probable human carcinogen), RPF=0.1	Inadequate data	Inadequate data	1994
	20	30.14	Benzo(k)fluoranthene	Not assessed	Not assessed	Group B2 (probable human carcinogen), RPF=0.01	Inadequate data	Inadequate data	1994

**Table 6. Toxicity Values for the Medium and High Carbon Range Aromatic Fractions:
C9–C16, EC9–EC < 22 and C17–C32, EC22–EC35^a**

Source	C	EC	Name	Derived Value		Cancer WOE, RPF	OSF (per mg/kg-day)	IUR (per µg/m ³)	Date ^b
				Oral (mg/kg-day)	Inhalation (mg/m ³)				
IRIS (U.S. EPA, 2009 ^o), RPF from U.S. EPA	20	31.34	Benzo(a)pyrene	Not assessed	Not assessed	Group B2 (probable human carcinogen), RPF=1	7.3× 10 ⁰ , fore-stomach (larynx, esophagus) 4 data sets	Not assessed	1994
	22	33.92	Dibenz(a,h)anthracene	Not assessed	Not assessed	Group B2 (probable human carcinogen), RPF=1	Inadequate data	Inadequate data	1994
	22	34.14	Benzo(g,h,i)perylene	Not assessed	Not assessed	Group D (not classifiable)	NA	NA	1990
	22	35.01	Indeno(1,2,3-c,d)pyrene	Not assessed	Not assessed	Group B2 (probable human carcinogen), RPF=0.1	Inadequate data	Inadequate data	1994

**Table 6. Toxicity Values for the Medium and High Carbon Range Aromatic Fractions:
C9–C16, EC9–EC < 22 and C17–C32, EC22–EC35^a**

Source	C	EC	Name	Derived Value		Cancer WOE, RPF	OSF (per mg/kg-day)	IUR (per µg/m ³)	Date ^b
				Oral (mg/kg-day)	Inhalation (mg/m ³)				
PPRTV (U.S. EPA, date in last column)	9	9.47	<i>n</i> -Propylbenzene	sRfD: 1×10^{-1} , liver and kidney toxicity, based on IRIS RfD for ethylbenzene, Wolf et al., 1956, using a surrogate analysis RfD: 1×10^{-1} , liver and kidney toxicity, based on IRIS RfD for ethylbenzene, Wolf et al., 1956, using a surrogate analysis (*Screening Values)	sRfC: 1×10^0 , developmental toxicity, based on IRIS RfC for ethylbenzene, Andrew et al., 1981; Hardin et al., 1981, using a surrogate analysis RfC: 1×10^0 , developmental toxicity, based on IRIS RfC for ethylbenzene, Andrew et al., 1981; Hardin et al., 1981, using a surrogate analysis (*Screening Values)	Inadequate data	NA	NA	2009j
PPRTV (U.S. EPA, date in last column)	9	9.62	1,3,5-Trimethylbenzene	sRfD: 1×10^{-1} , increased liver weight, Koch Industries, 1995 RfD: 1×10^{-2} , increased liver weight, Koch Industries, 1995 (*Screening Values)	sRfC: 1×10^{-2} , Wiaderna et al., 2002 RfC: Inadequate data	Inadequate data	NA	NA	2009k
	9	9.84	1,2,4-Trimethylbenzene	sRfD: Inadequate data RfD: Inadequate data	sRfC: 7×10^{-2} , decreased clotting time, Korsak et al., 2000 RfC: 7×10^{-3} , based on sRfC study	Inadequate data	Inadequate data	Inadequate data	2007f
	9	10.06	1,2,3-Trimethylbenzene						INPR OC

**Table 6. Toxicity Values for the Medium and High Carbon Range Aromatic Fractions:
C9–C16, EC9–EC < 22 and C17–C32, EC22–EC35^a**

Source	C	EC	Name	Derived Value		Cancer WOE, RPF	OSF (per mg/kg-day)	IUR (per µg/m ³)	Date ^b
				Oral (mg/kg-day)	Inhalation (mg/m ³)				
PPRTV (U.S. EPA, date in last column) (cont.)	10	9.84	tert-Butylbenzene	sRfD: Inadequate data RfD: Inadequate data	sRfC: Inadequate data RfC: Inadequate data	Inadequate data	Inadequate data	Inadequate data	2004a ,b,c
	10	9.98	sec-Butylbenzene	sRfD: Inadequate data RfD: Inadequate data	sRfC: Inadequate data RfC: Inadequate data	Inadequate data	Inadequate data	Inadequate data	2004a ,b,c
	10	10.5	n-Butylbenzene	sRfD: Inadequate data RfD: Inadequate data	sRfC: Inadequate data RfC: Inadequate data	Inadequate data	Inadequate data	Inadequate data	2004a ,b,c
	9-10		High-flash aromatic naphtha	sRfD: 3×10^{-1} , anemia, Bio/Dynamics, 1990b RfD: 3×10^{-2} , from sRfD study (*Screening Values)	sRfC: 1×10^0 maternal body weight depression, McKee et al., 1990 RfC: 1×10^{-1} , from sRfC study	Inadequate information to assess	Inadequate data	Inadequate data	2009g
PPRTV (U.S. EPA, date in last column)	11	12.84	2-Methylnaphthalene	sRfD: 4×10^{-3} , alveolar proteinosis, Morata et al., 1997 RfD: Not assessed	sRfC: Inadequate data RfC: Inadequate data	Inadequate data	NA	NA	2007c
	11	12.99	1-Methylnaphthalene	RfD: 7×10^{-3} (*Screening value)	sRfC: Inadequate data RfC: Inadequate data	Suggestive evidence	2.9×10^{-2}	Inadequate data	2008
PPRTV (U.S. EPA, date in last column)	12	15.06	Acenaphthylene	sRfD: Inadequate data RfD: Inadequate data	sRfC: Inadequate data RfC: Inadequate data	Inadequate data	NA	NA	2009l
	14	19.36	Phenanthrene	sRfD: Inadequate data RfD: Inadequate data	sRfC: Inadequate data RfC: Inadequate data	Group D (not classifiable)	NA	NA	2009m
	14	19.43	Anthracene	sRfD: 1×10^0 free standing NOEL, Wolfe, 1989 (RfD on IRIS)	sRfC: Inadequate data RfC: Inadequate data	Inadequate data	NA	NA	2009n
	16	20.8	Pyrene	sRfD: 3×10^{-1} , kidney damage, U.S. EPA, 1989e RfD: Not assessed	sRfC: Inadequate data RfC: Inadequate data	Not likely to be a human carcinogen	Inadequate data	Inadequate data	2007e

**Table 6. Toxicity Values for the Medium and High Carbon Range Aromatic Fractions:
C9–C16, EC9–EC < 22 and C17–C32, EC22–EC35^a**

Source	C	EC	Name	Derived Value		Cancer WOE, RPF	OSF (per mg/kg-day)	IUR (per µg/m ³)	Date ^b
				Oral (mg/kg-day)	Inhalation (mg/m ³)				
PPRTV (U.S. EPA, date in last column)	18	26.37	Benz(a)anthracene	sRfD: Not assessed RfD: Inadequate data	sRfC: Not assessed RfC: Inadequate data	Not assessed, RPF=0.1 (*Screening Value)	Inadequate data	Not assessed	2007b
(cont.)	20	31.34	Perylene	sRfD: Inadequate data RfD: Inadequate data	sRfC: Inadequate data RfC: Inadequate data	Inadequate data	Inadequate data	Inadequate data	2007d
Other Peer-Reviewed or Relevant Toxicity Values									
HEAST (U.S. EPA, 1997)	9	9.13	Cumene (isopropylbenzene)	sRfD: 4×10^{-1} , increased kidney weight, Wolf et al., 1956	sRfC: 9×10^{-2} CNS effect, nasal irritation, Monsanto Co., 1986 RfC: 9×10^{-3} , CNS effect, nasal irritation, Monsanto Co., 1986	Not assessed	Not assessed	Not assessed	–
	12	14.26	1,1-Biphenyl	sRfD: 5×10^{-2} kidney damage, Ambrose et al., 1960 (RfD on IRIS)	RfC: considered not verifiable by RfD/RfC Work Group	Not assessed	Not assessed	Not assessed	–
	12	15.5	Acenaphthene	sRfD: 6×10^{-1} , liver effects, U.S. EPA, 1989b	Not assessed	Not assessed	Not assessed	Not assessed	–
HEAST (U.S. EPA, 1997)	13	16.55	Fluorene	sRfD: 4×10^{-1} , decreased red blood cells, U.S. EPA, 1989c	Not assessed	Not assessed	Not assessed	Not assessed	–
	14	19.43	Anthracene	sRfD: 3×10^0 , freestanding NOEL, U.S. EPA, 1989d	RfC: considered not verifiable by RfD/RfC Work Group	Not assessed	Not assessed	Not assessed	–
	16	20.8	Pyrene	sRfD: 3×10^{-1} , kidney damage, U.S. EPA, 1989e	RfC: considered not verifiable by RfD/RfC Work Group	Not assessed	Not assessed	Not assessed	–

**Table 6. Toxicity Values for the Medium and High Carbon Range Aromatic Fractions:
C9–C16, EC9–EC < 22 and C17–C32, EC22–EC35^a**

Source	C	EC	Name	Derived Value		Cancer WOE, RPF	OSF (per mg/kg-day)	IUR (per µg/m ³)	Date ^b
				Oral (mg/kg-day)	Inhalation (mg/m ³)				
HEAST (U.S. EPA, 1997) (cont.)	16	21.85	Fluoranthene	sRfD: 4×10^{-1} , kidney, liver and hematologic effects, U.S. EPA, 1988	RfC: considered not verifiable by RfD/RfC Work Group	Not assessed	Not assessed	Not assessed	–
MADEP (2003)	9-10		High flash aromatic naphtha	Not assessed	RfC: 5×10^{-2} , increased liver weight and possible CNS effects, Clark et al., 1989	Not assessed	Not assessed	Not assessed	–
TPHCWG (1997b)	9	9.47	High-flash aromatic naphtha (called C9 Aromatics by TPHCWG)	Not assessed	RfC: 2×10^{-1} , increased liver and kidney weight, Clark et al., 1989	Not assessed	Not assessed	Not assessed	–
ATSDR (date in last column)	10	11.69	Naphthalene	Intermediate MRL: 6×10^{-1} , transient CNS signs rat dams, NTP, 1991 Chronic MRL: Inadequate data	Intermediate MRL: Inadequate data Chronic MRL: 7×10^{-4} ppm (3×10^{-3} mg/m ³), nasal lesions, NTP, 2000	Not assessed	Not assessed	Not assessed	2005
	11	12.84	2-Methylnaphthalene	Intermediate MRL: Inadequate data Chronic MRL: 4×10^{-2} , alveolar proteinosis, Murata et al., 1993	Intermediate and chronic MRL: Inadequate data	Not assessed	Not assessed	Not assessed	2005
ATSDR (date in last column)	11	12.99	1-Methylnaphthalene	Intermediate MRL: Inadequate data Chronic MRL: 7×10^{-2} , alveolar proteinosis, Morata et al., 1997	Intermediate and chronic MRL: Inadequate data	Not assessed	Not assessed	Not assessed	2005

**Table 6. Toxicity Values for the Medium and High Carbon Range Aromatic Fractions:
C9–C16, EC9–EC < 22 and C17–C32, EC22–EC35^a**

Source	C	EC	Name	Derived Value		Cancer WOE, RPF	OSF (per mg/kg-day)	IUR (per µg/m ³)	Date ^b
				Oral (mg/kg-day)	Inhalation (mg/m ³)				
ATSDR (date in last column) (cont.)	12	15.5	Acenaphthene	Intermediate MRL: 6 × 10 ⁻¹ , liver effects, U.S. EPA, 1989b Chronic MRL: Inadequate data	Intermediate and chronic MRL: Inadequate data	Not assessed	Not assessed	Not assessed	1995
	13	16.55	Fluorene	Intermediate MRL: 4 × 10 ⁻¹ , liver effects, U.S. EPA, 1989c Chronic MRL: Inadequate data	Intermediate and chronic MRL: Inadequate data	Not assessed	Not assessed	Not assessed	1995
	14	19.43	Anthracene	Intermediate MRL: 1 × 10 ¹ , free standing NOAEL (concern for liver effects), U.S. EPA, 1989d Chronic MRL: Inadequate data	Intermediate and chronic MRL: Inadequate data	Not assessed	Not assessed	Not assessed	1995
	16	21.85	Fluoranthene	Intermediate MRL: 4 × 10 ⁻¹ , liver effects, U.S. EPA, 1989d Chronic MRL: Inadequate data	Intermediate and chronic MRL: Inadequate data	Not assessed	Not assessed	Not assessed	1995

^aComplete citations for the principal studies can be found in the source documents (e.g., IRIS [U.S. EPA, 2009o]).

^bDate of IRIS assessment (last revision), PPRTV, or ATSDR toxicological profile; dates for HEAST, MADEP, and TPHCWG are provided in far left column of table.

*Screening values are developed in the Appendix of a PPRTV. For example, in cases where a high degree of uncertainty exists. Screening Values are intended for use in limited circumstances when no Tier 1, 2, or 3 values are available.

RPF = Relative potency factor (U.S. EPA, 1993) listed with IRIS Cancer WOE for convenience of the reader.

ATSDR = Agency for Toxic Substances and Disease Registry, C = carbon number, CNS = central nervous system, EC = equivalent carbon number index, HEAST = Health Effects Assessment summary Table, INPROC = in process, IRIS = Integrated Risk Information System, IUR = inhalation unit risk, MADEP = Massachusetts Department of Environmental Protection, MRL = Minimal Risk Level, NA = Not applicable, NOEL = no-observed-effect level, OSF = oral slope factor, p- = provisional, PPRTV = Provisional Peer-Reviewed Toxicity Value, PTV = Provisional Toxicity Value (draft), RfC = inhalation reference concentration, sRfC = subchronic RfC, RfD = oral reference dose, sRfD = subchronic RfD, RPF = Relative potency factor, TPHCWG = Total Petroleum Hydrocarbon Criteria Working Group, WOE = weight of evidence

A mixture of predominantly C9–C10 alkylbenzenes, high-flash aromatic naphtha, has been studied toxicologically. Basing a value for at least the alkyl benzenes on a mixture, rather than a single chemical, is preferable since the data support development of toxicity values. Although MADEP (2003) and TPHCWG (1997b) derived inhalation RfCs for this mixture, some additional studies were located, including oral studies, and it was considered advisable to perform an updated assessment using current U.S. EPA methods. Therefore, a PPRTV document was developed for high-flash aromatic naphtha (U.S. EPA, 2009g). The PPRTVs for high-flash aromatic naphtha, listed in Table 6, include subchronic and chronic p-RfCs. In addition, Table 6 contains several screening values for high-flash aromatic naphtha that may be useful in evaluating this fraction, developed in Appendix A of U.S. EPA (2009g). Because the toxicity data based on the three unpublished studies (Bio/Dynamics Inc., 1990a,b; Mobil Oil Corporation, 1994) are not peer-reviewed, only screening chronic or subchronic RfDs are available in Table 6. Subchronic and chronic RfD values for individual alkylbenzenes in Table 6 (*n*-propylbenzene, 1,3,5-trimethylbenzene) are also limited to screening values due to database weaknesses.

The effects of compounds in this fraction are commonly kidney, liver, and body weight effects. Hematological effects are seen with some of these compounds. The subchronic and chronic p-RfCs and subchronic and chronic screening RfDs derived for high-flash aromatic naphtha are the same order of magnitude as those for the single compounds in this fraction, including biphenyl and the low molecular weight PAHs. Exceptions on IRIS are the 2-methylnaphthalene RfD, which is an order of magnitude lower and is based on alveolar proteinosis, and the naphthalene RfC, which is two orders of magnitude lower and based on nasal lesions. Other exceptions are the p-RfD for 1-methylnaphthalene, which is, however, only a screening value, and subchronic p-RfC and p-RfC values for 1,3,5-trimethylbenzene and 1,2,4-trimethylbenzene.

According to MADEP (2003), both naphthalene and 2-methylnaphthalene are target analytes assessed separately under the Massachusetts Contingency Plan. The recommendation in this PPRTV is to assess exposure to these compounds separately if possible, using their specific toxicity values (oral RfD and subchronic p-RfD for 2-methylnaphthalene, oral RfD and inhalation RfC for naphthalene). Their mass should be subtracted from the total fraction mass before use of the high-flash aromatic naphtha toxicity values listed in Table 6 for the remaining fraction. Specific monitoring data are unlikely to be available for 1-methylnaphthalene or the trimethylbenzene isomers, but if such data are available, then these chemicals could be treated similarly to naphthalene and 2-methylnaphthalene.

Because high-flash aromatic naphtha is a mixture of predominantly C9–C10 alkylbenzenes, the provisional values for this mixture are most relevant to the alkylbenzene portion of this fraction. Although there may be greater uncertainty involved in using these values when the fraction includes less closely structurally-related compounds, the available toxicity values for these other compounds (1,1-biphenyl, and the lower molecular weight PAHs, listed in Table 6) are similar to those for high-flash aromatic naphtha, which supports the use of that mixture as a surrogate for the fraction. Carcinogenicity data are generally inadequate for compounds in this fraction and also for high-flash aromatic naphtha.

High Carbon Range Aromatic Fraction: C17–C32, EC22–EC35

To help readers understand clearly the U.S. EPA approach for this fraction, a brief explanation is provided here, followed by more extensive discussions below. For noncancer oral

toxicity values, fluoranthene, an IRIS and HEAST listed chemical, was selected as a surrogate. Since this fraction is basically nonvolatile, no inhalation toxicity values were attempted. For cancer toxicity values, seven PAH are to be evaluated together as indicator components for this fraction, using the RPF method. As shown in Table 6, these seven are IRIS-listed B2 carcinogenic PAHs with RPFs from U.S. EPA, 1993 (i.e., benzo[a]pyrene, benz[a]anthracene, chrysene, benzo[b]fluoranthene, benzo[k]fluoranthene, dibenz[a,h]anthracene, indeno[1,2,3-c,d]pyrene).

As explained previously, MADEP grouped the entire range of aromatics from C9–C32 into a single fraction for the assessment of oral noncancer toxicity and divided the fraction into C9–C18 and C19–C32 fractions for the assessment of inhalation noncancer toxicity. The TPHCWG (1997a) defined their transport fractions by EC number rather than C number, but in selecting and deriving toxicity values, they actually used the C number ranges. Because the EC value for aromatic hydrocarbons is higher than the C value, the low end of their fraction range actually was EC22, rather than the stated EC > 16 (TPHCWG, 1997b). The use of the EC number range of EC22–EC35 is recommended in this document, which corresponds to a C number range of about C17–C32, for the high carbon range aromatic fraction based on environmental transport and toxicological considerations, including volatility and carcinogenicity. This fraction is virtually the same as the fraction defined by the TPHCWG (1997b).

This fraction includes the medium and high molecular weight PAHs, which generally are not volatile when released to soil or water (ATSDR, 1995)⁴. Although PAHs can bind to soil particulates, methods and data to estimate toxicity values or assess risk from inhaled soil-particulate-bound PAHs are not available.

Data on noncancer toxicity are limited for the PAHs of this fraction, and RfDs, RfCs, and MRLs have not been derived for them. The noncancer oral toxicity of this fraction can be assessed through the use of the oral toxicity values for fluoranthene. Although fluoranthene is a C16 compound, it has an EC of 21.85, which is very close to the lower end (22) of the EC range for this fraction. The RfD for fluoranthene is available on IRIS and the subchronic RfD, based on the same study, is listed in the HEAST. Table 6 reports these values. The uncertainty involved in the use of fluoranthene as a surrogate for the noncancer oral toxicity of this fraction is high due to the lack of relevant data on the noncancer toxicity of the compounds in this fraction.

A cancer slope factor is available only for the Group B2 (probable human carcinogen) PAH benzo(a)pyrene. The other six Group B2 PAHs can be assessed using the RPFs estimated and recommended by U.S. EPA (1993). This is an indicator component method that assumes the carcinogenicity of the fraction is approximated by the components with known carcinogenicity and quantitative estimates (slope factor or RPF). When U.S. EPA develops new RPFs for additional PAHs or recommends changes in the current set of seven RPF values for evaluation of the PAHs, these can be incorporated into the risk assessment.

⁴When released to air through combustion processes, these PAHs exist primarily in the particulate phase—except for chrysene and benzo(a)anthracene, which can exist partially in the vapor phase (ATSDR, 1995). PAHs created and released to air by combustion, however, are not within the scope of this document on aliphatic and aromatic hydrocarbons.

CONCLUSIONS AND RECOMMENDATIONS

Building upon the contributions of MADEP and TPHCWG to the fractional approach for evaluation of hazard/risk of exposure to petroleum hydrocarbons (see Appendix A), this PPRTV document updates and expands the selection and derivation of toxicity values to include both subchronic and chronic RfDs and RfCs, as well as cancer WOE assessments, OSFs, and IURs. Newer data and updated U.S. EPA methods are used to provide new provisional assessments (U.S. EPA, 2009a-i) as needed and supported by the available data. The approach is generally consistent with the MADEP and the TPHCWG approaches, using toxicity values for a surrogate compound or similar mixture to represent the toxicity of the fraction. Where the components of the fraction vary in type or potency of toxic action, it is recommended that the more toxic component (e.g., *n*-hexane of the low range aliphatic fraction) be used as the surrogate when it exceeds the percentage in the surrogate mixture (e.g., commercial hexane, inhalation assessment), or when other suitable values are not available for the exposure route (oral). In some cases, a components method is recommended: i.e., for the BTEX (low carbon range aromatic fraction); and for seven PAHs of the high carbon range aromatic fraction, which are IRIS-listed Group B2 (probable human carcinogen) carcinogenic PAHs with RPFs from U.S. EPA (1993). A combination components and surrogate mixture approach is recommended for the medium carbon range aromatic fraction, with the target analytes naphthalene and 2-methylnaphthalene assessed separately using their specific toxicity values (oral for both compounds and inhalation for naphthalene). The mass of the target analyte(s) is subtracted from the fraction mass, which is then assessed using toxicity values for the surrogate mixture (high-flash aromatic naphtha).

The recommended toxicity values and cancer assessments and methods are summarized in Table 7 (noncancer oral), Table 8 (noncancer inhalation), and Table 9 (cancer oral and inhalation). The rationales for these recommendations have been presented in previous sections of this document. The use of additivity methods (U.S. EPA, 1986, 1989a, 1993, 2000) is recommended when applicable to assess potential risk within and across fractions. These methods include the HI for noncancer effects of oral and inhalation exposure, RPFs for the Group B2 (probable human carcinogen) PAHs, and response addition for assessing cancer risk across fractions. These methods are essentially component-based methods wherein the fractions (or in the cases described previously, individual chemicals in the fraction) are considered components of aliphatic and aromatic hydrocarbons.

Table 7. Recommended Oral Noncancer Toxicity Values for Aliphatic and Aromatic Hydrocarbon Fractions^a

Fraction: Surrogate or Components	sRfD (mg/kg-day)	Source	RfD (mg/kg-day)	Source
Aliphatics				
Low carbon range C5–C8, EC5–EC8:				
<i>n</i> -hexane	3 × 10 ⁻¹ , reduced nerve conduction velocity, Ono et al., 1981	PPRTV (U.S. EPA, 2009c)	Not assessed under IRIS program	IRIS (U.S. EPA, 2009j)
Medium carbon range C9–C18, EC > 8–EC16:				
Hydrocarbon streams or solvents within the range and containing <1% aromatics	1 × 10 ⁻¹ , liver, kidney and hematologic effects, Anonymous, 1990, 1991a,b (*Screening value)	PPRTV (U.S. EPA, 2009h)	1 × 10 ⁻² , liver, kidney and hematologic effects, Anonymous, 1990, 1991a,b (*Screening value)	PPRTV (U.S. EPA, 2009h)
High carbon range C19–C32, EC > 16–EC35:				
White mineral oils generally within the range	3 × 10 ¹ , lower end of human therapeutic dose range for laxative effects, NASPGHN, 2006	PPRTV (U.S. EPA, 2009i)	3 × 10 ⁰ , lower end of human therapeutic dose range for laxative effects, NASPGHN, 2006	PPRTV (U.S. EPA, 2009i)
Aromatics				
Low carbon range C6–C8, EC6–EC < 9:				
Benzene	1 × 10 ⁻² , decreased lymphocyte count, Rothman et al., 1996, extrapolated from inhalation, U.S. EPA, 2009j	PPRTV (U.S. EPA, 2009a)	4 × 10 ⁻³ , decreased lymphocyte count, Rothman et al., 1996, extrapolated from inhalation	IRIS (U.S. EPA, 2009j)
Toluene	8 × 10 ⁻¹ , increased kidney weight, NTP, 1990	PPRTV (U.S. EPA, 2009d)	8 × 10 ⁻² , increased kidney weight, NTP, 1990	IRIS (U.S. EPA, 2009j)
Ethylbenzene ^b	5 × 10 ⁻² , centrilobular hepatic hypertrophy, Mellert et al., 2007	PPRTV (U.S. EPA, 2009b)	1 × 10 ⁻¹ , liver and kidney lesions, Wolf et al., 1956	IRIS (U.S. EPA, 2009j)
Xylenes	4 × 10 ⁻¹ , reduced body weight, Wolfe, 1988	PPRTV (U.S. EPA, 2009e)	2 × 10 ⁻¹ , decreased body weight, increased mortality, NTP, 1986	IRIS (U.S. EPA, 2009j)

Table 7. Recommended Oral Noncancer Toxicity Values for Aliphatic and Aromatic Hydrocarbon Fractions^a

Fraction: Surrogate or Components	sRfD (mg/kg-day)	Source	RfD (mg/kg-day)	Source
Aromatics (cont'd)				
Medium carbon range C9–C16, EC9–EC < 22:				
High flash aromatic naphtha (except naphthalene and 2-naphthalene)	3×10^{-1} , anemia, Bio/Dynamics, 1990b (*Screening Value)	PPRTV (U.S. EPA, 2009g)	3×10^{-2} , anemia, Bio/Dynamics, 1990b (*Screening Value)	PPRTV (U.S. EPA, 2009g)
Naphthalene	Not available	–	2×10^{-2} , decreased body weight, BCL, 1980	IRIS (U.S. EPA, 2009j)
2-Methylnaphthalene	4×10^{-3} , alveolar proteinosis, Morata et al., 1997	PPRTV (U.S. EPA, 2007c)	4×10^{-3} , alveolar proteinosis, Morata et al., 1997	IRIS (U.S. EPA, 2009j)
High carbon range C17–C32, EC22–EC35:				
Fluoranthene	4×10^{-1} , kidney, liver and hematologic effects, U.S. EPA, 1988	HEAST (U.S. EPA, 1997)	4×10^{-2} , kidney, liver, hematologic and clinical effects, U.S. EPA, 1988	IRIS (U.S. EPA, 2009j)

^aComplete citations for the principal studies can be found in the source documents (e.g., IRIS [U.S. EPA, 2009j]).

^bThe lower sRfD relative to the RfD for ethylbenzene reflects the more recent derivation of the sRfD (new critical study, BMD modeling).

*Screening values are developed in the Appendix of a PPRTV. For example, in cases where a high degree of uncertainty exists. Screening Values are intended for use in limited circumstances when no Tier 1, 2, or 3 values are available.

C = carbon number, EC = equivalent carbon number index, HEAST = Health Effects Assessment summary Table, IRIS = Integrated Risk Information System, PPRTV = Provisional Peer-Reviewed Toxicity Value, RfD = oral reference dose, sRfD = subchronic RfD

Table 8. Recommended Inhalation Noncancer Toxicity Values for Aliphatic and Aromatic Hydrocarbon Fractions^a

Fraction: Surrogate or Components	sRfC (mg/m³)	Source	RfC (mg/m³)	Source
Aliphatics				
Low carbon range C5–C8, EC5–EC8:				
<i>n</i> -hexane, if present at >53% of fraction	2 × 10 ⁰ , Decreased motor nerve conduction velocity, Huang et al., 1989	PPRTV (U.S. EPA, 2009c)	7 × 10 ⁻¹ , peripheral neuropathy, Huang et al., 1989	IRIS (U.S. EPA, 2009j)
Commercial hexane, if <i>n</i> -hexane present at ≤53% of fraction	27 × 10 ⁰ , clinical and histopathological signs of neuropathy, IRDC, 1992a,b	PPRTV (U.S. EPA, 2009f)	6 × 10 ⁻¹ , nasal epithelial cell hyperplasia, Biodynamics, 1993a; Daughtrey et al., 1999	PPRTV (U.S. EPA, 2009f)
Medium carbon range C9–C18, EC > 8–EC16:				
Hydrocarbon streams or solvents within the range and containing <1% aromatics	1 × 10 ⁻¹ , nasal goblet cell hypertrophy, NTP, 2004	PPRTV (U.S. EPA, 2009h)	1 × 10 ⁻¹ , nasal goblet cell hypertrophy and adrenal hyperplasia, NTP, 2004	PPRTV (U.S. EPA, 2009h)
High carbon range C19–C32, EC > 16–EC35:				
White mineral oils generally within the range	NA, not volatile	PPRTV (U.S. EPA, 2009i)	NA, not volatile	PPRTV (U.S. EPA, 2009i)
Aromatics				
Low carbon range: C6–C8, EC6–EC < 9:				
Benzene	8 × 10 ⁻² , decreased lymphocyte count, Rothman et al., 1996	PPRTV (U.S. EPA, 2009a)	3 × 10 ⁻² , decreased lymphocyte count, Rothman et al., 1996	IRIS (U.S. EPA, 2009j)
Toluene	5 × 10 ⁰ , neurological effects, multiple studies, U.S. EPA, 2009j	PPRTV (U.S. EPA, 2009d)	5 × 10 ⁰ , neurological effects, multiple studies	IRIS (U.S. EPA, 2009j)
Ethylbenzene	9 × 10 ⁰ , ototoxic effects, Gagnaire et al., 2007	PPRTV (U.S. EPA, 2009b)	1 × 10 ⁰ , developmental effects, Andrew et al., 1981; Hardin et al., 1981	IRIS (U.S. EPA, 2009j)
Xylenes	4 × 10 ⁻¹ , neurological effects, Korsak et al., 1994	PPRTV (U.S. EPA, 2009e)	1 × 10 ⁻¹ , impaired motor coordination, Korsak et al., 1994	IRIS (U.S. EPA, 2009j)

Table 8. Recommended Inhalation Noncancer Toxicity Values for Aliphatic and Aromatic Hydrocarbon Fractions^a

Fraction: Surrogate or Components	sRfC (mg/m³)	Source	RfC (mg/m³)	Source
Aromatics (cont'd)				
Medium carbon range C9–C16, EC9–EC < 22:				
High flash aromatic naphtha (except naphthalene)	1 × 10 ⁰ , maternal body weight depression, McKee et al., 1990	PPRTV (U.S. EPA, 2009g)	1 × 10 ⁻¹ , maternal body weight depression, McKee et al., 1990	PPRTV (U.S. EPA, 2009g)
Naphthalene	Not available	–	3 × 10 ⁻³ , nasal lesions, NTP 1992	IRIS (U.S. EPA, 2009j)
High carbon range C17–C32, EC22–EC35:				
	NA, not volatile	–	NA, not volatile	–

^aComplete citations for the principal studies can be found in the source documents (e.g., IRIS [U.S. EPA, 2009j]).

C = carbon number, EC = equivalent carbon number index, IRIS = Integrated Risk Information System, NA = Not applicable, PPRTV = Provisional Peer-Reviewed Toxicity Value, RfC = inhalation reference concentration, sRfC = subchronic RfC

Table 9. Recommended Cancer Assessments for Aliphatic and Aromatic Hydrocarbon Fractions^a				
Fraction: Surrogate or Components	Cancer WOE, RPF	OSF (per mg/kg-day)	IUR (per µg/m³)	Source
Aliphatics				
Low carbon range C5–C8, EC5–EC8:				
Commercial hexane, if <i>n</i> -hexane present at ≤53% of the fraction	Suggestive evidence	Inadequate data	1.9×10^{-7} , pituitary adenoma or carcinoma, Biodynamics, 1993b; Daughtrey et al., 1999 (*Screening value)	PPRTV (U.S. EPA, 2009f)
Medium carbon range C9–C18, EC > 8–EC16:				
Petroleum streams or solvents within the range and containing <1% aromatics	Suggestive evidence	NA	4.5×10^{-6} , benign or malignant adrenal pheochromocytoma, NTP, 2004 (*Screening Value)	PPRTV (U.S. EPA, 2009h)
High carbon range C19–C32, EC > 16–EC35:				
White mineral oils generally within the range	Inadequate information to assess	Inadequate data	NA, not volatile	PPRTV (U.S. EPA, 2009i)
Aromatics				
Fraction: Surrogate or Components	Cancer WOE, RPF	OSF (per mg/kg-day)	IUR (per µg/m³)	Source
Low carbon range C6–C8, EC6–EC < 9:				
Benzene	Group A (human carcinogen); known/likely human carcinogen	1.5×10^{-2} to 5.5×10^{-2} , leukemia, several studies, extrapolated from inhalation	2.2×10^{-6} to 7.8×10^{-6} , leukemia, several studies	IRIS (U.S. EPA, 2009j)
Toluene	Inadequate data	NA	NA	IRIS (U.S. EPA, 2009j)
Ethylbenzene	Group D (not classifiable)	NA	NA	IRIS (U.S. EPA, 2009j)
Xylenes	Inadequate data	NA	NA	IRIS (U.S. EPA, 2009j)
Medium carbon range C9–C16, EC9–EC < 22:				
High flash aromatic naphtha (except naphthalene)	Inadequate information to assess	Inadequate data	Inadequate data	PPRTV (U.S. EPA, 2009g)
Naphthalene	Group C (possible human carcinogen)	Inadequate data	Inadequate data	IRIS (U.S. EPA, 2009j)

Table 9. Recommended Cancer Assessments for Aliphatic and Aromatic Hydrocarbon Fractions^a

Fraction: Surrogate or Components	Cancer WOE, RPF	OSF (per mg/kg-day)	IUR (per µg/m³)	Source
Aromatics (cont'd)				
High carbon range C17–C32, EC22–EC35:				
Benzo(a)pyrene	Group B2 (probable human carcinogen), RPF=1	7.3×10^0 , forestomach (larynx, esophagus) 4 data sets	NA, not volatile	IRIS (U.S. EPA, 2009j); U.S. EPA, 1993
Benz(a)anthracene	Group B2 (probable human carcinogen), RPF=0.1	Inadequate data, use RPF	NA, not volatile	IRIS (U.S. EPA, 2009j); U.S. EPA, 1993
Chrysene	Group B2 (probable human carcinogen), RPF=0.001	Inadequate data, use RPF	NA, not volatile	IRIS (U.S. EPA, 2009j); U.S. EPA, 1993
Benzo(b)fluoranthene	Group B2 (probable human carcinogen), RPF=0.1	Inadequate data, use RPF	NA, not volatile	IRIS (U.S. EPA, 2009j); U.S. EPA, 1993
Benzo(k)fluoranthene	Group B2 (probable human carcinogen), RPF=0.01	Inadequate data, use RPF	NA, not volatile	IRIS (U.S. EPA, 2009j); U.S. EPA, 1993
Dibenz(a,h)anthracene	Group B2 (probable human carcinogen), RPF=1	Inadequate data, use RPF	NA, not volatile	IRIS (U.S. EPA, 2009j); U.S. EPA, 1993
Indenol(1,2,3-c,d) pyrene	Group B2 (probable human carcinogen), RPF=0.1	Inadequate data, use RPF	NA, not volatile	IRIS (U.S. EPA, 2009j); U.S. EPA, 1993

^aComplete citations for the principal studies can be found in the source documents (e.g., IRIS [U.S. EPA, 2009j]).

*Screening values are developed in the Appendix of a PPRTV. For example, in cases where a high degree of uncertainty exists. Screening Values are intended for use in limited circumstances when no Tier 1, 2, or 3 values are available.

C = carbon number, EC = equivalent carbon number index, IRIS = Integrated Risk Information System, IUR = inhalation unit risk, NA = Not applicable, OSF = oral slope factor, PPRTV = Provisional Peer-Reviewed Toxicity Value, RPF = Relative potency factor (U.S. EPA, 1993), WOE = weight of evidence

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APPENDIX A. EXISTING APPROACHES FOR EVALUATING COMPLEX MIXTURES OF ALIPHATIC AND AROMATIC HYDROCARBONS

Massachusetts Department of Environmental Protection (MADEP) Approach

The MADEP recommended the use of a combination indicator compound and fraction approach for the assessment of health effects from petroleum hydrocarbons in soil and water, with a focus on oral exposure (Hutcheson et al., 1996; MADEP, 1994). Subsequently, MADEP (1996, 1997, 2001) published public comment and final drafts regarding implementation of their approach. These drafts and the final version of the implementation document (MADEP, 2002) contained some modifications to take into account the strengths of the TPHCWG approach (discussed in the next section of this document)—particularly the TPHCWG-determined transport properties of hydrocarbon fractions, which are related to the equivalent (or relative) carbon number indices for the compounds (TPHCWG, 1997a). In addition, these documents incorporated inhalation assessment and inhalation reference concentrations (RfCs). In 2003, MADEP updated the MADEP (1994) report, providing new and revised petroleum hydrocarbon fraction toxicity values, and a review of the literature to support the derivations of these values (MADEP, 2003). The MADEP approach is as follows:

Carcinogenic Effects

- Specific hydrocarbon indicator compounds that have U.S. EPA cancer potency factors are assessed; these are benzene and benzo(a)pyrene.
- MADEP is reviewing the U.S. EPA (1993) relative potency factors (RPFs) for PAHs, and in the meantime recommends the use of those values and the slope factor for benzo(a)pyrene for cancer assessment of the high-carbon-range aromatics (MADEP, 2008).

Noncarcinogenic Effects

- Hydrocarbon fractions are established based on molecular structure (aromatic versus aliphatic), and then on number of carbon atoms (C), using toxicologically similar groupings and excluding compounds with less than five carbons because their high volatility precludes chronic exposure from spills/releases. Analytical methods for these fractions are suggested.
- With the exception of the aromatic C5-C8 fraction, the toxicity of each fraction initially was represented by the RfD for a representative “reference compound” from the fraction, usually chosen because of the availability of an RfD on IRIS or adequate data to support derivation of an RfD. The toxicities of other compounds in the subclass were assumed to equal that of the reference compound. Some of these fractions include subfractions that were combined because of similarity of toxicity across fractions or limitations in the toxicity data. The approach is now broadened to include the selection of similar mixtures to represent the toxicity of a fraction and the inclusion of inhalation toxicity values.

The MADEP (1994, 2001, 2003; Hutcheson et al., 1996) approach assumes additivity of the hydrocarbon fractions and the indicator compounds in assessing the potential for adverse effects of petroleum hydrocarbons on human health (dose-addition using the hazard index [HI] approach for noncarcinogenic effects and RPF approach for carcinogenic PAHs; response addition for carcinogenic effects across fractions).

Total Petroleum Hydrocarbon Criteria Working Group (TPHCWG) Approach

The TPHCWG (1997a, b; Weisman, 1998) also recommended a combination indicator compound and fraction approach for TPH, which differed from the MADEP approach: (1) in its application only to soil contamination (to develop risk-based screening levels [RBSLs]); (2) in the elimination of assessment for noncarcinogenic effects if carcinogens are present above regulatory criteria; (3) in the basis for selection of the fractions; and (4) initially, in a more extensive use of toxicity data for mixtures to represent the toxicity of the fraction. Subsequently, the TPHCWG (1999) appeared to broaden its focus to include RBSLs for groundwater as well as for soil. Some of the TPHCWG hydrocarbon fractions include subfractions that were combined for toxicological assessment because of similarity of toxicity across fractions or limitations in the toxicity data. The TPHCWG approach is as follows:

Carcinogenic Effects

- Specific carcinogenic indicator compounds (i.e., benzene, benzo[a]pyrene) are assessed.
- The use of (relative) potency factors and the benzo(a)pyrene slope factor is mentioned for benzo(a)anthracene, indeno(1,2,3-cd)pyrene, dibenzo(a,h)anthracene, chrysene, benzo(b)fluoranthene and benzo(k)fluoranthene, but they are not further described or referenced.

Noncarcinogenic Effects

These effects are assessed only if the carcinogenic indicator compounds are not detected or are below regulatory criteria.

- Hydrocarbon fractions are established based on molecular structure (aromatic versus aliphatic) and then on the basis of equivalent carbon (EC) number index. This index is equivalent to the retention time of the compounds on a boiling point gas chromatography (GC) column (nonpolar capillary column), normalized to the *n*-alkanes. For example, benzene, a C6 aromatic compound, has an EC of 6.5 because its boiling point and GC retention time are approximately halfway between those of *n*-hexane (C6, EC6) and *n*-heptane (C7, EC7). Physical and chemical properties of hydrocarbons that are useful in predicting fate and transport (vapor pressure, solubility, partition coefficient, Henry's Law constants) are predictably related to the EC and can be estimated using algorithms. The mass of the carcinogenic indicator compounds is subtracted from the mass of the fraction.
- Following subtraction of the mass of the carcinogenic hydrocarbons, the noncancer effects of the remaining mass of each fraction are assessed by comparison with a surrogate compound or mixture.

The TPHCWG (1997a, b; 1999) approach assumes additivity of the hydrocarbon fractions and the indicator compounds in assessing the potential for adverse effects of petroleum hydrocarbons on human health, as in deriving risk-based screening levels for soil (dose-addition using HI approach for noncarcinogenic effects and RPFs for carcinogenic PAHs).

One caveat to this fate and transport fraction approach is that simplified models, such as the ones used by the TPHCWG (1997a) to perform the fraction groupings, neglect cosolvency effects and saturation of active sorption sites in soils (for nonionic hydrophobic chemicals, the organic carbon content of soil is the primary soil property controlling sorption). The actual transport properties at a waste site may be significantly influenced by the quantity of material

spilled or leaked into the soil (e.g., 500 gallons of gasoline will behave differently than 500 mL). For example, although PAHs may have a strong predicted adsorption to soil, when present in a large spill, they may initially have no or very low sorption due to cosolvent and saturation effects. As the spill migrates and becomes diluted, however, the influence of cosolvent and saturation effects will diminish. Another observation with regard to the approach to selection of fractions is that it appears to focus on petroleum hydrocarbons identified in petroleum fuels (JP-4, JP-5, JP-8, kerosene, diesel, and fuel oil #2) and crude oil. Although lubricating oils such as motor oil and mineral-based hydraulic fluids are included in the volumes on analytical methods and composition of petroleum mixtures (TPHCWG, 1998a, b), they are not included in the volume on selection of fractions (TPHCWG, 1997a). The lubricating oils contain high molecular weight branched alkanes and cyclic alkanes with >1 ring that are not well represented in the petroleum products of focus. Nevertheless, the toxicity assessments did consider these constituents in deriving toxicity values for the fractions that include them. The term “fate and transport fraction” is something of a misnomer as the fractions are based on properties that will affect transport, and do not take into account fate processes. The TPHCWG (1999) accordingly changed its nomenclature to “transport fraction” and that term is used in this PPRTV document.

American Society for Testing and Materials (ASTM) Approach

ASTM (1995) developed a Standard Guide for Risk-Based Corrective Action Applied at Petroleum Release Sites (RBCA, pronounced “Rebecca”). RBCA, reapproved in 2002 (ASTM, 2002) is a tiered decision-making framework for the integration of site assessment, remedial action selection and monitoring with U.S. EPA-recommended risk and exposure assessment. It includes any chemical that may be associated with petroleum product releases, including nonhydrocarbon constituents and additives, such as lead, methyl tert-butyl ether, and ethylene dibromide. The RBCA approach focuses on indicator compounds, assuming that a significant portion of the total potential impact on human health from all chemicals in a petroleum product spill is due to the indicator compounds, termed chemicals of concern. The risk or hazard of exposure to each chemical of concern is assessed separately during the derivation of Tier 1 (general) RBSLs, and Tier 2 and Tier 3 site-specific target levels (SSTLs) for contaminated media. The RBSLs and SSTLs are based on carcinogenicity for chemicals that have been classified as carcinogens and on RfDs or RfCs for chemicals that have not been classified as carcinogens. Each pathway of exposure is assessed separately. Thus, the RBSLs for toluene are based on hazard quotients of 1 for each potential pathway and the RBSLs for benzene are based on cancer risks of 1×10^{-6} and 1×10^{-4} for each potential pathway. The rationale presented for this approach is that the risk-based screening levels “are typically for a limited number of chemical(s) of concern considered at most sites.” RBCA mentions—but does not recommend or explain—the use of additivity approaches for mixtures of chemicals for Tier 2 and Tier 3 assessments.

Selection of the chemicals of concern for various petroleum products in the ASTM (1995, 2002) RBCA approach is based on concentrations in the product, solubility and mobility, toxicological properties, aesthetic characteristics (e.g., odor), and availability of sufficient information to conduct risk assessments. For gasoline, kerosene, and jet fuels, commonly selected hydrocarbon chemicals of concern are benzene, toluene, ethylbenzene, and xylene (BTEX). Additional chemicals of concern for kerosene and jet fuels are PAHs. For diesel fuel, light fuel oils, and heavy fuel oils, the commonly selected hydrocarbon chemicals of concern are PAHs. ASTM (1995, 2002) developed example Tier 1 RBSLs for benzene, ethylbenzene, toluene, mixed xylenes, naphthalene, and benzo(a)pyrene for various media and

exposure pathways, using U.S. EPA cancer and noncancer toxicity values and U.S. EPA exposure assessment methods.

The TPHCWG (1999) discussed how the TPHCWG fractions and toxicity criteria may be used with any risk-based decision framework, including the ASTM (1995) RBCA, and provided example calculations of RBSLs. MADEP (2001, 2002), under the Massachusetts Contingency Plan, uses a tiered risk assessment approach similar to the ASTM (1995, 2002) RBCA.

Agency for Toxic Substances and Disease Registry (ATSDR) Approach

ATSDR (1999a) developed a toxicological profile on TPH that recommended an indicator compound/fraction approach, based on an evaluation and synthesis of the MADEP and TPHCWG approaches, and a consideration of the ASTM approach. ATSDR (1999a) used ATSDR MRLs and U.S. EPA cancer assessments to evaluate the toxicity and carcinogenicity of the compounds and fractions. The recommendations with regard to selection of the fractions are similar to those in this report. ATSDR (1999a) noted that an assumption of additivity underlies use of a surrogate toxicity value from a representative compound to assess the health effects of the entire mass of the fraction. ATSDR discussed the use of an HI method (called index of concern by ATSDR) for the constituents (BTEX) of the low-carbon-range aromatics.