6. HEALTH EFFECTS

6.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of total petroleum hydrocarbons (TPH), and an understanding of various approaches used to assess petroleum hydrocarbons on the basis of fractions, individual indicator compounds, and appropriate surrogates. This chapter also provides descriptions and evaluations of toxicological studies and epidemiological investigations for these TPH fractions, indicator compounds, and surrogates, and provides conclusions, where possible, on the relevance of toxicity and toxicokinetics data to public health.

6.1.1 TPH Definition and Issues

Overview. The assessment of petroleum hydrocarbon-contaminated sites has involved analysis for "total petroleum hydrocarbons" or TPH. TPH is a loosely defined aggregate that depends on the method of analysis as well as the contaminating material, and represents the total mass of hydrocarbons without identification of individual components (see Chapter 3). As TPH is not a consistent entity, the assessment of health effects and development of health guidance values, such as Minimal Risk Levels (MRLs) for *TPH as a single entity* are problematic. Earlier in the profile (Chapters 2 and 3), various TPH approaches were presented that divide TPH into fractions or groups of compounds based on analytical, fate and transport, and exposure issues. Similarly, several different approaches have also been evolving to assess the health effects of TPH on the basis of indicator compounds for separate fractions, which consist of petroleum hydrocarbons with similar physical and chemical properties. ATSDR's approach to potential health effects from exposure to TPH uses surrogate health effects guidelines for each fraction, whether they represent an individual compound or a whole petroleum product. Additional discussions focusing on these various approaches to health effects assessment are presented in the remainder of this section (6.1). In particular, the ATSDR approach (Section 6.1.3) uses existing ATSDR MRLs for several individual TPH compounds and for specific petroleum products. The use of these MRLs to characterize the health effects of TPH, using an indicator compound and fraction/surrogate approach, is also discussed.

Scope of the Problem. Petroleum hydrocarbons are the principal components in a wide variety of commercial products (e.g., gasoline, fuel oils, lubricating oils, solvents, mineral spirits, mineral oils, and crude oil). Because of widespread use, disposal, and spills, environmental contamination is relatively common. It is important to understand that petroleum products are complex mixtures, typically containing hundreds of compounds. These include various amounts of aliphatic compounds (straight-chain, branched-chain, and cyclic alkanes and alkenes) and aromatic compounds (benzene and alkyl benzenes, naphthalenes, and PAHs). In addition, many petroleum products contain non-hydrocarbon additives such as alcohols, ethers, metals, and other chemicals that may affect the toxicity of the mixture.

The number of individual identified hydrocarbon components of the various petroleum products has been estimated at several hundred to over a thousand. Toxicity data are available for about 95 of these, but only about 25 were considered to have sufficient data to develop toxicity criteria according to the Total Petroleum Hydrocarbon Criteria Working Group (TPHCWG 1997b). ATSDR has derived MRLs for 12 of these compounds (anthracene, benzene, ethylbenzene, fluoranthene, fluorene, *n*-hexane, naphthalene, toluene, *m*-xylene, *p*-xylene, xylenes, and l-methyl naphthalene). EPA has derived Reference Doses (RfDs) and Reference Concentrations (RfCs) for some of the remaining compounds. The TPHCWG (1997c) and the Massachusetts Department of Environmental Protection (MADEP) (Hutcheson et al. 1996) have also derived other health guidance criteria for some of these compounds. Two of these compounds have EPA-derived cancer slope factors and/or unit risks, and a relative potency approach has been developed for some of the PAHs. However, it is not yet possible to assess the overall health implications of TPH from the individual hydrocarbon components because many of the known components lack appropriate, standardized, comparable toxicity data. In addition the cost of analysis for all TPH constituents is usually prohibitive.

Although health effects data are available for some petroleum products, and ATSDR-derived MRLs are available for fuel oil no. 2, JP-4, JP-5/JP-8, JP-7, and kerosene, there are limitations to applying MRLs for the whole products to TPH. A major limitation is that, when released to the environment, the composition of a petroleum product changes due to weathering (i.e., differential fate and transport of its components). Partitioning of fractions consisting of hydrocarbons with similar physical and chemical properties occurs, with migration of some fractions to other locations and environmental media, leaving the relatively nonmobile components (the weathered product) at the original location.

Thus, the actual petroleum hydrocarbon mixture to which a given population is exposed varies with location, time and environmental medium. Accordingly, health effects data for whole petroleum products that are relatively heterogeneous, such as gasoline and JP-4, are not necessarily applicable to the fractions to which exposure actually occurs as a result of transport and weathering. For example, acute inhalation exposure to a fresh spill of gasoline will be to the more volatile constituents, whereas intermediate or chronic oral exposure to drinking water contaminated by a gasoline release will be to the soluble constituents, and exposure to soil at the site of the original spill will be to the less volatile and less soluble constituents. Thus, none of these exposure scenarios would be well represented by experimental data using the whole product.

Additional limitations to the use of health effects data for whole petroleum products include the variable composition of each type of petroleum product due to differences in the crude oil from which it was refined, in the refining processes used, and in the formulation of the final product. Also, non-hydrocarbon additives and contaminants, many of which have significant toxicity, are often included in these whole products (e.g., methyl-*tert*-butyl ether (MTBE) or lead in gasoline). Finally, the identity of the originally released material may not be known or more than one such product may have been released.

Health effects data also are available for some petroleum fractions or process streams that are less heterogeneous. These materials are more representative of the fractions that may partition in the environment and are more useful for assessing health effects of intermediate and chronic exposure to petroleum hydrocarbons. These products are discussed further in Section 6.2. Additional discussion of these and also the more heterogeneous products is presented in Section 6.3.

Mixtures Issues. Petroleum products and their environmental transport fractions are complex mixtures. The preferred method for assessing the health effects of complex mixtures is to use exposure and toxicity data for the mixture of concern, because this approach takes into account toxicological interactions, such as synergism or antagonism, that may occur among the constituents of the mixture. If data for the mixture of concern are not available, then data for a similar mixture may be used. In the absence of pertinent data for the same or a similar mixture, data on the individual components of the mixture are used, taking into account the potential for toxicological interactions. The default assumption, when data regarding interactions are not available or do not clearly indicate

the direction of the interaction, is that the doses or effects are additive (ATSDR 1992; De Rosa et al. 1996; EPA 1986; Johnson and De Rosa 1995; Mumtaz et al. 1994). Other public health aspects of chemical mixtures and TPH have recently been reviewed (Hansen et al. 1998; Todd et al. 1999)

The mixtures of concern for TPH are not the heterogeneous petroleum products, but rather the transport fractions to which populations are more likely to be exposed. Thus, use of health effects data for these fractions would be preferable. When health effects data for petroleum products (mixtures) similar in composition to these fractions are not available, data for individual constituents could be used as surrogates, taking into account the potential for toxicologic interactions. Given the complexity of the interactions data for the individual constituents (Section 6.9) however, the assumption that the toxicity of the constituents is additive may be the most reasonable approach. This implicit assumption underlies the adoption of an MRL as a surrogate value to represent the toxicity of an entire fraction.

6.1.2 Existing Risk-Based Methods for TPH Health Assessment

This section presents approaches of other organizations. The ATSDR approach is presented in Section 6.1.3.

The American Society for Testing and Materials (ASTM) Approach. ASTM (1995) developed a Risk-Based Corrective Action (RBCA) approach for petroleum release sites. Additional information regarding this approach is provided in previous sections of this document and in Chapter 7. The present discussion is limited to health effects aspects of the approach. The RBCA approach is not limited to TPH, but includes any chemical that may be associated with petroleum product releases, including nonhydrocarbon constituents and additives. ASTM used an indicator compound approach that assumes 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 ASTM approach assesses the risk of exposure to each chemical of concern separately during the derivation of Tier 1 (general) risk-based screening levels, and Tier 2 and 3 site- specific target levels for contaminated media. Although the use of whole mixture toxicity data and the assumption of additivity for the toxicity of individual chemicals in a mixture were mentioned as options for Tier 2 and 3, neither approach was recommended by ASTM. The criteria to be used in selection of the chemicals of concern for various petroleum products are 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. Twelve PAHs, including benzo(a)pyrene, were selected for consideration.

The MADEP Approach. The MADEP (Hutcheson et al. 1996; MADEP 1997, 1999) recommends the use of a combination indicator compound and fraction approach for the assessment of health effects from TPH in soil and water as follows:

Carcinogenic Effects. Specific petroleum hydrocarbon indicator compounds that have EPA cancer potency factors are assessed; these are benzene and benzo(a)pyrene. EPA relative potency factors can be used for benz(a)anthracene, indeno(1,2,3-cd)pyrene, dibenz(a,h)anthracene, chrysene, benzo(b)fluoranthene, and benzo(k)fluoranthene.

Noncarcinogenic Effects. The following petroleum hydrocarbon fractions were established based on molecular structure (aromatic versus aliphatic) and then on number of carbon atoms, using toxicologically similar groupings and excluding compounds with less than 5 carbons because their high volatility precludes chronic exposure from spills/releases. With the exception of the aromatic C_5-C_8 fraction, the toxicity of each fraction is represented by the RfD for a representative "reference compound" from the fraction. Analytical methods for these fractions have also been suggested (Section 3.3). Some of these fractions include subfractions that were combined because of similarity of toxicity across fractions or limitations in the toxicity data.

Aromatic fractions

C_5-C_8 , assessed on the basis of the individual indicator compounds-benzene (MADEP RfD derived from inhalation study), toluene, ethylbenzene, and xylenes (EPA RfDi).

C_9-C_{10}, using an EPA RfD for pyrene (the lowest RfD for compounds in this group) as a surrogate and an RfC for xylenes.

$C_{11}C_{12}$, using and EPA RfD for pyrene and an RfC for naphthalene.

Aliphatic fractions

C_5-C_8, using an EPA RfD and RfC for *n*-hexane as a surrogate.

C_9-C_{12}, using a MADEP RfD and RfC for *n*-nonane as a surrogate, based on estimated relative potency of *n*-nonane as compared with *n*-hexane.

C_{13}-C_{18}, using a MADEP RfD and RfC for naphthalene as a surrogate.

$C_{19}C_{35}$,using a MADEP RfD for white mineral oil (but listing eicosane as the reference compound).

The MADEP (1997) has published a draft report for public comment regarding implementation of their approach. This report references the TPHCWG (1997a, 1997b, 1997c) approach (below), particularly in defining fractions with regard to transport properties, which are related to the equivalent (or relative) carbon number indexes for the compounds.

The TPHCWG Approach. The TPHCWG (1997a, 1997b, 1997c) also recommends a combination indicator compound and fraction approach for TPH, but it differs from the MADEP approach in the elimination of assessment for noncarcinogenic effects if carcinogens are present above regulatory criteria, in the basis for selection of the fractions, and in a more extensive use of toxicity data for mixtures to represent the toxicity of the fraction. Some petroleum hydrocarbon fractions listed below include subfractions that were combined because of similarity of toxicity across fractions or limitations in the toxicity data.

Carcinogenic Effects. Specific petroleum hydrocarbon indicator compounds that have EPA cancer potency factors are assessed (i.e., benzene and benzo(a)pyrene).

Noncarcinogenic Effects. These effects are assessed only if the carcinogenic indicator compounds are not detected or are below regulatory criteria. The following petroleum hydrocarbon fractions, minus the carcinogenic indicator compounds, were selected as representing compounds with similar transport properties. Toxicity values for constituents of the fraction or for a similar mixture were selected to represent the toxicity of the fraction. Aromatic and aliphatic hydrocarbons are considered separately and further subdivided on the basis of equivalent carbon number index (EC). This index is equivalent to the retention time of the compounds on a boiling point GC column (non-polar capillary column), normalized to the *n*-alkanes. Physical and chemical properties of hydrocarbons that are

useful in predicting transport (vapor pressure, solubility, partition coefficient, Henry's law constants) are predictably related to the EC and can be estimated using algorithms (see Chapter 5).

Aromatic fractions

EC_5-EC_8, using EPA RfD and RfC for toluene as a surrogate.

$EC_{>8}$-EC_{16}, using EPA RfDs (all the same value) for two compounds (cumene [isopropylbenzene] and naphthalene) as a surrogate and an RfC for C_9 aromatics (hi-flash aromatic naphtha).

$EC_{>16}EC_{35}$, using the EPA RfD for pyrene (C_{16}) as a surrogate. Anthracene, fluorene, and fluoranthene are also in this group; however, pyrene was selected because it had the lowest RfD.

Aliphatic fractions

EC_5-EC_8, using TPHCWG RfD (derived from inhalation data) as a surrogate and RfC for commercial hexane, a mixture of C_6 hydrocarbons containing 53% *n*-hexane.

$EC_{>8}$-EC_{16}, using TPHCWG RfD and RfC for dearomatized petroleum streams (white spirit).

$EC_{>14}$-EC_{35}, using TPHCWG RfD for white mineral oils.

The MADEP (Hutcheson et al. 1996; MADEP 1997) and the TPHCWG (1997a, 1997b, 1997c) approaches both assume additivity of the indicator compounds and the hydrocarbon fractions in assessing the potential for adverse effects of TPH on health. In contrast, the ASTM approach ten to assess each individual TPH indicator chemical separately and without regard to the presence of other petroleum hydrocarbons and the potential for additivity or interactions, although it does not preclude a consideration of these factors.

6.1.3 Overview of the ATSDR Approach

In formulating an approach to health assessment of TPH, ATSDR has drawn on the experience of other groups that have been developing approaches to health-based assessment for TPH (i.e., ASTM [1995]; Hutcheson et al. [1996]; and TPHCWG [1997a, 1997b, 1997c]), but has developed an approach designed to address its own specific concerns and mandates. A notable difference between ATSDR and these other groups is that the other groups have focused on longer-term exposure

scenarios, whereas ATSDR is concerned with the entire spectrum of possible exposure periods from acute through chronic. In addition, the health guidance values developed by ATSDR, MRLs, are intended to serve as screening levels by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. **MRLs are not intended to define clean-up or action levels.**

The ATSDR approach, as reflected in this profile, focuses on an assessment of the health effects of petroleum hydrocarbon transport fractions, as suggested by the TPHCWG (1997a, 1997b, 1997c). This approach is the most universally useful, given the limitations to using data for the whole petroleum products or individual constituents, discussed in Chapter 2 and in Section 6.2.1 above. Methods of analysis for these fractions are available, and modeling can be performed to predict exposure to the fractions. The assessment of the health effects of the fractions by ATSDR is similar but not identical to that of the TPHCWG. In addition, to capitalize on the best features of the MADEP (Hutcheson et al. 1996) and TPHCWG (1997a, 1997b, 1997c) approaches, the aromatic EC_5-EC_8 fraction has been redefined as an EC_5-EC_9 fraction, so that it includes all the BTEXs. The aromatic $EC_{>8}$-EC_{16} fraction is then redefined as an $EC_{>9}$-EC_{16} fraction.

Carcinogenic Effects. Specific hydrocarbon indicator compounds that have EPA cancer risk estimates are assessed; these are benzene and benzo(a)pyrene. EPA relative potency factors can be used for benz(a)anthracene, indeno(1,2,3-cd)pyrene, dibenz(a,h)anthracene, chrysene, benzo(b)fluoranthene, and benzo(k)fluoranthene.

Noncarcinogenic Effects. The following petroleum hydrocarbon fractions, including the carcinogenic indicator compounds, were selected as representing compounds with similar transport properties, based on the recommendations of the TPHCWG (1997b, 1997c), with an adjustment of the lower EC aromatic fractions in order to include all the BTEXs in the first fraction, as discussed above. As with the MADEP and TPHCWG approaches, some of the fractions include subfractions that have been combined because of similarity of health effects across fractions or limitations in the health effects data. Provisional recommendations regarding suitable MRLs are made, using a surrogate approach as needed and appropriate. The MRL for the surrogate compound or for a petroleum product similar in composition to the fraction is used to indicate the potential toxicity of the entire mass of the fraction.

Aromatic Fractions

EC_5-EC_9, using inhalation and oral MRLs specific to each individual indicator compound-benzene, toluene, ethylbenzene, and the xylenes.

$EC_{>9}$-EC_{16}, using a chronic inhalation MRL and acute and intermediate oral MRLs for naphthalene as surrogates.

EC_{16}-EC_{35}, using an intermediate oral MRL for fluorene and fluoranthene as a surrogate.

Aliphatic Fractions

EC_5-EC_8, using a chronic inhalation MRL for *n*-hexane as a surrogate.

$EC_{>8}$-EC_{16}, using a chronic inhalation MRL for JP-7.

$EC_{>16}$-$EC_{>35}$, using health effects data for mineral oils, but no MRLs are available.

The health effects of these fractions are discussed in Section 6.2, and details of the selection of the fraction-specific MRLs can be found in Section 6.6. These fraction-specific values are provisional values, reflecting the uncertainty inherent in this approach, as discussed in Section 6.6. Further information on ATSDR MRLs is given in Appendix A, while information on other toxicity criteria such as RfDs and RfCs, is provided in Chapter 7.

ATSDR has already prepared toxicological profiles on a large number of individual constituents of TPH and on a number of whole petroleum products. In order to give an overall perspective on the toxicology of TPH, without duplicating the existing profiles, this toxicological profile will present brief summaries of the health effects of these individual petroleum hydrocarbon compounds and petroleum products. MRLs have been derived for a number of these compounds, which serve as indicator and surrogate compounds for the ATSDR approach as outlined above. Thus, consideration of these compounds as part of the TPH contamination profile is useful. Similarly, information regarding the extent and identity of petroleum product contamination may be available, and toxicity information and MRLs for these original products may be useful in some circumstances for assessing potential health effects. These brief summaries of information on the individual compounds and on petroleum products that are representative of particular fractions occur during the discussion of the health effects of the fractions in Section 6.2. Information on petroleum products, including the more heterogenous mixtures, also is presented in Section 6.3. The reader is encouraged to consult the original toxicological profiles listed in Appendix A and other cited sources for more detail.

The content of this chapter and this document is different from that of a standard toxicological profile, in recognition of the extensive assessments of individual petroleum hydrocarbons already performed by ATSDR and other agencies, and the need for an approach that focuses on the most important information. This chapter presents the ATSDR perspective and approach, and serves as a guide to sources of more detailed information.

6.2 DISCUSSION OF HEALTH EFFECTS BY FRACTION AND ROUTE OF EXPOSURE

Because of the complexity of TPH, and the existence of extensive ATSDR and TPHCWG documentation for constituents of TPH and for petroleum products and mixtures corresponding to some of the fractions, this section of the document adopts a "handbook approach" to delineating the health effects of TPH. The organization and content of this section, while retaining an emphasis on route and duration of exposure and on type of health effect, is streamlined in order to avoid duplication of existing resources and to help public health professionals, and others who address the needs of people living or working near hazardous waste sites, to gain an understanding of the characteristic health effects of TPH fractions. The juxtaposition of information on fraction composition with information on health effects for fraction constituents facilitates evaluation of the suitability of the existing health effects information to represent the potential health effects of the entire fraction. Further discussion of the suitability and representativeness of the information is presented in Section 6.6.

Thus, for each fraction, the components of the fraction are delineated first. Health effects for the fraction are then discussed by route of exposure. This discussion includes information on individual constituents of the fraction and on mixtures that correspond to the fraction. The text focuses on the major, sensitive, and/or characteristic end points.

The figures give a *condensed picture* of exposure-effect relationships for each fraction. They show the lowest reliable lowest-observed-adverse-effect-level (LOAEL) in animals and humans for each route, exposure period, and end point, including cancer. The three exposure periods-acute (14 days or less), intermediate (15-365 days), and chronic (365 days or more)-are represented. Different symbols are used to represent different compounds or mixtures, with open symbols for animals and

closed for humans. For additional information, including no-observed-adverse-effect levels (NOAELs), classification of LOAELs into “less serious” or “serious” effects, and details of the actual studies, the reader is encouraged to consult the sources referenced in the figures. Because cancer effects could occur at lower exposure levels than the exposures plotted in some of the figures, these figures also show a range for the upper bound of estimated excess risks, ranging from an estimate of 1 in 10,000 to 1 in 10,000,000 ($l0^{-4}$ to 10^{-7}), as developed by EPA.

In addition, estimates of minimal risk to humans (MRLs) are plotted. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 199Oc), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

The figures in this section were compiled primarily from the tables and figures showing *Levels of Significant Exposure* in ATSDR toxicological profiles. To fill data gaps for some of the fractions, pertinent additional health effects information from EPA sources and from the TPHCWG (1997c) was included. MADEP also was consulted, but did not appear to provide significant additional information for this purpose. (RfCs and RfDs from these sources are reported in Chapter 7.)

6.2.1 Aromatic EC_5-EC_9 Indicator Compounds

This fraction consists of indicator compounds: benzene, toluene, ethylbenzene, and xylene (mixture and individual isomers *o*-, *m*-, *p*-). These indicator compounds are often referred to as the BTEXs, and are commonly assessed using MRLs (or EPA toxicity values) specific to each compound. Styrene also would fall in this fraction, but does not appear to be a significant constituent of the petroleum products whose composition was reported by TPHCWG (1997c). The BTEXs are the subject of separate ATSDR toxicological profiles (ATSDR 1994, 1995b, 1997a, 1999a); these profiles should be consulted for detailed information on these compounds. The information in Sections 6.2.1.1 through 6.2.1.3 is taken from these profiles; for the sake of readability, references to these ATSDR profiles will not be repeated in these sections.

6.2.1.1 Inhalation Exposure

All the BTEXs cause neurological effects. Neurological effects are the basis for MRLs for both acute and chronic exposures to toluene and mixed xylenes, and for intermediate exposures to benzene; neurological effects are not as sensitive for ethylbenzene. The neurological effects consist primarily of central nervous system depression. Toluene's neurotoxicity also includes ototoxicity. Evidence of hearing loss has been seen in both occupationally exposed humans and in animals. There is limited evidence that chronic inhalation exposure to benzene may affect the peripheral nervous system; this evidence is from a single study of occupationally exposed humans who also had aplastic anemia.

Benzene is the only BTEX that has well characterized hematological, immunological, and lymphoreticular effects in humans and animals at low levels of inhalation exposure. Immunological and lymphoreticular effects are the basis for the derivation of the acute inhalation MRL for benzene. Benzene affects hematopoiesis, decreasing the production of all major types of blood cells, and can also cause hyperplasia.

Developmental effects are the basis for intermediate MRLs for ethylbenzene and mixed xylene, indicating that the embryo/fetus may be particularly sensitive to these two BTEXs.

Benzene is considered to be carcinogenic to humans by the inhalation route of exposure (EPA weight-of-evidence Group A, human carcinogen). Occupational exposure to benzene was associated with

increased incidences of nonlymphocytic leukemia. Studies in animals also found increased incidences of neoplasia in animals treated by inhalation or gavage with benzene.

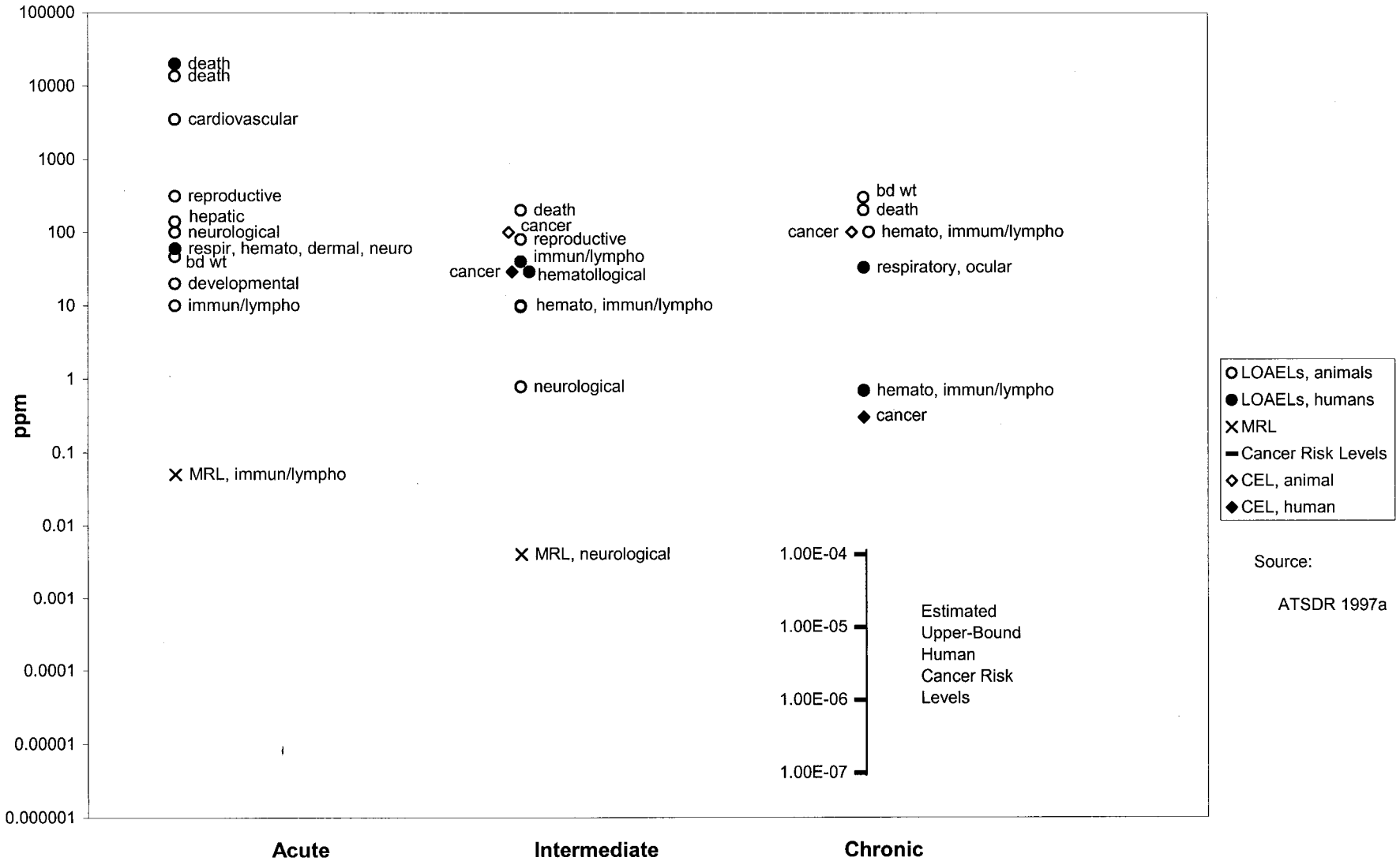
Although ethylbenzene was classified in EPA weight-of-evidence Group D (not classifiable as to human carcinogenicity), subsequent publication of a chronic inhalation study of ethylbenzene provides evidence of carcinogenicity in rats and mice, and indicates a need for reassessment. Toluene and mixed xylene are classified in Group D.

The lowest reliable LOAEL values for the BTEXs are summarized in Figure is 6-l through 6-4, as are MRLs and cancer risk levels. The data for each compound are presented in a separate figure because of the voluminous data available for each and because these compounds are commonly assessed using the exposure data and MRLs (or EPA toxicity values) specific for each. The data for mixed xylene are extensive, and MRLs are available for all three durations, whereas little data and no MRLs are available for the individual isomers (*o*-, ***m*-,** and *p*-). The inhalation toxicity data for the individual isomers are reasonably similar to those for the mixture. Accordingly, only the data for mixed xylene are included in the figure. More detailed information is available in the ATSDR toxicological profiles on the individual compounds (ATSDR 1994, 1995d, 1997a, 1999a), from which the information in this section is drawn.

6.2.1.2 Oral Exposure

Data for the oral route of exposure are less extensive. The BTEXs cause neurological effects, generally central nervous system depression, by the oral route. This is a sensitive effect for toluene and *p*-xylene, for which it is the basis of acute and/or intermediate MRLs. Renal and hepatic effects are also seen with oral exposure to these compounds. Renal effects are the basis for the intermediate MRL for mixed xylenes and hepatic effects are the basis for the intermediate MRL for *m*-xylene. The hepatic effects tend to be mild, including increased liver weight and cytochromes P-450 and b5 contents. Benzene causes hematological effects by the oral route that are similar to those seen from inhalation exposure.

Figure 6-1. Aromatic EC_5-EC_9 Exposures Associated with Health Effects - Inhalation - Benzene



Source:

ATSDR 1997a

Figure 6-2. Aromatic EC_5-EC_9 Exposures Associated with Health Effects - Inhalation - Toluene

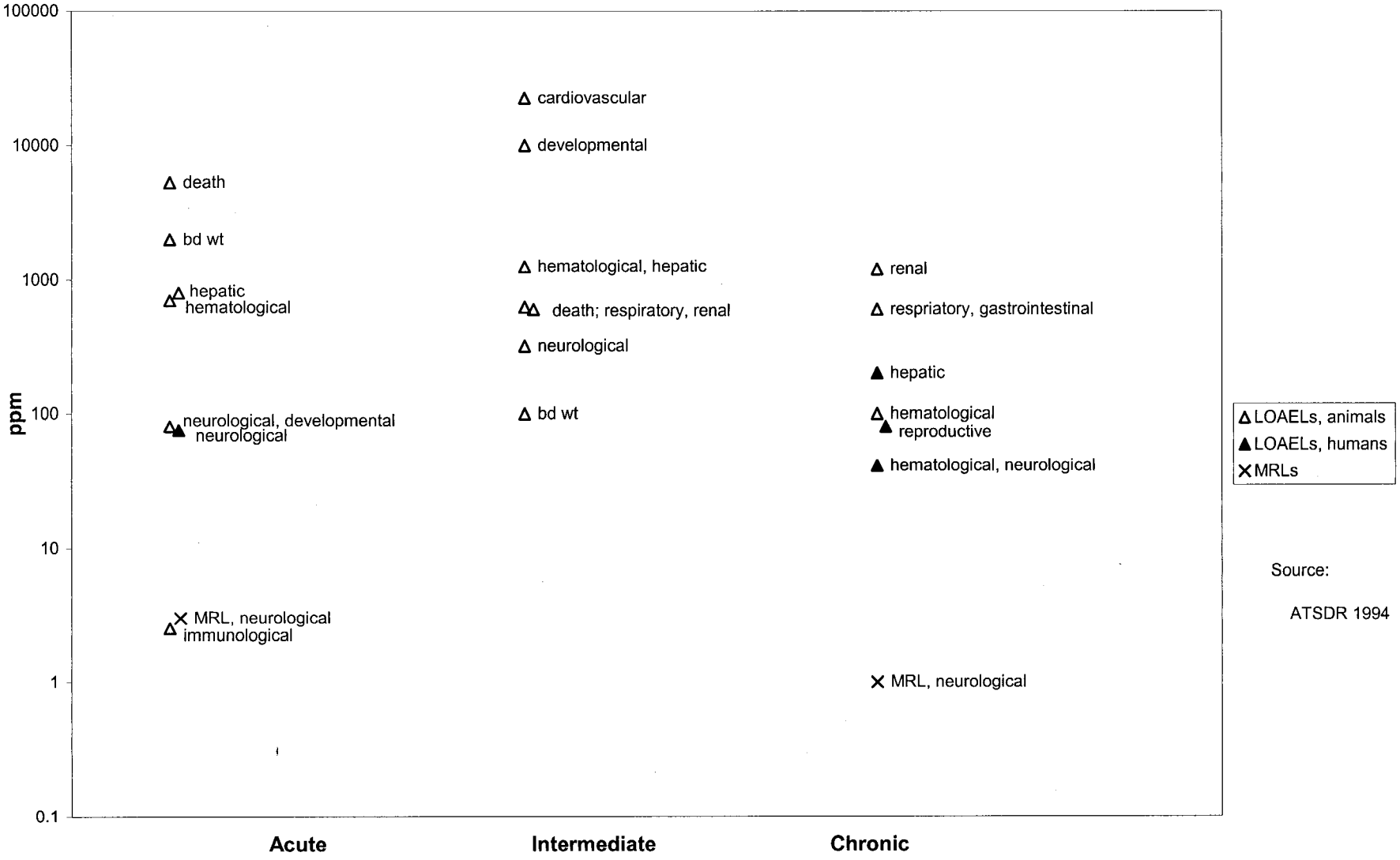


Figure 6-3. Aromatic EC_5-EC_9 Exposures Associated with Health Effects - Inhalation - Ethylbenzene

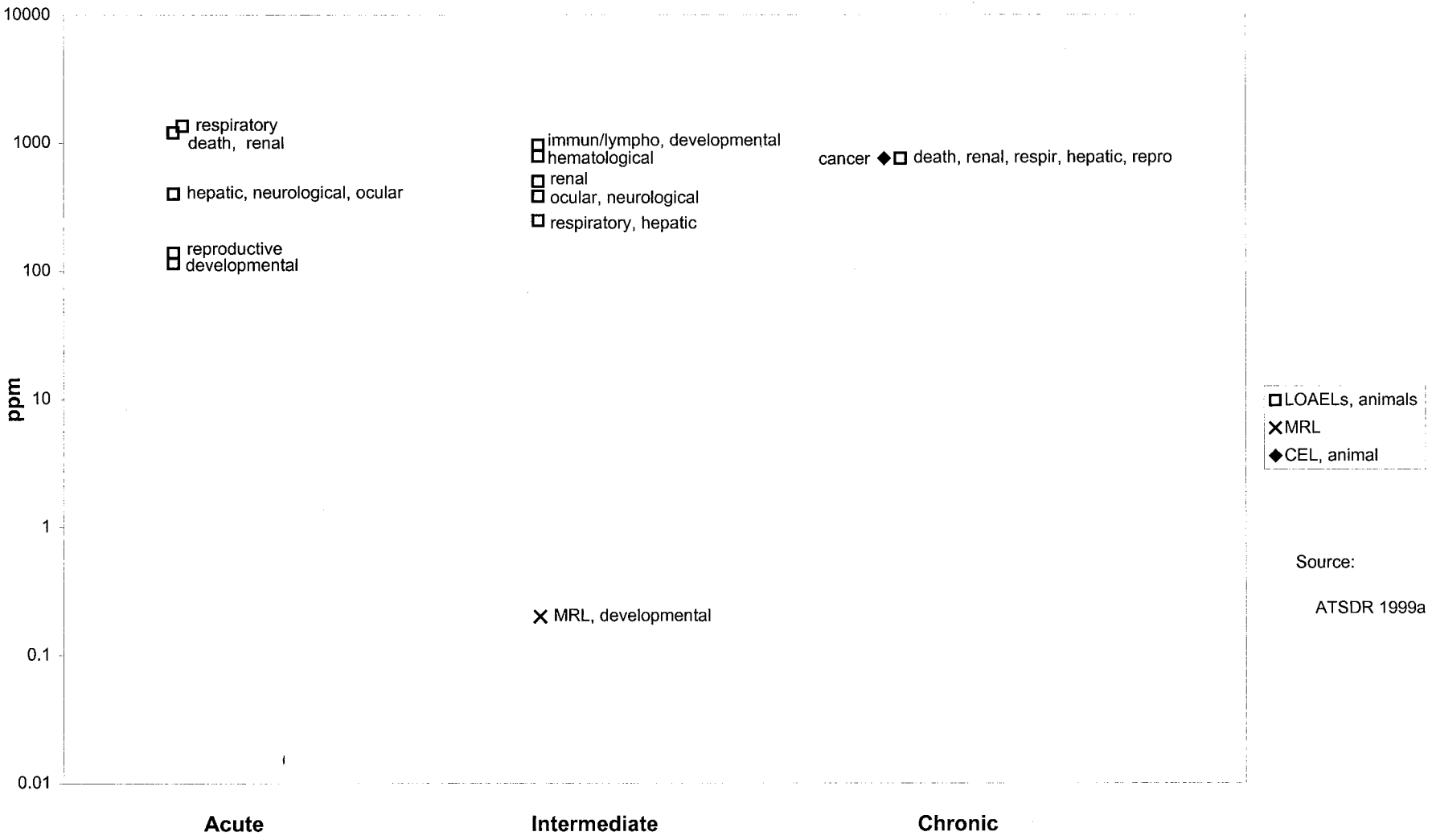
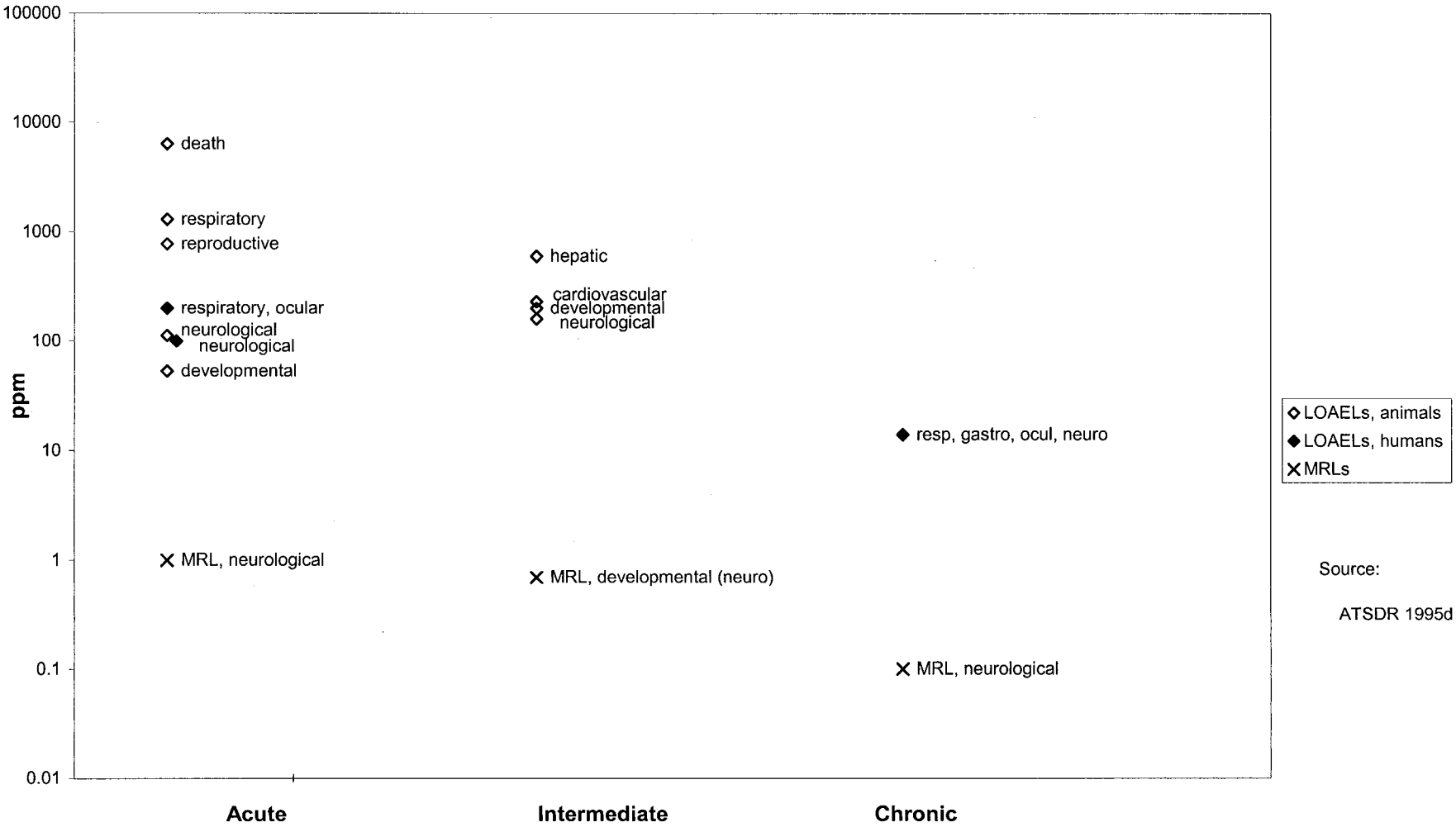


Figure 6-4. Aromatic EC_5-EC_9 Exposures Associated with Health Effects - Inhalation - Mixed Xylene



Source:

ATSDR 1995d

Benzene is considered to be carcinogenic (EPA weight-of-evidence Group A) to humans by either inhalation or oral exposure, based on occupational studies that showed increased incidences of nonlymphocytic leukemia in humans exposed by inhalation, with supporting data from oral and inhalation studies in animals. Results of a recently published study of ethylbenzene in animals indicate carcinogenicity by the inhalation route, but there is no evidence of carcinogenicity by the oral route. Toluene and mixed xylene are classified in EPA weight of evidence Group D (not classifiable as to human carcinogenicity).

The lowest reliable LOAEL values for the BTEXs are summarized in Figures 6-5 through 6-7, as are MRLs and cancer risk levels. With the exception of ethylbenzene, the data for each of the BTEXs are presented in a separate figure because of the voluminous data available for each and because these compounds are commonly assessed using the exposure data and MRLs (or EPA toxicity values) specific for each. There are only two pertinent LOAELs and no MRLs for ethylbenzene, so the LOAELs for ethylbenzene are plotted with those for toluene, and indicated by a different symbol. More detailed information is available in the ATSDR toxicological profiles on the individual compounds (ATSDR 1994, 1995d, 1997a, 1999a), from which the information in this section is drawn.

6.2.1.3 Dermal Exposure

Information on the health effects of dermal exposure to the BTEXs is limited. Skin and eye irritation are well documented, but effects from systemic absorption are not. ATSDR (1997a) concluded that it is reasonable to expect that adverse hematological and immunological effects might occur following dermal exposure to benzene, because benzene is absorbed through the skin and absorption through any route would increase the risk of these effects. For more detailed information, see the ATSDR toxicological profiles on the individual compounds (ATSDR 1994, 1995d, 1997a, 1999a), from which the information in this section is drawn.

6.2.2 Aromatic $EC_{>9}$-EC_{16} Combined Fractions

$EC_{>9}$-EC_{10} fraction: includes cumene (isopropylbenzene), *n*-propylbenzene, the methyl-ethylbenzenes, some trimethylbenzene isomers, and the branched-chain butylbenzenes. None of these compounds is the subject of an ATSDR toxicological profile.

Figure 6-5. Aromatic EC_5-EC_9 Exposures Associated with Health Effects - Benzene - Oral

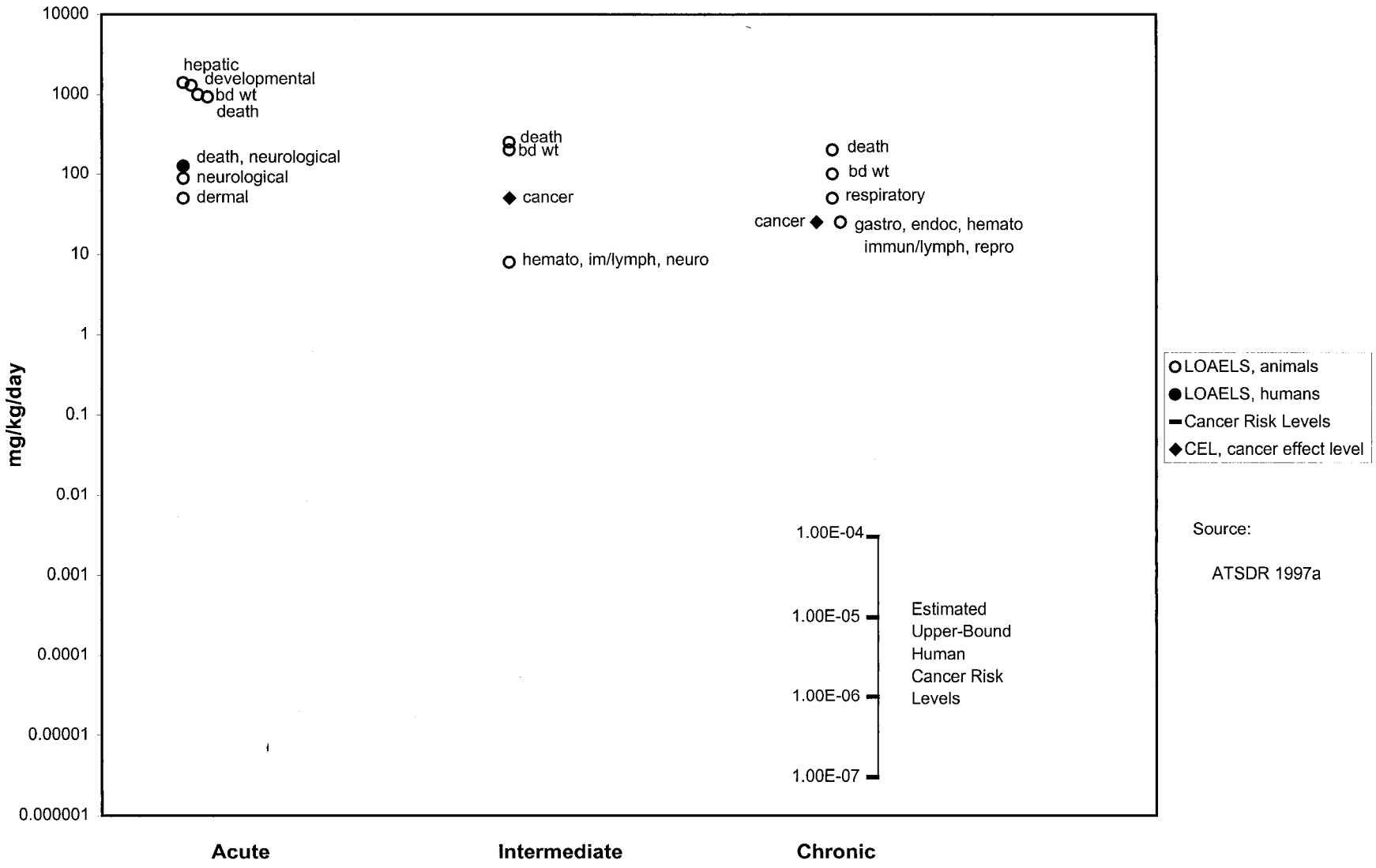
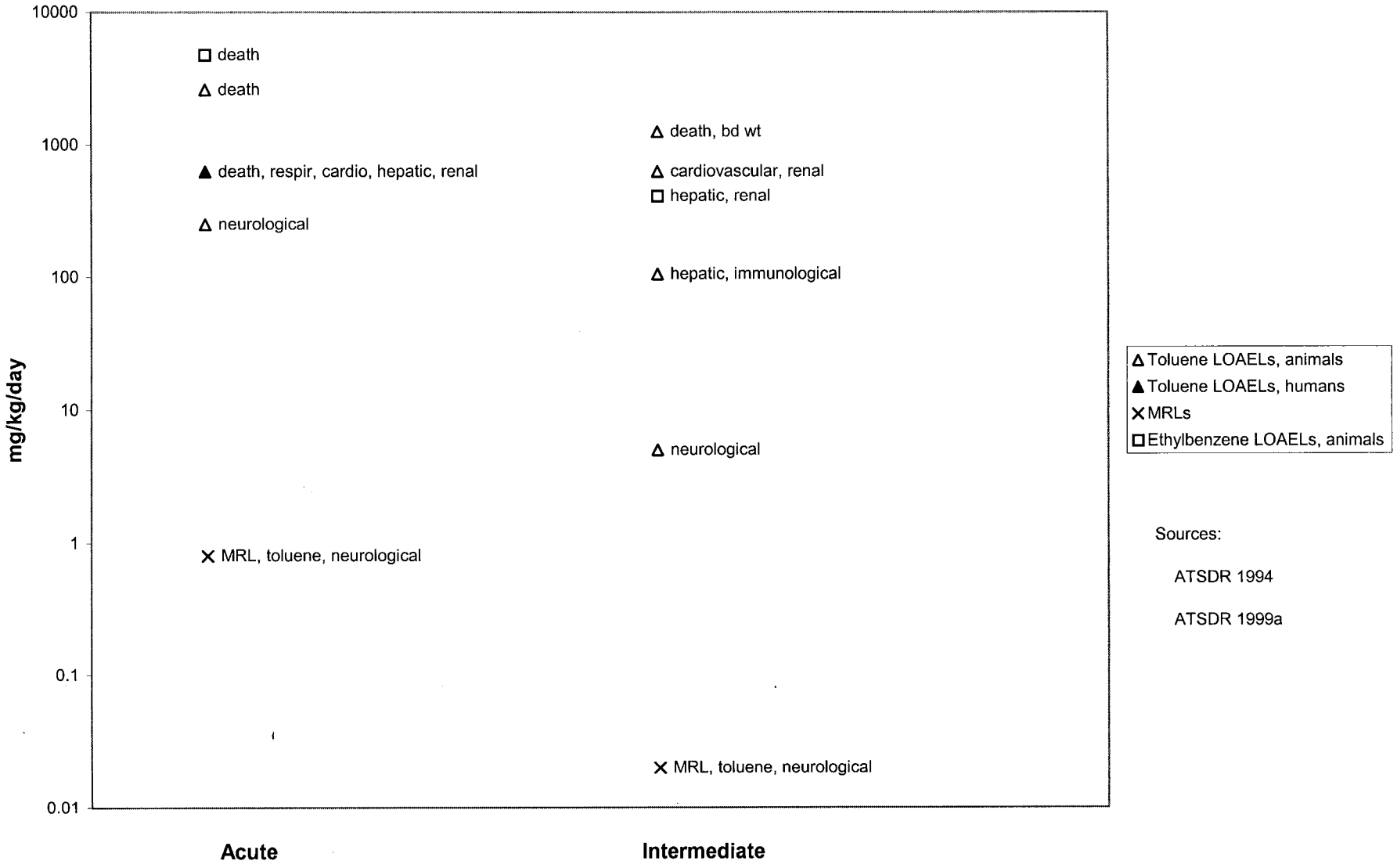


Figure 6-6. Aromatic EC_5-EC_9 Exposures Associated with Health Effects - Oral - Toluene and Ethylbenzene

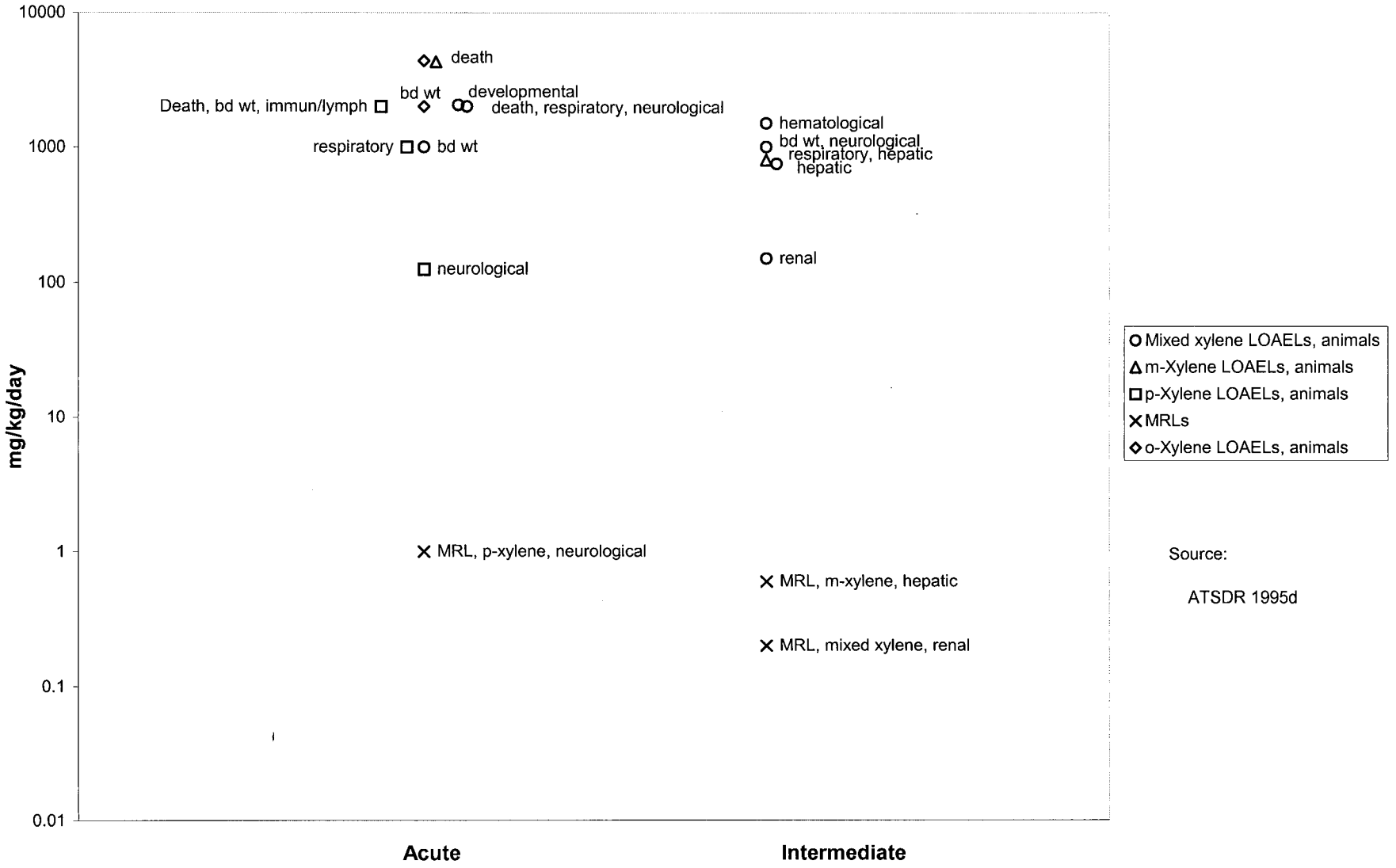


Sources:

ATSDR 1994

ATSDR 1999a

Figure 6-7. Aromatic EC_5-EC_9 Exposures Associated with Health Effects - Oral - Xylenes



Source:

ATSDR 1995d

$EC_{>10}$-EC_{12} fraction: includes *n*-butyl and *n*-pentylbenzene, a trimethylbenzene isomer and various other multi-substituted alkylbenzenes, as well as indan, methylindans and naphthalene. The only compound in this fraction for which an ATSDR toxicological profile is available is naphthalene (ATSDR 1995e).

$EC_{>12}$- EC_{16} fraction: includes a few longer-chain and multi-substituted alkyl benzenes, biphenyls, the mono- and dimethylnaphthalenes, and PAHs, including acenaphthene and acenaphthylene. The monomethylnaphthalenes (l- and 2-methyl naphthalene) are discussed in the ATSDR toxicological profile on naphthalene (ATSDR 1995e) and acenaphthene and acenaphthylene are included in the ATSDR toxicological profile on PAHs (ATSDR 1995f).

6.2.2.1 Inhalation Exposure

No toxicological profiles are available for petroleum hydrocarbons in the $EC_{>9}$-EC_{10} fraction. Inhalation exposure to isopropylbenzene (cumene) and to the trimethylbenzene is known to have neurological and respiratory irritant effects (EPA 1997a, 1998b; TPHCWG 1997c), but these may not be the most sensitive effects of inhalation exposure to the compounds in this fraction. EPA (1998b) concluded that the critical effect of inhalation exposure to isopropylbenzene was increased renal weights in female rats and increased adrenal weights in both sexes of rats in a 13-week inhalation study (Cushman et al. 1995). An RfC was based on these data. Toxicity data for a mixture of C_9 aromatics, consisting primarily of trimethylbenzene and methylethylbenzene isomers, have been assessed (as the basis for an RfC) by the TPHCWG (1997c). The critical effects were hepatic and renal.

Hemolytic anemia is a frequent consequence of acute inhalation exposure to naphthalene in humans, particularly infants and those with a G6PD genetic defect. Exposure-effect relationships for hemolytic anemia are not well characterized. Ocular effects, including cataracts, have been reported in humans exposed to naphthalene vapors, but exposure levels were not known. In mice, respiratory effects are a sensitive effect of inhalation exposure to naphthalene. A chronic MRL has been derived for naphthalene based on respiratory effects in mice-chronic inflammation and regeneration of the nasal epithelium and inflammation of the lung epithelium. In addition, the same study in mice reported an increased incidence of lung adenomas in female but not in male mice (ATSDR 1995e).

The EPA classified naphthalene in Group D (not classifiable as to human carcinogenicity) prior to publication of this study, but notes that naphthalene may be more appropriately classified in Group C (possible human carcinogen) (EPA 1998b).

No MRLs have been developed for compounds in the $EC_{>9}$ –EC_{16} fraction. Only acenaphthylene has been assessed by the EPA for carcinogenicity; the data were considered inadequate (Group D) (ATSDR 1995e, 1995f).

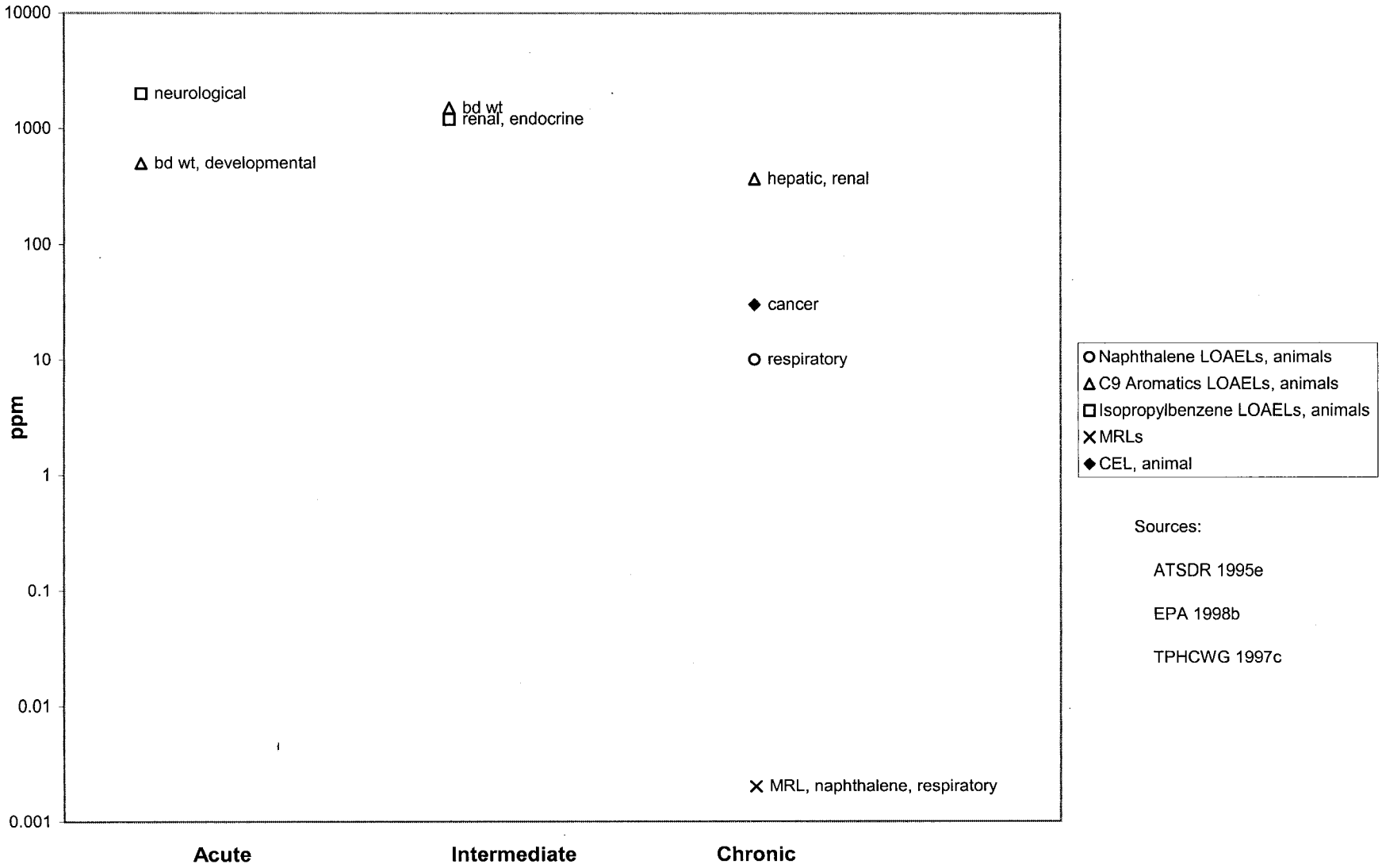
The lowest reliable LOAEL values for the combined aromatic $EC_{>9}$-EC_{16} fraction are summarized in Figure 6-8, as are MRLs. Because so few of the compounds in this fraction have been assessed by ATSDR, additional information from EPA sources and the TPHCWG (1997c) have been added. More detailed information is available in the ATSDR toxicological profiles on the individual compounds and in the other sources noted above.

6.2.2.2 Oral Exposure

There are no toxicological profiles or MRLs for compounds in the $EC_{>9}$-EC_{10} fraction. Toxicity data, primarily from subchronic oral studies in rats, have been assessed by EPA during the derivation of RfDs for two of the compounds-isopropylbenzene (cumene) (EPA 1997a) and 1,3,5-trimethylbenzene (EPA 1996). The critical effect for isopropylbenzene was renal; for 1,3,5trimethylbenzene, the critical effect was a combination of renal, hepatic, and other systemic effects. Oral data for these compounds were limited. Isopropylbenzene has been classified in Group D (not classifiable as to human carcinogenicity) (EPA 1998b). 1,3,5-Trimethylbenzene has not been classified and does not appear to have been studied for carcinogenicity.

Naphthalene, a constituent of the $EC_{>10}$-EC_{12} fraction, produces hemolytic anemia in humans when ingested. As mentioned previously, individuals with a genetic G6PD deficiency have an increased susceptibility to this effect. Little dose-effect information is available for this effect in humans or in animals; dogs appear to be more susceptible than other animal species. Ocular effects occur with high-dose oral administration of naphthalene in animals. The most common effect is cataract formation, but retinal damage has also been noted (ATSDR 1995e). More sensitive effects in animals are neurological effects (central nervous system depression in pregnant animals) and mild hepatic

Figure 6-8. Aromatic $EC_{>9}$-EC_{16} Exposures Associated with Health Effects - Inhalation



Sources:

ATSDR 1995e

EPA 1998b

TPHCWG 1997c

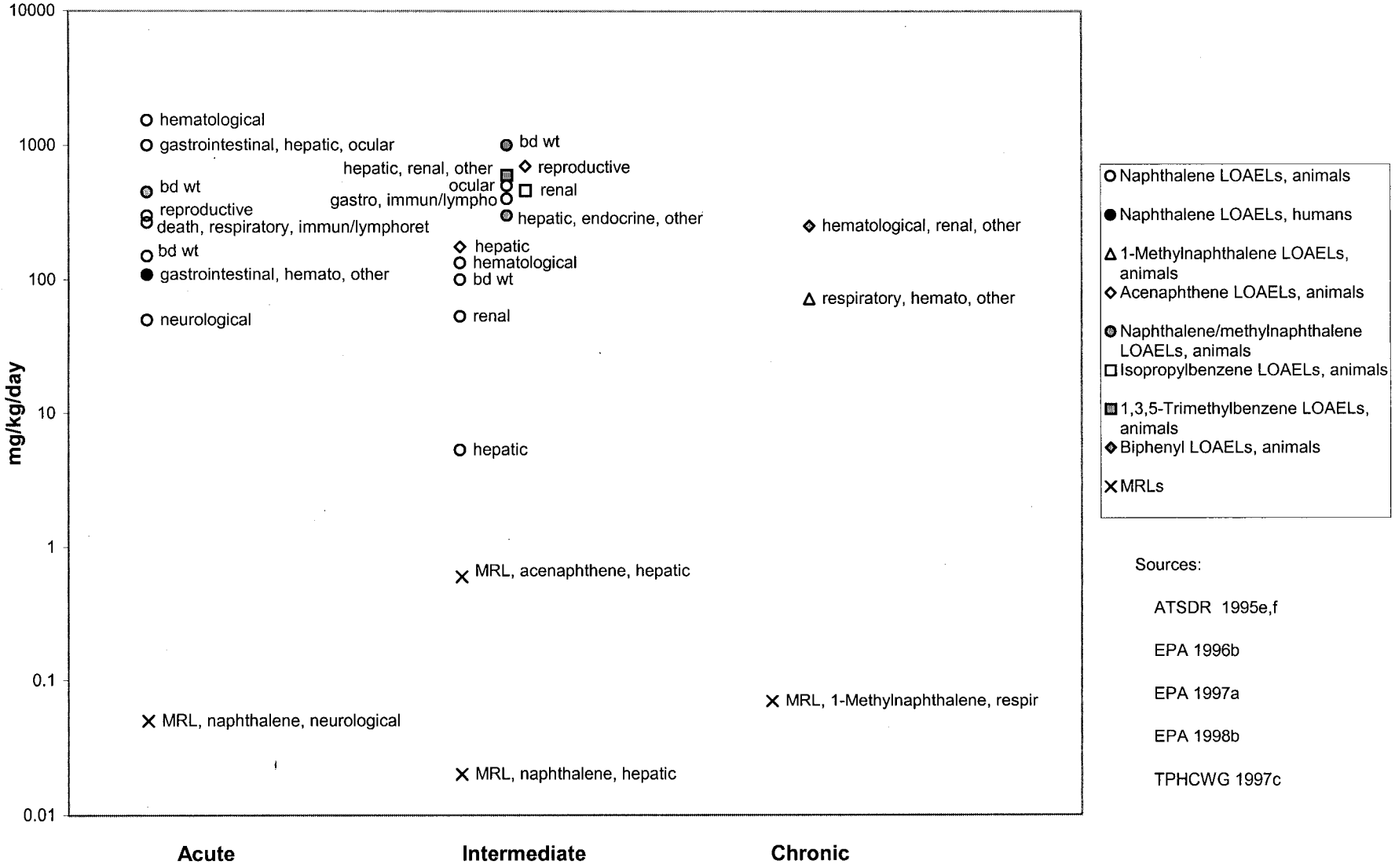
effects (altered microsomal enzyme activities and blood chemistry findings). The EPA classified naphthalene in Group D (not classifiable as to human carcinogenicity) prior to publication of an inhalation study that reported an increased incidence of pulmonary adenomas in female mice, but notes that naphthalene may be more appropriately classified in Group C (possible human carcinogen) (EPA 1998b). No studies documenting carcinogenic effects by the oral route were found (ATSDR 1995e).

Some of the constituents of the $EC_{>12}$-EC_{16} fraction have been evaluated in ATSDR toxicological profiles. Although the database for l-methyl naphthalene is very limited, it includes a chronic study in mice, which serves as the basis for a MRL (ATSDR 1995e). The only effects seen were respiratory (nodular alveolar proteinosis) and hematological (slight increases in hemoglobin parameters and elevated monocyte counts). The limited database for acenaphthene indicates that hepatic effects may be a sensitive consequence of intermediate exposure in mice; the intermediate MRL was based on this finding (ATSDR 1995f). Biphenyl, not included in an ATSDR toxicological profile, has been evaluated by EPA (1998b), which derived an RfD based on renal effects in a chronic study in rats. Hematological effects (reduced hemoglobin), decreased food intake, and decreased longevity also occurred, but renal effects appeared more sensitive. Although the database for this compound is limited, it indicates that reproductive and developmental end points are not as sensitive as renal.

Biphenyl (EPA 1998b) and acenaphthylene (ATSDR 199X) have been classified in Group D (not classifiable as to human carcinogenicity).

The lowest reliable LOAEL values and the available MRLs for the combined aromatic $EC_{>9}$-EC_{16} fraction are summarized in Figure 6-9. Because only a few of the compounds in this fraction have been assessed by ATSDR, additional information from EPA sources and the TPHCWG (1997c) has been added. More detailed information is available in the ATSDR toxicological profiles on the individual compounds and in the other sources noted above.

Figure 6-9. Aromatic $EC_{>9}$-EC_{16} Exposures Associated with Health Effects - Oral



Sources:

ATSDR 1995e,f

EPA 1996b

EPA 1997a

EPA 1998b

TPHCWG 1997c

6.2.2.3 Dermal Exposure

The compounds in the combined $EC_{>9}$-EC_{16} fraction are known to be irritating to the skin, but little information is available to suggest systemic toxicity from dermal exposure alone. Naphthalene, however, has caused hematological effects in human infants exposed to diapers that had been treated with naphthalene moth balls (ATSDR 1995e).

6.2.3 Aromatic $EC_{>16}$- EC_{35} Combined Fractions

This fraction consists entirely of PAHs. The more environmentally and toxicologically significant PAHs are the subjects of the ATSDR toxicological profile on PAHs (ATSDR 1995f); two of these PAHs, acenaphthene and acenaphthylene, are constituents of the $EC_{>12}$-EC_{16} fraction, discussed previously, and the remaining 15 are constituents of the $EC_{>16}$- EC_{35} combined fraction, described below.

$EC_{>16}$- EC_{21} fraction: includes anthracene, fluorene, phenanthrene and pyrene, which are discussed in ATSDR (1995f), and other, less well known PAHs such as substituted fluorenes, anthracenes, and phenanthrenes.

$EC_{>21}$- EC_{35} fraction: includes benz(a)anthracene; benzo(b)-, benzo(j)-, and benzo(k)fluoranthene; benzo(g,h,i)perylene; benzo(a)- and benzo(e)pyrene; chrysene; dibenz(a,h)anthracene; fluoranthene; and indeno(1,2,3-c,d)pyrene, which are discussed in ATSDR (1995f), as well as other, less well known PAHs, that include substituted pyrenes, fluorenes, and fluoranthenes.

6.2.3.1 Inhalation Exposure

Little information regarding the inhalation toxicity of PAHs in the $EC_{>16}$-EC_{35} combined fraction is available, and no inhalation MRLs have been derived. A 4-week study of nose-only inhalation exposure of rats to an aerosol of benzo(a)pyrene identified no treatment-related lesions in the respiratory tract or the kidneys at the single exposure level tested. Respiratory effects, including reduced lung function and abnormal chest X-ray, have been seen in humans exposed occupationally to benzo(a)pyrene and particulate matter. Hamsters exposed by inhalation of benzo(a)pyrene particles developed respiratory tract tumors (nasal, pharyngeal, laryngeal, and tracheal) (ATSDR 1995f).

Assessments of carcinogenicity by EPA have placed some of these compounds in EPA Weight-of-Evidence Group B2 (probable human carcinogen) and others in D (not classifiable as to human carcinogenicity). These classifications were based on evidence from dermal and parenteral studies, and for a few PAHs, oral and inhalation studies, all in animals. See Section 6.2.3.2 and Section 6-6 for specific information regarding EPA cancer assessments. The compounds in this EC range are not volatile (TPHCWG 1997c), so inhalation exposure to any of these PAHs as a result of contamination at hazardous waste sites is expected to be minimal under most circumstances. However, people may be exposed by inhaling dust or particles containing PAHs, or by inhaling PAHs released to the air, as vapors or aerosols, from shower water as a result of contamination of groundwater at hazardous waste sites.

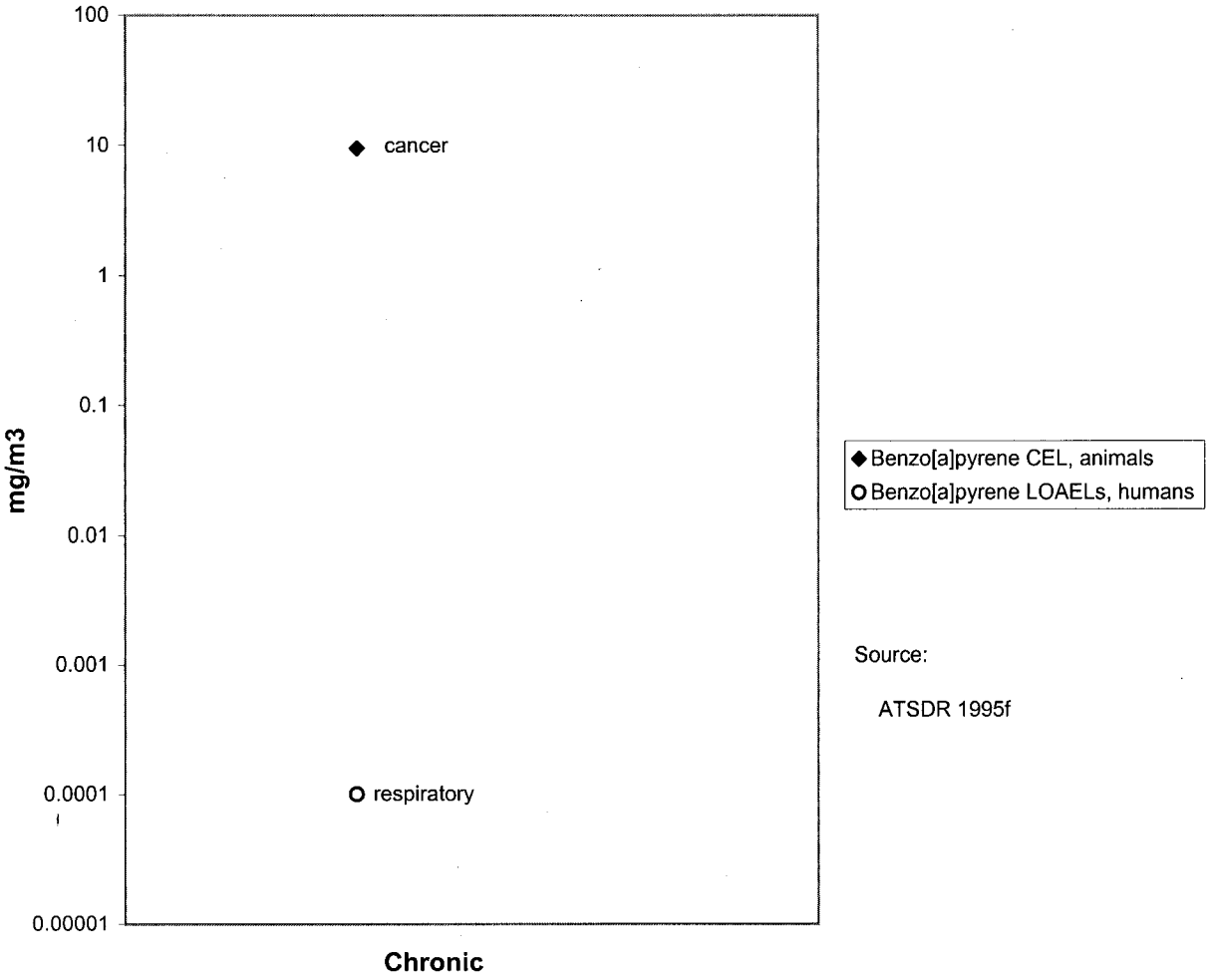
The few available inhalation LOAEL values for the combined aromatic E_{16}-EC_{35} fraction are summarized in Figure 6-10. More detailed information is available in the ATSDR (199%) toxicological profile.

6.2.3.2 Oral Exposure

Data for oral exposure, while more extensive than for inhalation exposure, are nonetheless limited. Hepatic effects appear to be a common sensitive end point of oral exposure to the PAHs in this combined fraction. Renal effects have been seen with some (ATSDR 1995f; EPA 1998b). Aplastic anemia and immunological/lymphoreticular effects have been seen at higher exposure levels.

Intermediate oral MRLs are available for two of the compounds in the $EC_{>16}$–EC_{21} fraction, fluorene and anthracene, based on subchronic studies in mice. The MRL for fluorene was based on hepatic effects (increased liver weight); the MRL for anthracene was based on the absence of any effects, including hepatic, in a similar study (ATSDR 1995f). An EPA-sponsored subchronic oral study of pyrene in mice was used by that agency as the basis for developing subchronic and chronic RfDs (EPA 1997a, 1998b). The critical effect was renal (nephropathy). Hepatic effects were not seen in this study, which is the only subchronic or chronic oral toxicity study of pyrene encountered. All four of the PAHs in this fraction that have been assessed for carcinogenicity by EPA have been classified in EPA Weight-of-Evidence Group D (not classifiable as to human carcinogenicity) (ATSDR 199%).

Figure 6-10. Aromatic $EC_{>16}$-EC_{35} Exposures Associated with Heath Effects - Inhalation



Source:

ATSDR 1995f

The only oral MRL available for compounds in the $EC_{>21}$- EC_{35} fraction is an intermediate MRL for fluoranthene, based on hepatic effects in mice. The sensitive noncancer effect of oral exposure to benzo(a)pyrene is developmental, also determined in animals.

Studies of the compounds in this fraction have focused primarily on potential carcinogenicity. Of the nine compounds in this EC range that have been assessed for carcinogenicity by EPA, seven have been classified in Group B2 (probable human carcinogen), and the remaining two, fluoranthene and benzo(g,h,i)perylene, in group D (ATSDR 1995f; EPA 1997a, 1998b). The evidence has come in large part from parenteral and dermal studies. Oral studies of carcinogenicity have been conducted for six of the PAHs in this EC fraction, with positive results for benzo(a)pyrene, benz(a)anthracene, and dibenz(a,h)anthracene, and with negative results for anthracene, fluoranthene, and fluorene (ATSDR 1995f).

The lowest reliable LOAEL values and the available MRLs for the combined aromatic $EC_{>16}$-EC_{35} combined fraction are summarized in Figure 6- 11, as are cancer risk levels. Information on pyrene is discussed above in this section. Additional information from EPA sources has been added for pyrene. More detailed information on the constituents of this fraction is available in the ATSDR (1995f) toxicological profile.

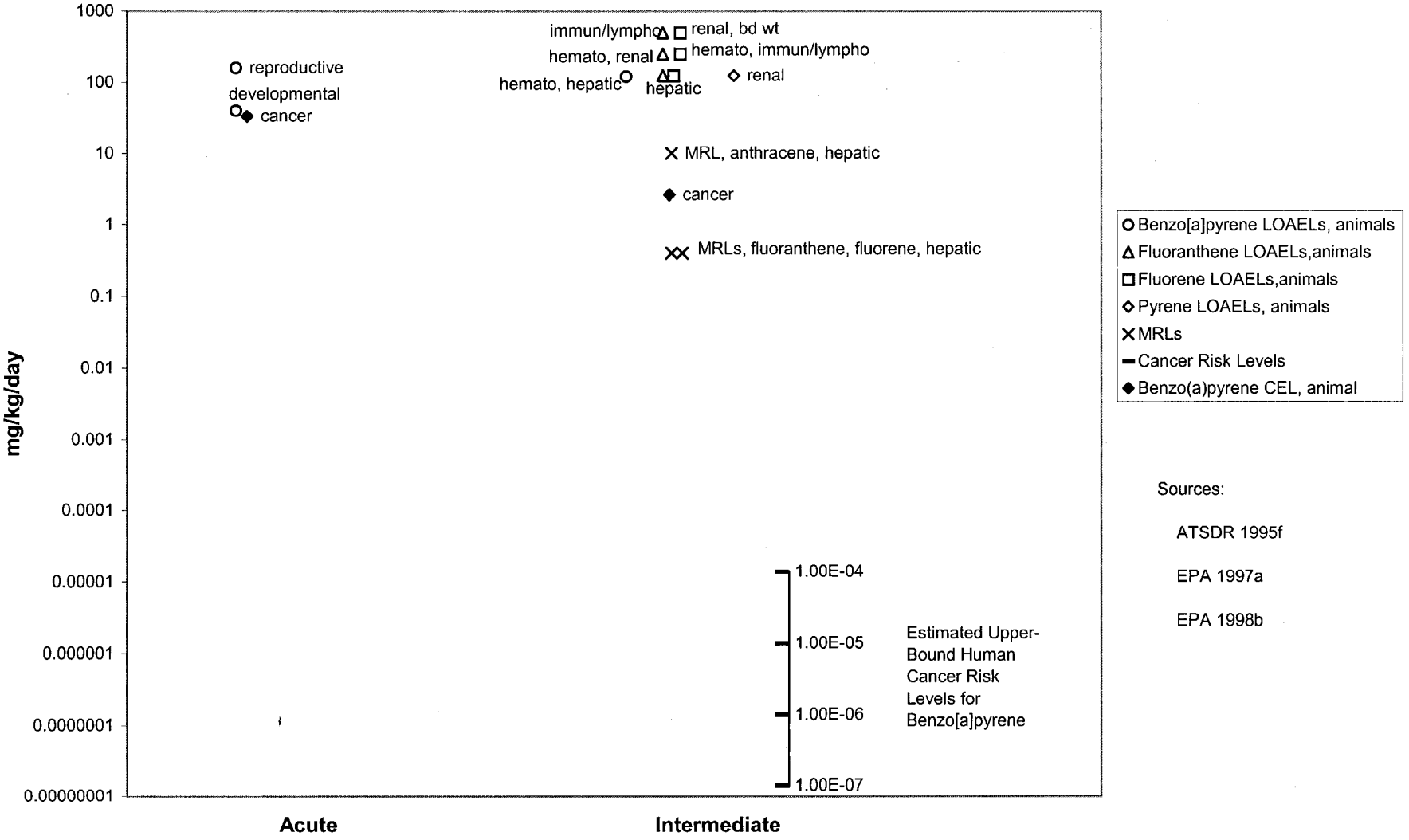
6.2.3.3 Dermal Exposure

The PAHs tend to be irritating to the skin. In addition, benzo(a)pyrene has been shown to cause immunological/lymphoreticular effects evidence as contact hypersensitivity or suppression of this response to other sensitizers. The PAHs classified as B2 carcinogens induce skin tumors following intermediate dermal application to animals (ATSDR 1995f).

6.2.4 Aliphatic EC_5-EC_8 Combined Fractions

EC_5-EC_6 Fraction: includes *n*-pentane, *n*-hexane, the dimethylbutanes and methylpentanes, cyclopentane, and some alkenes. *n*-Hexane is the only compound in this group that is the subject of an ATSDR toxicological profile; some information on commercial hexane (*n*-hexane plus branched and cyclic C_6 alkanes) is included in the same toxicological profile (ATSDR 1999b).

Figure 6-11. Aromatic $EC_{>16}$-EC_{35} Exposures Associated with Health Effects - Oral



Sources:

ATSDR 1995f

EPA 1997a

EPA 1998b

$EC_{>6}$-EC_8 Fraction: includes *n*-heptane, *n*-octane, some branched chain C_6-C_9 alkanes including the trimethylpentanes (note that other branched chain C_9 alkanes fall in the $EC_{>8}$ category) and cycloalkanes, including cyclohexane, methylcyclopentane, and methylcyclohexane, as well as some alkenes. None of these is the subject of an ATSDR toxicological profile.

6.2.4.1 Inhalation Exposure

Inhalation exposure for acute, intermediate or chronic durations to *n*-hexane causes peripheral neuropathy in humans and animals (ATSDR 1999b). The chronic MRL for *n*-hexane is based on this effect in humans. Respiratory and renal effects have been seen in animals exposed to *n*-hexane by inhalation at higher exposure levels than associated with peripheral neuropathy in the same studies. Calculation of human equivalent concentrations (HECs) using EPA dosimetric methodology, however, indicates that respiratory effects were seen in mice exposed subchronically to *n*-hexane at a HEC similar to that for neurological effects in the human study used as the basis for the chronic MRL (EPA 1998b). Thus, respiratory effects also may be sensitive, although confirmation of this in human studies is not available. The other compounds in the EC_5-EC_6 fraction do not appear to cause peripheral neuropathy (ATSDR 1999b; TPHCWG 1997c). Depression of the central nervous system has been seen at relatively high levels of exposure to *n*-hexane. *n*-Hexane has been classified as in weight-of-evidence Group D (not classifiable as to human carcinogenicity) (EPA 1989a).

Commercial hexane, which consists of a mixture of C_6 aliphatic compounds including 20-80% *n*-hexane and other straight, branched, and cyclic alkanes in the range of $EC_{5.68}$-$EC_{6.59}$,has been the subject of extensive recent testing as part of a EPA Test Rule under TSCA Section 4. Commercial hexane mixtures have the potential to represent the toxicity of the EC_5-EC_8 combined fraction better than any single compound. The non *n*-hexane components of commercial hexane, when tested separately as a mixture, do not cause peripheral neuropathy, whereas the commercial mixture containing *n*-hexane has been demonstrated to cause peripheral neuropathy in one study in rats (ATSDR 1999b; IRDC 1981). The commercial hexane mixtures tested under the Test Rule contained 53% *n*-hexane, 16% 3-methylpentane, 14% methylcyclopentane, 12% 2-methylpentane, 3% cyclohexane, 1% 2,3-dimethylbutane, and <1% other constituents. According to the TPHCWG (1997c), which developed an RfC for commercial hexane based on preliminary reports of these unpublished studies, the critical effects were respiratory (mucosal irritation in nasal turbinates and

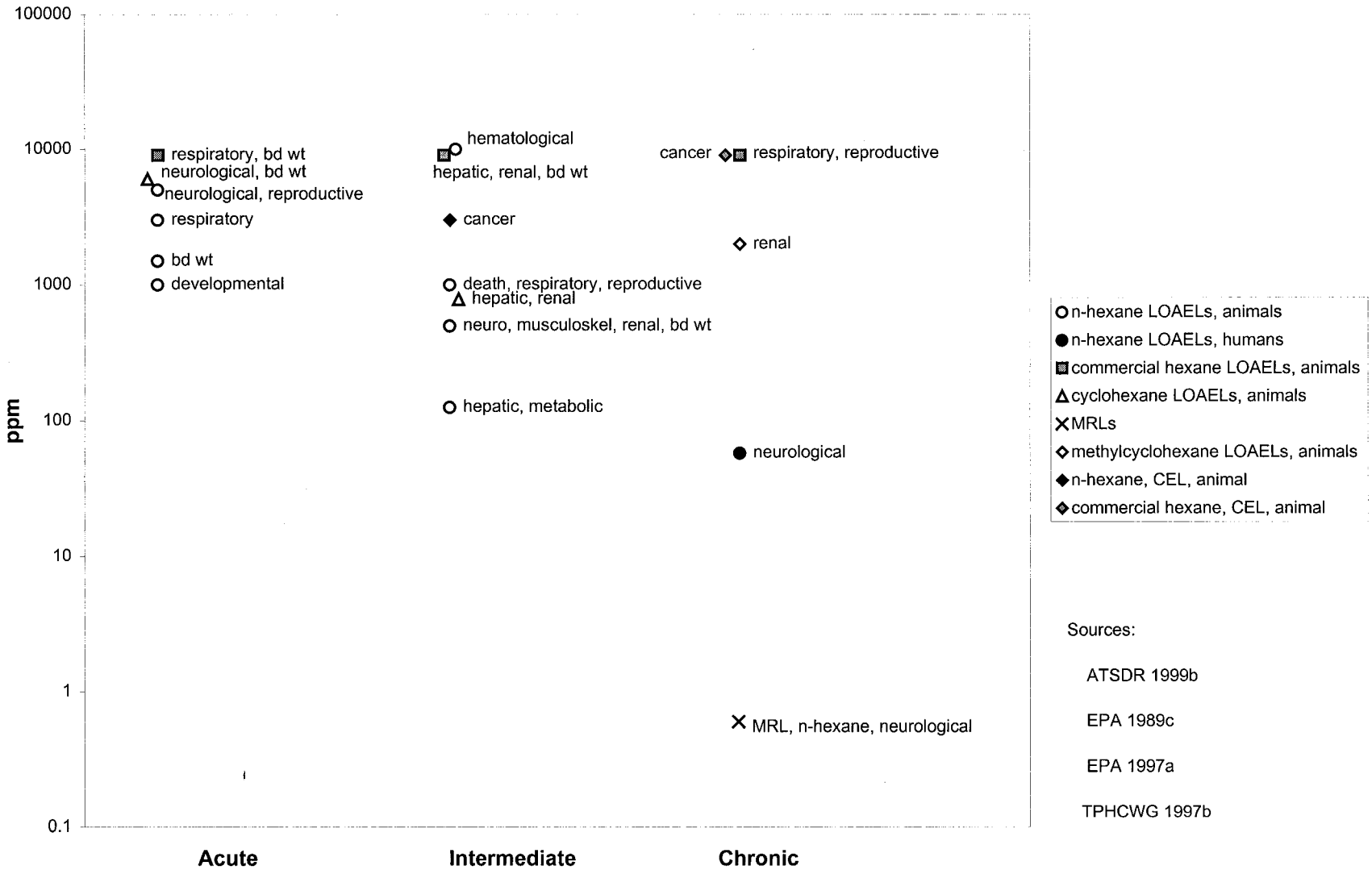
larynx in rats) and reproductive (decreased severity and incidence of cystic uterine endometrial hyperplasia in mice) in chronic studies. In addition, liver tumors developed in the female mice, indicating carcinogenic potential.

Cyclohexane also has undergone testing under EPA TSCA Section 4. The TPHCWG (1997c) summarized the preliminary report of the developmental toxicity study in rats, which indicates neurological effects (reduced response to a sound stimulus) in the dams exposed to cyclohexane by inhalation. Hepatic and renal effects were seen in published subchronic studies in animals. No histopathological changes in the peripheral nervous system were seen in a chronic study in animals (TPHCWG 1997c).

Two additional chemicals in the $E_{>6}$-EC_8 fraction that have been the subject of limited toxicity testing are *n*-heptane and methylcyclohexane. Both appear to cause depression of the central nervous system following relatively high inhalation exposures (EPA 1989b, 1989c). *n*-Heptane was suspected to have the potential to cause peripheral neuropathy because of its structural similarity to *n*-hexane and because it is metabolized, although to a much lesser extent, to the same type of metabolite (a γ-diketone) as is thought to mediate the neurotoxicity of *n*-hexane. The available human occupational and animal experimental studies, however, give no clear evidence that *n*-heptane causes peripheral neuropathy (EPA 1989b). Methylcyclohexane caused renal effects (medullary mineralization and papillary hyperplasia) in male but not in female rats or in other species exposed for 1 year by inhalation followed by an observation period; this study is the basis for an RfC derived by EPA (1997a). The renal effect appears to be associated with $\alpha_{2\mu}$-globulin nephropathy and, therefore, may be of questionable significance to human health. Both these compounds have been classified in Group D (not classified as to human carcinogenicity) (EPA 1989c, 1998b).

The lowest reliable LOAEL values for *n*-hexane are summarized in Figure 6-12, along with the available MRL. Because so few of the compounds in this fraction have been assessed by ATSDR, limited additional information from EPA sources and the TPHCWG (1997c) regarding commercial hexane, cyclohexane, and methylcyclohexane has been added. More detailed information is available in ATSDR (1997c) and the EPA and TPHCWG sources noted above.

Figure 6-12. Aliphatic EC_5-EC_8 Exposures Associated with Health Effects - Inhalation



Sources:

ATSDR 1999b

EPA 1989c

EPA 1997a

TPHCWG 1997b

6.2.4.2 Oral Exposure

Oral health effects information for the EC_5-EC_6 fraction is limited and is available mainly for *n*-hexane. *n*-Hexane caused peripheral neuropathy in rats given the compound subchronically and in chickens given the compound acutely and subchronically. The chicken is considered to be a valuable model for human neurotoxicity of this type. 2-Methylpentane and methylcyclopentane affected nerve conduction velocity in a subchronic study in rats, but were not as effective as *n*-hexane in that same study. Reproductive (testicular) and developmental effects have been seen in animals at higher doses of *n*-hexane than associated with neurological effects. No oral MRLs were derived for *n*-hexane because of the incompleteness of the database (ATSDR 1999b). *n*-Hexane has been classified as a Group D agent (not classifiable as to human carcinogenicity) (EPA 1989a).

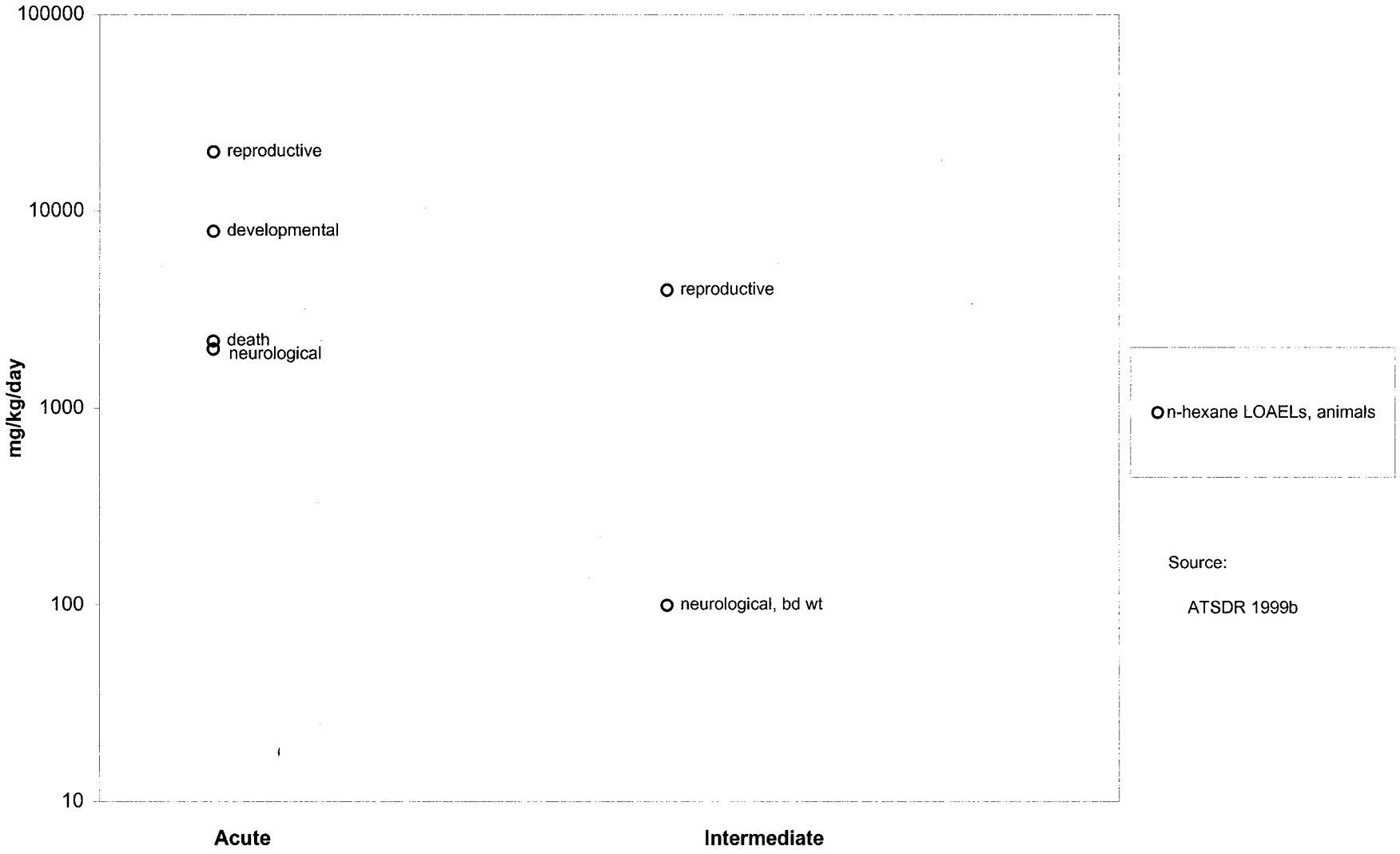
An oral 90-120-day study in rats of a commercial hexane containing 40% *n*-hexane, 24% each of 3-methylpentane and dimethylbutane, 9% cyclopentane, 2.5% cyclohexane, and 12% 2-methylpentane was conducted in comparison with *n*-hexane. This mixture includes compounds in both the EC_5-EC_6 and $EC_{>5}$-EC_8 range. Peripheral neuropathy was not seen when commercial hexane was tested at the same dose as was effective for pure *n*-hexane (ATSDR 1999b), but the dose of *n*-hexane resulting from this dose of commercial mixture was only 40% the effective dose of the pure *n*-hexane. Some evidence of carcinogenic potential has been reported in chronic inhalation studies in mice, as discussed in the previous section.

The lowest reliable LOAELs for *n*-hexane are plotted in Figure 6- 13. More detailed information, including some information on oral toxicity of related isomers and commercial hexane, is available in ATSDR (1997c).

6.2.4.3 Dermal Exposure

Some of the compounds in the combined $EC_{>9}$-EC_{16} fraction are known to be irritating to the skin and eyes, but little information is available to suggest systemic toxicity from dermal exposure.

Figure 6-13. Aliphatic EC_5-EC_8 Exposures Associated with Health Effects - Oral



6.2.5 Aliphatic $EC_{>8}$- EC_{16} Combined Fractions

$EC_{>8}$-EC_{10} fraction: includes *n*-nonane, *n*-decane, branched-chain C_9 -C_{10}, compounds, a few substituted cycloalkanes, and a few alkenes

$EC_{>10}$- EC_{12} fraction: includes *n*-undecane, *n*-dodecane, and pentylcyclopentane

$EC_{>12}$- EC_{16}fraction: *n*-tri-, tetra-, penta-, and hexadecane (Note that EC values for a number of branched and cyclic alkanes that potentially belong in these fractions were not listed by the TPHCWG [1997c1; see Appendix D: Table D-l for listing).

None of the individual compounds in the combined aliphatic $EC_{>8}$-EC_{16} fraction is the subject of an ATSDR toxicological profile. Some petroleum products, however, are mixtures primarily of aliphatic hydrocarbons in the range covered by this fraction. The TPHCWG (1997c) identifies JP-8 jet fuel as a mixture containing aliphatic petroleum hydrocarbons ranging from C_9-C_{16} and ATSDR has developed a toxicological profile on JP-8 (ATSDR 1998b). JP-8 contains up to 20% aromatics (C_{10}-C_{11}, $EC_{10.5}$-$EC_{12.99}$) (ATSDR 1998b; TPHCWG 1997b). Other petroleum products that are composed primarily of C_9 -C_{16}, aliphatics are JP-5, JP-7, and kerosene (fuel oil #l). These fuels also are the subjects of ATSDR toxicological profiles, and have at least one MRL (ATSDR 1995c, 1995g, 1998b). They contain approximately 16%, a maximum of 5%, and approximately 24% aromatic hydrocarbons, respectively. The jet fuels contain a number of additives such as antioxidants, metal deactivators, fuel system icing inhibitors, corrosion inhibitors, and static dissipaters. Stoddard solvent contains primarily C_9-C_{16}, aliphatics, with approximately 14% aromatics, and is also the subject of an ATSDR toxicological profile, but has no MRLs (ATSDR 1995b).

TPHCWG (1997c) also identifies a number of published and unpublished studies on dearomatized petroleum streams that correspond to portions of this range, and that contain at most 1.5% aromatics and more typically less than 0.1% aromatics. These studies on dearomatized petroleumstreams would appear to be a better basis for the assessment of health effects of this fraction, because they contain much smaller amounts of aromatics than do the petroleum products discussed in the previous paragraph and no additives. Their exact compositions and EC ranges were not reported, but EC numbers for the aliphatics tend to be close to the actual carbon numbers.

6.2.5.1 Inhalation Exposure

Hepatic effects are the most sensitive end points for inhalation exposure to JP-5, JP-7, JP-8, and kerosene (ATSDR 1995c, 199.58, 1998b). The available intermediate and chronic MRLs for these fuels are based on hepatic effects in animals. Neurological effects, particularly central nervous depression, have been seen in humans exposed acutely to JP-5 vapors, but exposure-effect relationships have not been established. Male rat $\alpha_{2\mu}$-globulin nephropathy occurred with exposure to JP-5 and JP-7, but this effect is not considered relevant to humans. A l-year exposure to JP-7 produced a small increase in the incidence of C-cell adenomas and kidney adenomas in male rats exposed to the vapor; the kidney adenomas may have been related to male rat $\alpha_{2\mu}$-globulin nephropathy, an effect with questionable relevance to human health.

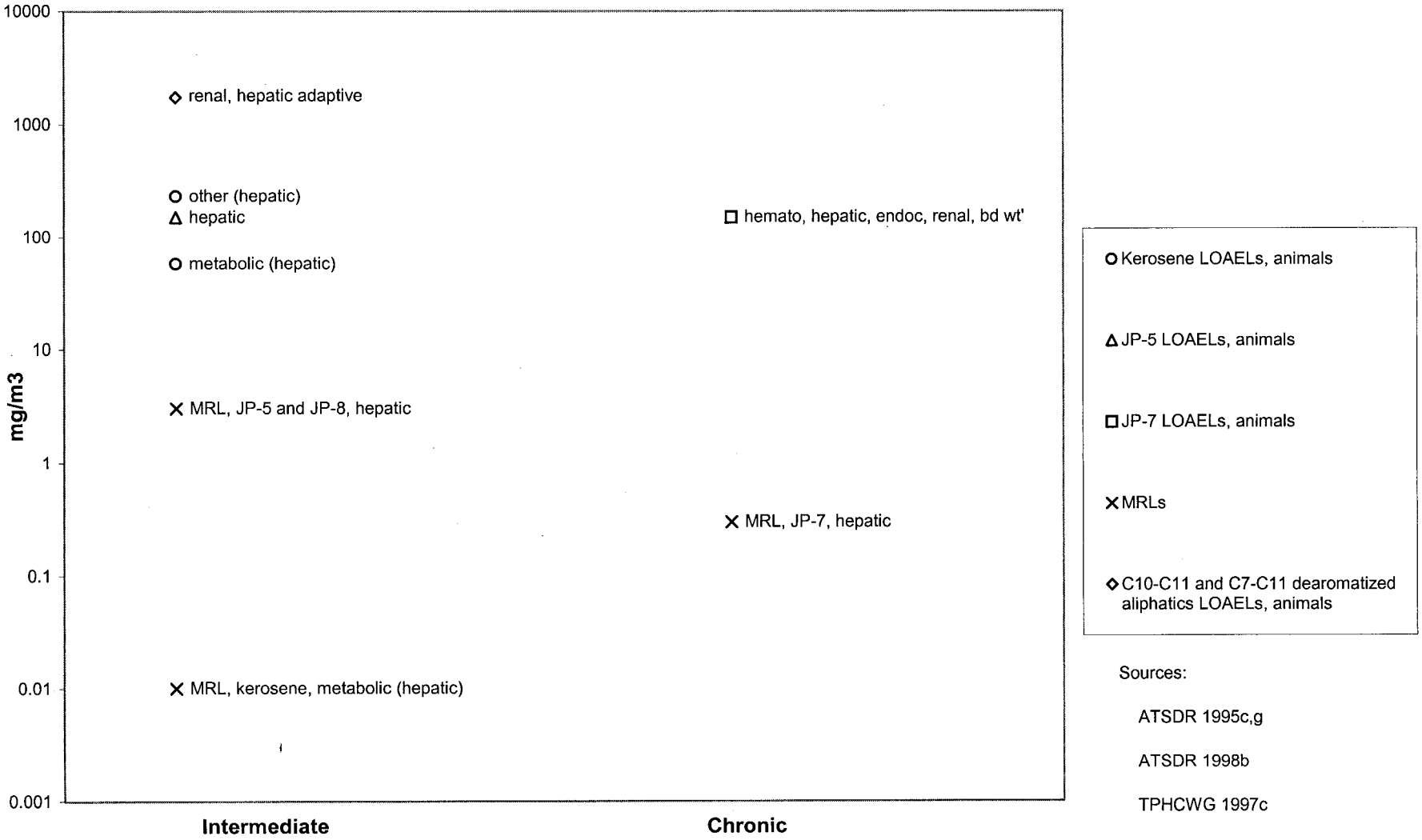
The inhalation studies of dearomatized petroleum streams included a C_{10}-C_{11} isoparaffinic solvent (branched chain alkanes), and C_7-C_{11} dearomatized white spirit (branched, straight and cyclic alkanes). Subchronic toxicity studies of these streams reported male rat nephropathy of the type that is of questionable relevance to humans health, according to the TPHCWG (1997c). In addition, increased liver weights were observed in male rats, but were said to be not significant. Developmental toxicity studies of these streams in rats revealed no developmental or maternal toxicity at the same exposure levels. These unpublished studies have been used as the basis for RfCs by the TPHCWG (1997c).

The lowest reliable LOAEL values for the jet fuels and kerosene discussed in this section are summarized in Figure 6-14, along with the available MRLs. Because these products have a significant aromatic component, limited additional information from the TPHCWG (1997c) regarding dearomatized petroleum streams has been added. More detailed information is available in the ATSDR toxicological profiles and the TPHCWG source noted above.

6.2.5.2 Oral Exposure

Oral data regarding JP-5, JP-7, JP-8, and kerosene were limited and judged inadequate for MRL development (ATSDR 19958, 1995c, 1998b). Hepatic effects and neurological effects have been seen from acute-duration oral exposure, but dose-effect relationships are either not well defined, or effects occurred at doses that also were fatal. Male rat nephropathy and decreased body weight were seen in

Figure 6-14. Aliphatic $EC_{>8}$-EC_{16} Exposures Associated with Health Effects - Inhalation



Sources:

ATSDR 1995c,g

ATSDR 1998b

TPHCWG 1997c

a 90-day oral study of JP-8 in male rats (Mattie et al. 1995) that was used by the TPHCWG (1997c) as the basis for an RfD, but ATSDR declined to derive an intermediate oral MRL because of the general lack of data and limitations of this study.

Subchronic studies of the dearomatized petroleum streams in rats were conducted on C_9-C_{12}, and C_{10}-C_{13} dearomatized aliphatic mixtures containing branched, straight, and cyclic alkanes, and a C_{11}-C_{17} isoparaffinic solvent containing branched and cyclic alkanes. Two of these studies reported male rat nephropathy. All three studies reported hepatic effects including hepatocellular hypertrophy and increased liver weight. Developmental toxicity was not seen at the same doses in a study of a similar mixture in rats. These unpublished subchronic studies were used as the basis for RfDs by the TPHCWG (1997c).

The lowest reliable LOAEL values for the jet fuels and kerosene discussed in this section are summarized in Figure 6-15. Because these products have a significant aromatic component, limited additional information from the TPHCWG (1997c) regarding dearomatized petroleum streams has been added. More detailed information is available in the ATSDR toxicological profiles, the TPHCWG source noted above, and Section 6.3.

6.2.5.3 Dermal Exposure

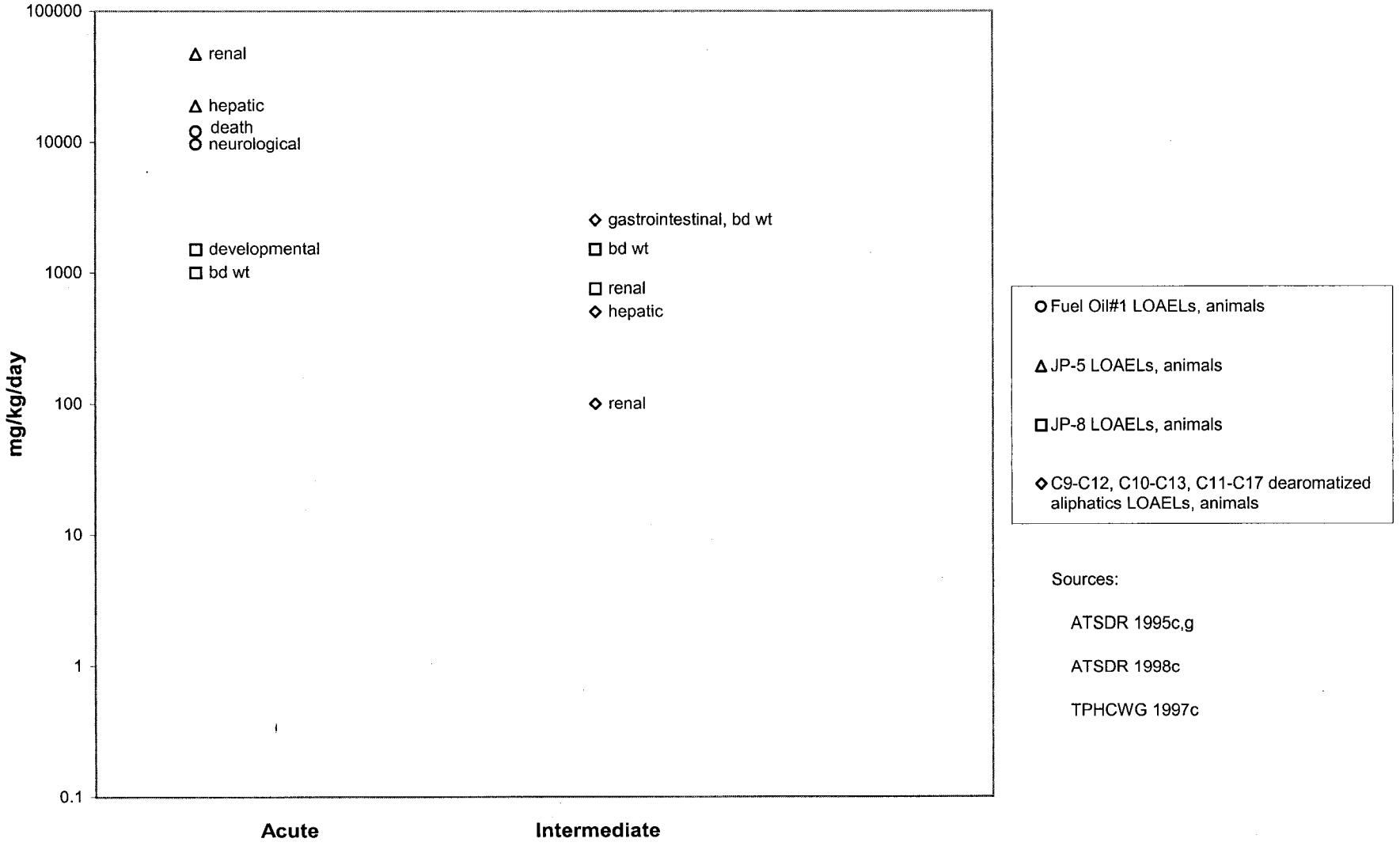
Information on the health effects of dermal exposure to JP-5, JP-7, and JP-8, and kerosene is limited. Skin and eye irritation are well documented, but effects from systemic absorption are not (ATSDR 1995c**,** 19958, 1998b).

6.2.6 Aliphatic $EC_{>16}$-EC_{35} Combined Fractions

$EC_{>16}$-EC_{21} fraction: includes *n*-hepta-, *n*-octa-, and *n*-nonadecane; and *n*-eicosadecane

$EC_{>21}$-EC_{35} fraction: includes *n*-heneicosane, *n*-docosane, *n*-tetracosane, and *n*-hexacosane. (Note that aliphatic compounds other than the above straight-chain alkanes were not listed by the TPHCWG [1997b] as constituents of petroleum and petroleum-based fuels that are the focus of the fraction-selection approach. See Appendix D, Table D-l.) Petroleum products such as mineral-based crankcase oil and mineral-based hydraulic fluids, however, contain branched and cyclic

Figure 6-15. Aliphatic $EC_{>8}$-EC_{16} Exposures Associated with Health Effects - Oral



Sources:

ATSDR 1995c,g

ATSDR 1998c

TPHCWG 1997c

aliphatics within these equivalent carbon ranges, as do food-grade and medicinal-grade mineral oils. Although ATSDR toxicological profiles are available for mineral-based used crankcase oil and mineral-based hydraulic fluids (ATSDR 1997b, 1997c), these products contain additives and contaminants, including substantial levels of aromatics and metals (used crankcase oil) and organophosphate esters (hydraulic fluids). Little information is available regarding health effects of these products. No MRLs have been derived. The TPHCWG (1997c) has reviewed data regarding food and medicinal grade mineral oils, which are relatively pure and therefore a better choice to represent this fraction.

6.2.6.1 Inhalation Exposure

No information was located on the potential health effects of inhalation exposure to compounds or mixtures of petroleum hydrocarbons that fall within this fraction.

6.2.6.2 Oral Exposure

Purified mineral oils have been used medicinally and in foods. Subchronic toxicity studies of selected mixtures of mineral oil hydrocarbons (composed primarily of branched chain alkanes or cyclic alkanes) in F344 rats have identified the liver and the mesenteric lymph nodes as potential targets of toxicity for these mineral oils. The TPHCWG (1997c) derived chronic RfDs for low and high molecular weight mineral oils based on the hepatic effects (lipid granulomas) seen in these studies. The effect on the mesenteric lymph nodes (histiocytosis), which occurred at lower exposure levels than did the hepatic effects, was judged a nonadverse, adaptive response to the ingestion of foreign material (TPHCWG 1997c). Subchronic oral toxicity testing has also been conducted with low- and intermediate-molecular weight paraffin waxes, which contain a high proportion of straight chain alkanes and also branched alkanes and small amounts of cyclic alkanes, with C ranges primarily within this fraction range (Smith et al. 1996). Results indicate that these mixtures have toxicity similar to that of the oils for which the RfDs were derived. Strains of rats other than F344 appeared to be less sensitive to these mixtures.

Hepatic lipid granulomas have also been seen in humans exposed to mineral oils through the diet and by ingestion of medicinal mineral oils, but doses associated with the effect in humans are not known. According to TPHCWG (1997c), the granulomas in humans were circumscribed lesions with no

inflammation, fibrosis, or significant liver dysfunction, whereas the granulomas in F344 rats were reactive with associated inflammation and occasional parenchymal cell necrosis.

The LOAELs identified for the “low” molecular weight mineral oils (C_{16}-C_{35}) are plotted in Figure 6-16. Additional information on health effects is provided in the review by TPHCWG (1997c).

6.2.6.3 Dermal Exposure

Information regarding health effects of dermal exposure to this fraction was not encountered in the cited source (TPHCWG 1997c).

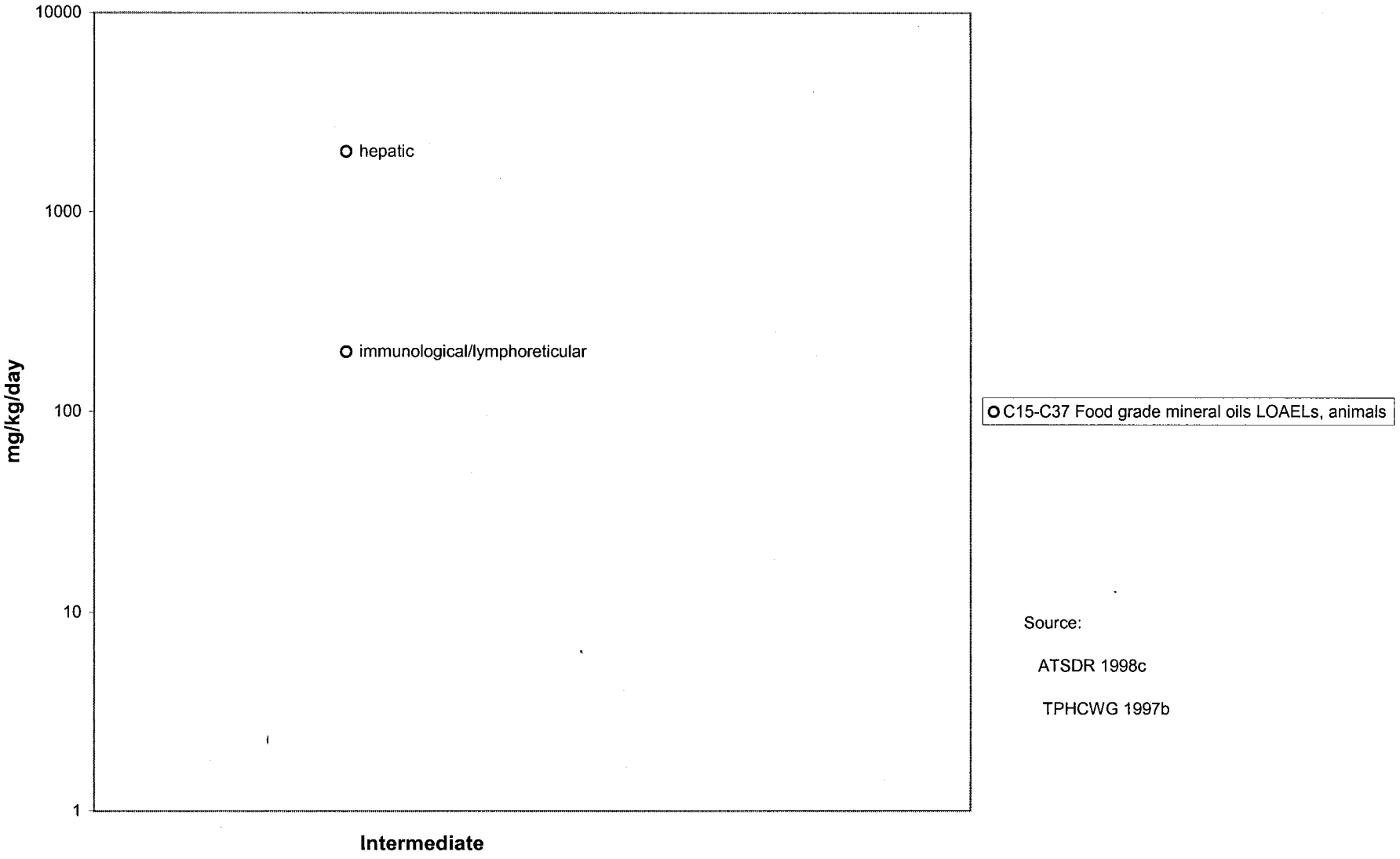
6.3 DISCUSSION OF HEALTH EFFECTS FOR WHOLE PETROLEUM PRODUCTS

Whole petroleum products are generally complex mixtures of hydrocarbons of varying carbon number and additives (usually representing a smaller weight percentage of the whole mixture) of varying chemical identities that are added to impart special qualities or enhance particular functional properties of the whole petroleum product. Additional impurities may be generated during use of the product. Non-hydrocarbon additives and impurities are not included in the definition of TPH. Toxicological information on important petroleum products that are the subjects of other ATSDR toxicological profiles, and on other petroleum products that are the subject of assessment by other agencies, is briefly reviewed in this section. Such information may be useful in characterizing acute exposure to fresh spills of petroleum products, but its usefulness is limited because of the limited availability of MRLs, the variability in the composition of petroleum products, and the change in composition due to environmental fate and transport processes. The whole petroleum products that have compositions similar to the transport fractions have been discussed in Section 6.2.

6.3.1 Jet Fuels

Jet fuels are middle distillates of petroleum crude oils that are composed of hydrocarbons generally coming off distillation columns at temperatures between 150 and 300 ºC (ATSDR 1998b; IARC

Figure 6-16. Aliphatic $EC_{>16}$-EC_{35} Exposure Levels Associated with Health Effects - Oral



1989c). Kerosene-type jet fuels such as JP-5, JP-7, and JP-8 have the same basic composition as kerosene (consisting predominately of hydrocarbons with carbon numbers in the range of C_9-C_{16}), whereas "wide-cut" jet fuels such as JP-4 are blends of kerosene and lower-boiling naphtha streams (C_4-C_{16}). Jet fuels are refined under more stringent conditions than kerosene and contain various additives (anti-oxidants, dispersants and/or corrosion inhibitors) not found in kerosene. The exact chemical composition varies depending on the source of crude oil and additives included in the formulated product. Generally, aliphatic hydrocarbons represent the major part and aromatic hydrocarbons represent about 10-20% of kerosene and jet fuels. The benzene content of kerosenetype jet fuels is generally <0.02%, whereas "wide-cut" jet fuels typically contain more benzene (normally <0.5%). PAHs, with boiling points above 300 ºC, are generally excluded from jet fuels and kerosene.

Health effects of concern from exposure to jet fuels include eye and skin irritation from acute direct contact; respiratory, neurotoxic and gastrointestinal effects from acute accidental ingestion; and possible hepatic damage from inhalation exposure of intermediate duration as indicated by results from animal studies (ATSDR 1998b).

ATSDR (1998b) derived an intermediate-duration inhalation MRL of 3 mg/m^3 for jet fuels JP-5 and JP-8, based on a LOAEL for hepatocellular fatty changes and vacuolization in mice exposed continuously for 90 days to vapors of JP-5 at a concentration of 150 mg/m^3 (Gaworski et al. 1984). The exposure concentration was converted to a human equivalent exposure concentration (853 mg/m^3) by multiplying by the ratio of the alveolar ventilation rate divided by the body weight of mice to the same parameters for humans. The human equivalent concentration was divided by an uncertainty factor of 300 (10 for interspecies variability, 3 for intraspecies variability, and 10 for the use of a LOAEL) to derive the MRL.

ATSDR (1998b) derived no other MRLs for JP-5 or JP-8 (e.g., for acute or chronic inhalation exposures, or for oral exposures of any duration), due to the lack of data suitable for MRL derivation.

ATSDR (1995c) derived an intermediate-duration inhalation MRL of 9 mg/m^3 for JP-4 based on a LOAEL of 500 mg/m^3 for hepatic fatty degeneration in mice exposed continuously to the vapor for

90 days. The MRL was derived from this LOAEL by dosimetrically adjusting to a human equivalent concentration and applying an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for interspecies extrapolation, and 10 for human variability). ATSDR (199%) derived a chronic-duration inhalation MRL of 0.3 mg/m^3 for JP-7, based on a LOAEL of 150 mg/m^3 for hepatic inflammation in rats exposed to the vapor (6 hours/day, 5 days/week) for 1 year and observed for an additional year. The MRL was calculated from this LOAEL by dosimetrically adjusting to a human equivalent continuous exposure concentration and applying an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for interspecies extrapolation, and 10 for human variability).

ATSDR (199%) derived no other MRLs for jet fuels JP-4 and JP-7, due to the lack of additional suitable inhalation data and the absence of data for oral exposure to these jet fuels.

ATSDR (1995c) found no studies regarding cancer in humans exposed to the jet fuels JP-4 and JP-7. Inhalation animal studies provided no evidence that JP-7 was carcinogenic (Air Force 1991). A l-year study of rats and mice exposed by inhalation to vapors of JP-4 was identified in which increased tumors were found in the respiratory tract of female rats and mice, increased renal tumors (associated with the $\alpha_{2\mu}$-globulin nephropathy syndrome) were found only in male rats, and increased liver tumors were found in female, but not male mice (Bruner et al. 1993). ATSDR (1995c) concluded that the animal data provided equivocal evidence for the carcinogenicity of JP-4 and that there was insufficient evidence to draw conclusions regarding the carcinogenic potential of JP-4 or JP-7 in humans.

ATSDR (1998b) concluded from a review of several studies of mice dermally exposed to jet fuels (including JP-5 and Jet A) that chronic dermal application of jet fuels can act as a skin carcinogen, but noted that further investigation is needed to more fully elucidate “the impact of dermal exposure of jet fuels on humans.”

IARC (1989d) concluded that there was inadequate evidence for the carcinogenicity of jet fuel in humans and animals, but noted that there is limited evidence for the carcinogenicity in experimental animals of straight-run kerosene and hydrotreated kerosene. IARC’s review included: a cohort mortality study that found no increased cancer risk in men exposed to jet fuel, aviation kerosene, and other fuels in the Swedish Air Force; elevated risk for kidney cancer in men exposed to jet fuel in a

Canadian case-control study; and both positive and negative findings for skin cancer in studies of mice dermally exposed to jet fuels.

6.3.2 Fuel Oils

Fuel oils refined from crude petroleum can be classified either as *distillate fuels* consisting predominately of distilled process streams or as *residual fuels* consisting of residues remaining after distillation or blends of residues and distillates (ATSDR 19958; IARC 1989b). Both types of fuel oils are complex mixtures of aliphatic hydrocarbons (representing approximately 80-90% of these oils) and aromatic hydrocarbons (representing 10-20%). Light distillate fuels (e.g., fuel oil #l, straight-run kerosene) consist primarily of hydrocarbons in the C_9-C_{16}, whereas hydrocarbons in middle distillate fuels (e.g., fuel oil #2) may range from approximately C_{11}-C_{20}. Diesel fuels are similar to fuel oils with the exception that the diesel fuels contain additives. Light and middle distillate fuels generally contain less than 5% polycyclic aromatic hydrocarbons. Heavier fuel oils (e.g., fuel oil #4 and marine diesel fuel) may contain up to 15% distillation residues and more than 5% polycyclic aromatic hydrocarbons. Residual fuel oils are more complex in composition than distillate fuels, and can contain significant portions of compounds with sulfur and nitrogen.

Reports of cases of accidental ingestion of kerosene identify respiratory effects (e.g., pulmonary edema and difficulty in breathing from aspiring the liquid into the lungs), nervous system depression, and gastrointestinal irritation as effects of concern from acute exposure to fuel oils (ATSDR 1995g). These effects (and others including skin and eye irritation, and increased blood pressure) have been observed in humans in a few cases after inhalation and/or dermal acute exposures. Animal studies provide supporting data for neurological impairment from acute inhalation exposure to fuel oil #2 and hepatic effects (including decreased blood glucose levels and hepatocellular fatty changes and vacuolization) from intermediate-duration exposure to fuel oil #l and jet fuel JP-5.

ATSDR (19958) derived an acute-duration inhalation MRL of 0.02 mg/m^3 for diesel fuel (fuel oil #2) based on observations of mild transient ataxia and disturbed gait in mice exposed for 8 hours/day for 5 days to vapors of diesel fuel #2 at concentrations as low as 65 mg/m^3 (Kainz and White 1984). The LOAEL was adjusted to a continuous exposure basis and divided by an uncertainty factor of 1,000 (10 for intraspecies variability, 10 for interspecies variability, and 10 for the use of a LOAEL). ATSDR (1995g) did not discuss the potential applicability of this MRL to other fuel oils.

ATSDR (19958) derived an intermediate-duration MRL of 0.01 mg/m^3 for kerosene (also called fuel oil #l) based on a LOAEL for decreased blood glucose levels (thought to be indicative of hepatic effects) in rats exposed 6 hours/day, 6 days/week for 14 weeks to fuel oil #l at concentrations of 58 mg/m^3 (Starek and Vojtisek 1986). The LOAEL was adjusted to a continuous exposure basis and divided by an uncertainty factor of 1,000 (10 for intraspecies variability, 10 for interspecies variability, and 10 for the use of a LOAEL). ATSDR (19958) did not discuss the potential applicability of this MRL to other fuel oils, but cited, as supporting data for the MRL, findings of hepatocellular changes and vacuolization in mice exposed continuously to 150 mg/m^3 IP-5 for 90 days, and findings of no systemic or neurological effects in rats or dogs exposed to a deodorized kerosene concentration of 100 mg/m^3, 6 hours/day, 5 days/week for 13 weeks.

ATSDR (1995g) did not derive chronic inhalation MRLs or any oral MRLs (for any duration of exposure) because suitable data were not available.

From a review of available human and animal studies, ATSDR (1995g) concluded that epidemiological studies have provided “only equivocal evidence of an association between cancer and exposures to fuel oils” and that animal studies suggest that dermal exposure to fuel oils can produce skin or liver cancer. ATSDR (1995g) noted that the animal studies are restricted to one species (mice) and not all studies found carcinogenic responses. The conclusion was drawn that “further investigation utilizing other species is required to more fully elucidate the mechanism of dermal carcinogenesis and the impact of dermal exposure of fuel oils on humans.”

Based on their review, IARC (1989b) concluded that there was inadequate evidence for the carcinogenicity in humans of fuel oils; sufficient evidence for the carcinogenicity in experimental animals of residual (heavy) fuel oils; limited evidence for the carcinogenicity in experimental animals of fuel oil #2; sufficient evidence for the carcinogenicity in experimental animals of light and heavy catalytically cracked distillates, of light and heavy vacuum distillates and of cracked residues, all derived from the refining of crude oil; and limited evidence for the carcinogenicity in experimental animals of straight-run kerosene. Overall evaluations were made that residual (heavy) fuel oils are possibly carcinogenic to humans (Group 2B), and that distillate (light) fuel oils are not classifiable as to their carcinogenicity to humans (Group 3).

6.3.3 Automotive Gasoline

Gasoline is a complex mixture of volatile petroleum-derived hydrocarbons, additives, and blending agents (ATSDR 1995a; IARC 1989a). The composition of gasoline varies widely depending on the composition of the crude oil from which it is refined, the refining processes used, the type and relative amount of different petroleum refining streams blended in the finished product, and the types and amounts of nonhydrocarbon compounds added to enhance or impart specific functional properties of the gasoline. Specific market conditions, partly in response to regulations, mandate the refining and manufacturing of certain gasolines. Gasoline contains predominately hydrocarbons in the C_4-C_{12} range, with the following typical distributions: alkanes (4-8 wt%); alkenes (2-5 wt%); isoalkanes (25-40 wt%); cycloalkanes (3-7 wt%); cycloalkenes (l-4 wt%); and total aromatics (20-50 wt%). The benzene content of gasoline is 0.12-3.5% (see Table E-l .b for additional detail regarding individual hydrocarbon constituents). Additives found in gasoline include anti-knock agents (e.g., tetraethyllead), lead scavengers (e.g., 1,2-dibromoethane), detergents, anti-rust agents (e.g., sulfonates), antioxidants (e.g., p-phenylenediamine), and anti-icing agents (e.g., alcohols). Leaded gasoline is no longer allowed to be used by on-road vehicles, though it still is used in farm machinery boats, competetive vehicles, and in piston engine airplanes. (EPA 1998d). A variety of products are added to gasoline to boost octane, including ethanol and MTBE.

Acute-duration inhalation, oral, or dermal exposures to gasoline have been associated with irritation at portals of entry in humans, and high-level inhalation or oral acute exposure produces symptoms of transient neurological impairment such as headache, nausea, dizziness, euphoria, and drowsiness (ATSDR 1995a). Acute ingestion of large amounts of gasoline also produces respiratory effects such as pneumonitis and pulmonary edema due to the aspiration of gasoline. Chronic exposure to gasoline vapors by intentional inhalation also has been associated with symptoms providing evidence for more permanent neurological damage in humans such as postural tremor, abnormal gait, and affected speech. The relative degrees to which hydrocarbons and additives such as lead contribute to gasoline-induced neurological impairment are unknown. Studies with rats and mice with chronic inhalation exposure to gasoline vapors have found hepatocellular tumors in female mice, and $\alpha_{2\mu}$-globulin nephropathy and related renal tumors in male rats. The renal tumors are believed to be unique to male rats and of questionable relevance to humans.

ATSDR (1995a) derived no inhalation or oral MRLs for gasoline, “because of the variability in the composition of gasoline;” the toxicity would depend on the specific composition. ATSDR (1995a)

also commented, regarding oral exposure, that there is no "quantitative information on adverse effects other than $\alpha_{2\mu}$-globulin nephropathy in male rats," an end point that is considered "not relevant to human risk assessment."

Numerous epidemiology studies have examined possible relationships between exposure to gasoline and development of various types of cancer in humans, but none of the studies were adequate to conclusively demonstrate that exposure to gasoline causes cancer in humans (ATSDR 1995a). The most common problems with these studies were the failure to adequately characterize exposure and the failure to control for confounding exposures to other fuels and exhaust emissions. In a chronic inhalation study, exposure to whole vapors of unleaded gasoline produced an increased incidence of renal tumors in male rats and liver tumors in female mice (MacFarland et al. 1984b). The renal tumors in male rats were considered to arise as a result of a process involving $\alpha_{2\mu}$-globulin accumulation, a process not expected to occur in humans. ATSDR (1995a) further questioned the relevance of the MacFarland findings, because the animals were exposed to whole vapors of gasoline and "gasoline emissions found in the environment contain lower concentrations of hydrocarbons with very low vapor pressures" than those found in whole vapors of gasoline.

EPA (1987c) classified gasoline as a Group B2 compound, a probable human carcinogen, based on inadequate evidence of carcinogenicity in humans and sufficient evidence in animals. This evaluation was made before EPA adopted a policy excluding $\alpha_{2\mu}$-globulin-related renal tumors in male rats from cancer weight-of-evidence classifications. EPA derived an inhalation unit risk of 2.1×10^{-3} ppm for gasoline based on an analysis of tumor incidence data for hepatocellular adenomas and carcinomas in female mice exposed to unleaded gasoline vapors for 2 years (MacFarland et al. 1984b). EPA has not published a more recent classification for gasoline.

IARC (1989a) concluded that there was inadequate evidence for carcinogenicity of gasoline in humans and limited evidence for carcinogenicity of unleaded automotive gasoline in experimental animals (the evidence in MacFarland et al. [1984a]). IARC (1989a) classified gasoline-as "possibly carcinogenic to humans (Group 2B)," based on the preceding conclusions and supporting data showing that gasoline induces unscheduled DNA synthesis in mice *in vivo* and in mouse, rat and human hepatocytes *in vitro;* that light, straight-run naphtha and light catalytically cracked naphtha petroleum refinery streams used to blend gasoline produce skin tumors in dermally exposed mice; ant that gasoline components such as benzene and 1,3-butadiene are known or suspected carcinogens.

6.3.4 Various Petroleum Refinery Streams

A number of health effects studies in animals of petroleum streams that correspond with the transport fractions have been reviewed by the TPHCWG (1997c); however, most of these are unpublished industry studies.

6.3.5 Stoddard Solvent

Stoddard solvent is a petroleum distillate mixture of C_7-C_{l2} hydrocarbons, approximately 80-90% aliphatics (30-50% linear and branched alkanes, and 30-40% cyclic alkanes) and l0-20% aromatics (not PAHs). It is similar to white spirits, which is also included in the toxicological profile on Stoddard solvent (ATSDR 1995b). For additional detail, see Section 3.2 and Table E-2.b. Data regarding the health effects of Stoddard solvent in either humans or animals are limited and were judged inadequate for MRL development. Upper respiratory irritant effects were seen in animals exposed by inhalation for acute and intermediate durations; these appear to be the most sensitive effects by the inhalation route. Male rat nephropathy has been reported in intermediate inhalation studies, but is not considered relevant to human health. No oral studies were located. Information on the potential carcinogenicity of Stoddard solvent is inadequate.

6.3.6 Mineral-Based Crankcase Oil

Mineral-based crankcase oil is a petroleum product that is a complex mixture of low and high molecular weight (C_{15}-C_{50}) aliphatic and aromatic hydrocarbons, metals, and additives. The chemical composition of mineral-based crankcase oil varies widely, depending on the original crude oil, the processes used in refining, the types of additives included in the oil, the efficiency and type of engine in which it is used, the type of fuel used in the engine, and the length of time the oil was used in an engine. The hydrocarbon constituents are mainly straight and branched chain alkanes, cycloalkanes, and aromatics (see Table E-5.b for additional detail). Additives (which can account for-up to 20% of the weight of oil formulations) include detergents, metallic salts (e.g., molybdenum and zinc salts), and organometallic compounds. Metals (e.g., cadmium, lead and zinc) and PAHs have been demonstrated to increase in oil with continued use in an engine.

Studies examining petroleum-stream stocks used to formulate mineral-based crankcase oil indicate that these stocks are nontoxic relative to used crankcase oils; therefore, the toxicity of used oils has been attributed to additives present in the oil or to decomposition products or contaminants that accumulate in the oil with use (ATSDR 1997c). Studies of mechanics and auto-workers exposed to used mineral-based crankcase oil found elevated incidence of skin rashes, anemia, headaches and tremors, but these studies do not establish a causal relationship with exposure to used crankcase oil, due to several limitations of the studies including the likelihood that the workers were exposed to other chemicals which may have caused the effects. There are only a few toxicological studies of animals exposed to mineral-based crankcase oil. Acute exposures to mists of used mineral-based crankcase oil were irritating to the eyes and upper respiratory tract of some volunteer human subjects. Studies of rats ingesting large single doses (9,000-22,500 mg/kg) of used mineral-based crankcase oil found no adverse health effects other than diarrhea. Cattle that ingested an unknown amount of used mineral-based crankcase oil while grazing in contaminated pastures exhibited several health effects including death, anemia, and neurological dysfunction; it was postulated that the observed effects were caused by metals (molybdenum and lead) in the oil. Long-term dermal application of used mineral-based crankcase oil to the skin of mice produced an increased incidence of dermal papillomas and carcinomas and increased levels of DNA adducts associated with reactive metabolites of PAHs. The carcinogenicity of used mineral-based crankcase oil has been correlated with the PAH content of oils. ATSDR (1997e) judged that no meaningful MRL values could be derived for used mineral-based crankcase oil, due to the limitations of the toxicological data on used mineral-based crankcase oils and the wide compositional variance among used mineral-based crankcase oils.

EPA (1998b) and IARC (1996) have not classified used mineral-based crankcase oil as to its carcinogenicity in humans. IARC (1984, 1987) noted that exposure to mineral oils used in a variety of occupations (including mulespinning, metal machining, and jute processing) has been strongly and consistently associated with increased occurrence of squamous-cell cancers of the skin, especially of the scrotum, but that production processes have changed over time so that more modern, highly refined oils contain smaller amounts of “contaminants, such as polycyclic aromatic hydrocarbons.” IARC (1987) judged that there was sufficient evidence for the carcinogenicity of untreated and mildly-treated mineral oils in humans and animals, whereas there was inadequate evidence for the carcinogenicity of highly-refined mineral oils in humans or animals.

6.3.7 Mineral Oil Hydraulic Fluids

Most mineral oil hydraulic fluids are made from processed petroleum crude oils that are blended with various types of nonhydrocarbon additives to impart specific, use-related properties to the fluid (ATSDR 1997b). The carbon number range of hydrocarbons in hydraulic fluids varies depending on the intended application of the fluid, but mostly is in the range of C_{15}-C_{50}. Toxicity data for mineral oil hydraulic fluids are restricted to acute lethality studies of rats exposed by gavage or by inhalation to several types of mineral oil hydraulic fluids, and single-dose gavage neurotoxicity tests that found no effects in chickens.

ATSDR (1997b) did not derive inhalation or oral MRLs for mineral oil hydraulic fluids for any duration of exposure, because of the lack of suitable data.

IARC (1984) reviewed the evidence that certain types of mineral oils are carcinogenic in animals, whereas other types are not. IARC (1984) concluded that mineral oil is not classifiable as to its carcinogenicity, because of the apparent dependence of mineral oil's carcinogenic activity in animals on the chemical makeup of the crude oil starting material, the presence of additives and the conditions of use.

6.3.8 Asphalt

Asphalts are complex mixtures containing relatively high molecular weight hydrocarbons, predominantly cyclic alkanes and aromatic compounds (IARC 1985). They also contain some sulfur-, nitrogen- and oxygen-containing compounds and heavy metals. They are viscous liquids or solids. Inhalation studies of these mixtures in animals have involved heating the materials to produce fumes, which is relevant to human occupational exposure (e.g., roofing, road surfacing), but not particularly relevant to exposure resulting from contamination at hazardous waste sites. Respiratory effects were seen in these studies. Respiratory effects were reported in workers who were exposed to fumes of asphalts. No oral studies were reported. IARC concluded that there is sufficient evidence that extracts of asphalts (applied to the skin of experimental animals in solvents such as benzene or toluene or injected subcutaneously) are carcinogenic to animals. Evidence for undiluted asphalts ranged from limited to inadequate, depending on type of asphalt. IARC (1985) concluded that there is inadequate evidence that asphalts alone are carcinogenic to humans

6.3.9 Crude Oil

ATSDR has not prepared a toxicological profile on crude oil. IARC (1989c) prepared a monograph on crude oils, from which the following information is summarized. Crude oils are exceedingly complex mixtures that vary greatly depending on their source. The bulk of chemicals in crude oils are hydrocarbons: straight, branched and cyclic alkanes; and aromatics including benzene, alkylbenzenes, naphthalenes and PAHs. Non-hydrocarbon constituents of crude oil include sulfur-, nitrogen-, oxygen-and metal-containing compounds.

No studies of potential health effects from inhalation exposure were located. Acute oral administration of crude oil to animals has resulted in hepatic effects and development effects. Aspiration of crude oil by a laborer resulted in pneumonia and hepatic and renal effects. Petroleum field workers who had direct dermal contact with crude oil developed adverse dermal effects, including dryness and hyperkeratosis.

A number of studies of the carcinogenicity of dermal application of crude oil to animals have been reviewed by IARC (1989c), which concluded that there is limited evidence for the carcinogenicity of crude oil to experimental animals. A cohort study of U.S. petroleum-producing and pipeline workers, and case control studies that included exposure during crude oil exploration and production, were evaluated by IARC (1989c), which concluded that there is inadequate evidence for the carcinogenicity of crude oil in humans.

An additional monograph on occupational exposures in petroleum refining (IARC 1989e) concluded that there is limited evidence that working in petroleum refineries entails a risk of skin cancer and leukemia. Exposures during refining, however, are not particularly relevant to exposures resulting from contamination of hazardous waste sites with crude oil.

6.4 TOXICOKINETICS

Overview. Because TPH is a broadly defined entity consisting of complex mixtures of hydrocarbons of varying chemical composition (due to differences in original petroleum products and differential, time-dependent, fate and transport of components within any particular TPH mixture), this section discusses available information for absorption, distribution, metabolism and excretion of components and petroleum products corresponding to the transport fractions of TPH. Limited additional information regarding the

more heterogenous whole petroleum products can be found in the ATSDR toxicological profiles and other assessments of these products referenced in Section 6.3. In general, however, there is little information regarding toxicokinetics of these heterogeneous products and the discussions often deal with the individual constituents, including additives and impurities that are not petroleum hydrocarbons, and hydrocarbon mixtures that are similar to portions of the product.

Hydrocarbons in the aromatic $EC_{>9}$ –EC_{16}, fraction may be readily absorbed following inhalation or oral exposure, based on studies with humans and animals exposed to the BTEXs. BTEXs are absorbed by the skin to a lesser extent, especially with exposure to vapors. BTEXs and their metabolites are widely distributed throughout tissues and organs following absorption. BTEXs are metabolized (via oxidative metabolic pathways involving cytochrome P-450 oxidases and conjugation reactions with glucuronides, sulfates, glutathione, or amino acids) to more water-soluble metabolites that are excreted predominately in urine. Metabolism represents a toxification pathway for some effects of certain BTEXs (e.g., cancer and hematopoietic effects appear to be caused by reactive metabolic intermediates of benzene) and a detoxification pathway for other effects (e.g., neurological effects from acute exposure to toluene). In addition to urinary excretion of metabolites, BTEXs are eliminated by exhalation of unchanged parent compound and fecal excretion (ATSDR 1994, 1995d, 1997a, 1999a).

Hydrocarbons in the aromatic $EC_{>9}$ –EC_{16} fraction may be absorbed following inhalation, oral, or dermal exposure, based on studies of humans and animals exposed to cumene, naphthalene or monomethyl-naphthalenes, but data concerning the rate and extent of absorption are limited. Animal studies indicate that these indicator compounds and their metabolites are widely distributed following absorption and that urinary excretion of metabolites is the primary route of elimination. Metabolism of cumene, naphthalene, and methyl naphthalenes involves *aromatic ring oxidation* (especially for naphthalene)-forming epoxide, alcohol, dihydrodiol, and quinone derivatives that can be conjugated to glutathione, glucuronic acid, or sulfate-and *oxidation of the alkyl side groups* (i.e., in cumene or methyl naphthalenes)-forming alcohol and carboxylic acid derivatives that can be conjugated to glucuronic acid or amino acids (ATSDR 1995e; EPA 1987a, 1997b).

Hydrocarbons in the aromatic $EC_{>16}$ –EC_{35} fraction may be absorbed to varying extents following inhalation, oral, or dermal exposure, depending on the lipophilicity and molecular size of the compound and the vehicle of administration, as indicated by studies of humans exposed to workplace-air complex

mixtures containing PAHs (i.e., hydrocarbons with more than two 5- or 6-carbon aromatic rings) and studies of animals exposed to individual PAHs by inhalation, oral administration, or dermal application. Increasing lipophilicity of vehicles or of the PAH compound tends to increase absorption, whereas adsorption to particles of increasing size (especially for inhalation exposure) or increasing molecular weight of the PAH compound tends to decrease absorption. Following absorption, PAHs are widely distributed to tissues and organs and eliminated by urinary and biliary excretion of metabolites. Metabolism of PAHs involves the production of arene oxides, phenols, quinones, dihydrodiols (i.e., diols), phenol-diols, and diol-epoxides, and the conjugation of these oxidized intermediates to glutathione, glucuronic acid or sulfate. Reactive metabolic intermediates, including stereospecific isomers of arene oxides and diol-epoxides, are thought to cause the genotoxic and carcinogenic effects produced by carcinogenic PAHs (ATSDR 1995f).

Hydrocarbons in the aliphatic EC_5 –EC_8 fraction may be readily absorbed in the lungs, as indicated by studies of humans and animals exposed to *n*-hexane, but absorption by the oral and dermal route is not well characterized. Aspiration to the lungs can occur following ingestion of hydrocarbons in this fraction. Absorbed *n*-hexane, based on determined partition coefficients in human and animal tissues, is expected to be widely distributed to tissues and organs with preferential partitioning into fatty tissues and well perfused tissues. Studies with humans and animals indicate that *n*-hexane is oxidatively metabolized to alcohol, ketone, carboxylic acid, dihydrodiol, and diketone derivatives, predominately in the liver. Urinary excretion of metabolites and, to a lesser extent, exhalation of unchanged *n*-hexane are the predominant means of elimination with low-level exposure, whereas exhalation of unchanged compound becomes a more important elimination pathway with high exposures (ATSDR 1999b).

Hydrocarbons in the aliphatic $EC_{>8}$ –EC_{16} fraction may be readily absorbed in the lungs, widely distributed to tissues with preferential distribution and accumulation occurring in fatty tissues, and slowly eliminated from fatty tissue, as indicated by studies of humans exposed by inhalation to a mixture of C_{10}-C_{12} alkanes (“white spirit”) and studies of rats exposed by inhalation to single alkanes or cycloalkanes in the C_6-C_{10} range. Results from these studies suggest that metabolism of hydrocarbons in this fraction, especially following distribution to fatty tissue, may be slow relative to aromatic hydrocarbons. Aspiration to the lungs may occur following ingestion of hydrocarbons in this fraction, especially those at the lower end of the ranges of molecular weight and viscosity for the fraction. Studies with rats indicate

that percentage absorption of ingested aliphatic hydrocarbons decreases with increasing carbon number from about 60% for C_{l4} compounds to 5% or less for hydrocarbons with 228 carbons.

Hydrocarbons in the aliphatic $EC_{>16}$ –EC_{35} fraction may be poorly absorbed, regardless of the route of exposure, preferentially distributed to the liver and fatty tissues, slowly metabolized to fatty acids or triglycerides, and slowly excreted in the feces via the bile and as urinary metabolites, as indicated by studies with animals exposed to food-grade mineral oil or motor oil (ATSDR 1997b). The common presence of lipogranulomata in human autopsies (benign structures in human liver and spleen tissue which are composed of lipoid droplets surrounded by lymphocytes and macrophages and caused by dietary exposure to mineral oils) is consistent with the concept that aliphatic hydrocarbons in this fraction are slowly metabolized.

6.4.1 Absorption

6.4.1.I Inhalation Exposure

Aromatic EC_5 –EC_9 Fraction. Studies with humans and animals are available for each of the BTEXs; these studies indicate that BTEX compounds are rapidly and efficiently absorbed following inhalation exposure. Published retention percentages for inspired BTEXs in human studies range from approximately 30% to 70-80% (see ATSDR 1994, 1995d, 1997a, 1999a).

Aromatic $EC_{>9}$ –EC_{16} Fraction. Studies measuring the rate and extent of absorption in humans or animals following inhalation exposure to naphthalene or the monomethyl naphthalenes were not available, but observations of systemic health effects in humans and animals provide qualitative evidence of absorption of these indicator compounds (ATSDR 1995e). Studies of humans following inhalation exposure to isopropylbenzene (cumene) indicated a retention percentage of about 50% (EPA 1987a, 1997b).

Aromatic $EC_{>16}$ –EC_{35} Fraction. Studies directly measuring the rate and extent of absorption in humans or animals following inhalation exposure to PAHs were not available, but measurement of the appearance of radioactivity in blood, tissues, and excreta within hours of exposure of animals to airborne, radioactively labeled benzo(a)pyrene indicate that rapid absorption can occur. Particle size and vehicle are expected to influence the absorption of inhaled PAHs, as indicated by measurements of lung clearance

following inhalation exposure of rats to benzo(a)pyrene adsorbed onto particles of differing sizes and measurements of excretion rates in rats following intratracheal instillation of benzo(a)pyrene in various vehicles (ATSDR 1995f)

Aliphatic EC_5 –EC_8 Fraction. Studies with humans exposed to vapors of *n*-hexane indicate that 20-25% of inhaled compound is absorbed and retained (ATSDR 1999b). In studies with rats exposed by inhalation, 12 hours/day for 3 days, to 100 ppm single hydrocarbons in the C_6-C_{10} alkane series (*n*-hexane through *n*-decane) and a C_6-C_{10}, naphthene series (cyclohexane, methylcyclohexane, dimethylcyclohexane, trimethylcyclohexane and *t*-butylcyclohexane), absorption was demonstrated by the measurement of concentrations of hydrocarbons in blood, brain, liver, kidneys, and fat (Zahlsen et al. 1992). Within each series, tissue concentrations (μmol/kg) generally increased with increasing carbon number.

Aliphatic $EC_{>8}$ –EC_{16} Fraction. Hydrocarbons in this fraction may be readily absorbed following inhalation, as indicated by studies of humans exposed to airborne mixtures of mostly C_{10}-C_{12} hydrocarbons and by the studies of rats exposed to single hydrocarbons conducted by Zahlsen et al. (1992).

For human volunteers exposed by inhalation to 100 ppm white spirit for 3 hours, a mean pulmonary uptake of 392 mg white spirit was measured, based on concentrations of white spirit in inspiratory and expiratory air (Pedersen et al. 1987). Following exposure to the same concentration, 6 hours/day for 5 consecutive days, the mean pulmonary uptake was 3,464 mg white spirit. The test material was a mixture of aliphatic hydrocarbons containing 99% linear and branched alkanes (0.99% C_8-C_9, 15% C_{10}, 39% C_{11}, and 44% C_{12}), and 1% C_9-C_{10} cycloalkanes.

Absorption of inhaled hydrocarbons in the lower range of this fraction was demonstrated by detection of hydrocarbons in blood, brain, liver, kidneys, and fat in rats following exposure to single hydrocarbons (C_6 -C_{10}, *n*-alkanes [*n*-hexane through *n*-decane] and C_6-C_{10}, naphthenes [cyclohexane, methylcyclohexane, dimethylcyclohexane, trimethylcyclohexane, and *t*-butylcyclohexane]) at 100 ppm, 12 hours/day, for 3 days (Zahlsen et al. 1992).

Aliphatic $EC_{>16}$ –EC_{35} Fraction. Studies measuring the rate and extent of absorption of aliphatic hydrocarbons in this fraction were not located, but animal studies with mineral oil aerosols suggest that

absorption is not rapid and lung clearance may be mediated by macrophages. Mice, rats, and rabbits exposed to aerosols of diesel-engine lubricating oil for up to 343 days showed oil in alveolar macrophages, mediastinal lymph nodes, lymphatic channels of the lungs, and the pleura; in mice, concentrations (w/w) of oil were 0.13% in lungs and 0.03% in livers (ATSDR 1999b).

6.4.1.2 Oral Exposure

Aromatic EC_5 –EC_9 Fraction. Animal studies are available for each of the BTEXs, indicating that these compounds are rapidly and efficiently absorbed following oral exposure. Published absorption percentages for oral doses of BTEXs in animal studies range from about 80% to 97% (see ATSDR 1994, 1995d, 1997a, 1999a).

Aromatic $EC_{>9}$ –EC_{16} Fraction. No data regarding the extent or rate of absorption of ingested naphthalene or monomethyl naphthalenes were available, except for a report that 80% of an oral dose of 2-methyl naphthalene was recovered as metabolites in the urine of rats within 24 hours (ATSDR 1995e). Studies with animals indicate that orally administered isopropylbenzene (cumene) rapidly appeared in the blood and that 90% of the administered dose was accounted for in urinary metabolites (EPA 1987a, 1997b).

Aromatic $EC_{>16}$ –EC_{35} Fraction. Studies with animals following oral exposure to benzo(a)pyrene and other PAHs indicate that the extent of oral exposure to PAHs can vary depending on lipophilicity of the PAH compound and lipophilicity of the vehicle in which it is administered (ATSDR 1995f).

Aliphatic EC_5 –EC_8, $EC_{>8}$ –EC_{16}, and $EC_{>16}$ –EC_{35} Fractions. No studies were located regarding absorption of hydrocarbons in these fractions after oral exposure in humans. Studies in rats show that absorption of ingested aliphatic hydrocarbons (*n*-alkanes, isoparaffins, and naphthenes) is inversely related to molecular weight, ranging from complete absorption at the lower end of the molecular weight range to about 60% for C_{14} hydrocarbons, 5% for C_{28} hydrocarbons, and essentially no absorption for aliphatic hydrocarbons with >32 carbons (Albro and Fishbein 1970; Miller et al. 1996)

6.4.1.3 Dermal Exposure

Aromatic EC_5 –EC_9 Fraction. Studies with animals indicate that BTEXs are dermally absorbed, but to a lesser extent than absorption via inhalation or oral exposure, especially when exposure is to vapors of these compounds (as opposed to the liquids or liquid solutions) (see ATSDR 1994, 1995d, 1997a, 1999a).

Aromatic $EC_{>9}$ –EC_{16} Fraction. Data regarding the rate and extent of dermally administered isopropylbenzene (cumene), naphthalene, or monomethyl naphthalenes were restricted to observations of systemic effects in humans and animals following dermal exposure to these compounds (ATSDR 1995e; EPA 1987a, 1997b).

Aromatic $EC_{>16}$ –EC_{35} Fraction. Studies that monitored radioactivity in rat tissues, organs, and excreta following the dermal application of individual radiolabeled PAHs in an organic solvent measured absorption percentages in the approximate range of 50-80% (% of applied dose that was absorbed), but found that absorption percentages declined to less than 20% when soil particles were included in the applied material (ATSDR 1995f).

Aliphatic EC_5 –EC_8 Fraction. *In vitro* studies with human skin indicate that the permeability of *n*-hexane through skin was about l00-fold lower than the permeability of benzene, suggesting that hydrocarbons in this fraction may have a low potential for skin absorption (ATSDR 1999b).

Aliphatic $EC_{>8}$ –EC_{16} Fraction. No studies were located regarding absorption of hydrocarbons in this fraction after dermal exposure in humans or animals.

Aliphatic $EC_{>16}$ –EC_{35} Fraction. No studies were located that measured the rate or extent of dermal absorption of hydrocarbons in mineral oil or similar materials in animals or humans. Dermal absorption of hydrocarbons in this fraction, however, may be expected to be slow, based on studies with monkeys administered subcutaneous doses of radiolabeled mineral oil in an aqueous emulsion. Radioactivity remaining at the sites of injection accounted for 85-99% and 25-33% of the administered radioactivity, at 1 week and 10 months following injection, respectively (ATSDR 1997b).

6.4.2 Distribution

Aromatic EC_5 –EC_9 Fraction. Studies with humans and animals exposed predominately to vapors of individual BTEXs (there are fewer data for oral and dermal exposure) indicate that, following absorption, compounds in this fraction are widely distributed, especially to lipid-rich and highly perfused tissues (see ATSDR 1994, 1995d, 1997a, 1999a). Studies of rats exposed by inhalation to single hydrocarbons at 100 ppm, 12 hours/day, for 3 days found that C_6-C_{10} aromatics (benzene, toluene, xylene, trimethylbenzene, and *t*-butylbenzene), compared with C_6-C_{10}, *n*-alkanes (*n*-hexane through *n*-decane) and C_6-C_{10}, naphthenes (cyclohexane, methylcyclohexane, dimethylcyclohexane, trimethylcyclohexane, and *t*-butylcyclohexane), showed high concentrations (μmol/kg) in blood, low concentrations in organs, and a lower potential for accumulation in fat and other organs presumably due to faster metabolic disposition (Zahlsen et al. 1992).

Aromatic $EC_{>9}$ –EC_{16} Fraction. Studies of swine after oral exposure to naphthalene, rats after dermal exposure to naphthalene, and guinea pigs after oral exposure to 2-methyl naphthalene indicate that these compounds, and their metabolites, are distributed throughout tissues and organs following absorption (ATSDR 1995e). Studies with rats exposed to isopropylbenzene (cumene) by inhalation, oral administration, or intravenous injection indicated that absorbed isopropylbenzene (cumene) is distributed to many tissues and organs with some preferential distribution in fatty tissues (EPA 1987a, 1997b).

Aromatic $EC_{>16}$ –EC_{35} Fraction. Studies with animals exposed to individual radiolabeled PAHs by inhalation, oral administration, or dermal administration indicate that, following absorption, PAHs are widely distributed to tissues and organs (ATSDR 1995f). Studies with pregnant animals found that, following oral exposure to radiolabeled benzo(a)pyrene, placental levels of radioactivity were higher than levels in embryonic tissue, suggesting that benzo(a)pyrene does not readily cross the placental barrier (ATSDR 199%).

Aliphatic EC_5 –EC_8 Fraction. Determination of partition coefficients (blood:air and tissue:air) for *n*-hexane in human and rat tissues indicates that hydrocarbons in this fraction, once absorbed, will be widely distributed to tissues and organs with preferential distribution to fatty tissues and well perfused tissues (ATSDR 1999b). Asphyxia and chemical pneumonitis can be a health concern from ingestion of hydrocarbons in this fraction, due to aspiration to the lungs. The aspiration potential of ingested

hydrocarbons increases with decreasing viscosity; within the alkane series, C_6-C_{10}, viscosity decreases with decreasing molecular weight (Cavender 1994).

Studies of rats exposed by inhalation to single hydrocarbons at 100 ppm, 12 hours/day, for 3 days found that C_6-C_{10} *n*-alkanes (*n*-hexane through *n*-decane) and C_6-C_{10} naphthenes (cyclohexane, methylcyclohexane, dimethylcyclohexane, trimethylcyclohexane, and *t*-butylcyclohexane), compared with C_6-C_{10} aromatics (benzene, toluene, xylene, trimethylbenzene, and *t*-butylbenzene), generally showed low concentrations (μmol/kg) in blood, high concentrations in brain and other organs, and a high potential for accumulation in fat (Zahlsen et al. 1992). Within any of these three categories of hydrocarbons, hydrocarbon concentrations in tissues (blood, brain, kidney, liver and fat) generally increased with increasing carbon number (Zahlsen et al. 1992). Twelve hours after cessation of exposure, concentrations of alkanes and naphthenes in fat and brain were 2- to 3-fold higher than concentrations of aromatics, suggesting faster metabolic disposition for the aromatics.

Aliphatic $EC_{>8}$ –EC_{16} Fraction. Studies of rats exposed by inhalation to individual C_6-C_{10}, *n*-alkanes and cycloalkanes indicate that hydrocarbons in this fraction are distributed widely to tissues and organs after absorption and can accumulate in fat (Zahlsen et al. 1992). Aspiration to the lungs can occur following ingestion of hydrocarbons in this fraction (Cavender 1994). Following absorption from the gastrointestinal tract, smaller molecular weight aliphatic hydrocarbons and/or their metabolites are transported in the body via the blood and the lymph system, whereas larger molecular weight aliphatic hydrocarbons may be distributed predominately via the lymph system (see for review Albro and Fishbein 1970; Miller et al. 1996).

Aliphatic $EC_{>16}$ –EC_{35} Fraction. Lung accumulation of hydrocarbons from this fraction is of concern with prolonged or high-level exposure to aerosols or ingestion, as indicated by numerous case reports of lipoid pneumonia in humans exposed to mineral oil through intranasal application of liquid petrolatum in medicinal nose drops and by a case of lipoid pneumonia in a child who ingested a 5-10 mL dose of mineral oil automobile transmission fluid (ATSDR 1997b). Following absorption, hydrocarbons in this fraction may be expected to accumulate to some degree in liver and fatty tissues, as indicated by the observation that, 24 hours after administration of an oral dose of tritiated mineral oil to rats, concentrations of tritiated mineral oil were about 7-fold greater in fatty tissues and liver than in kidney and brain (ATSDR 1997b). Lipogranulomata (clusters of lipoid droplets surrounded by lymphocytes and

macrophages) are commonly found in human autopsies, particularly in liver, spleen, and abdominal lymph nodes (Miller et al. 1996; Wanless and Geddie 1985). These structures are associated with dietary exposure to mineral oils and waxes, and are considered a benign response without adverse consequences (Miller et al. 1996; Wanless and Geddie 1985).

6.4.3 Metabolism

Aromatic EC_5 –EC_9 Fraction. As indicated by studies with humans and animals exposed to individual BTEXs, compounds in this fraction may be expected to be metabolized via cytochrome P-450 oxidases, either at carbons in the aromatic ring or in alkyl side groups, to metabolic intermediates that can be conjugated with glucuronides, sulfates, glutathione, or ammo acids (e.g., cysteine or glycine). The resultant oxidated metabolites or conjugated metabolites are more water-soluble than parent compounds and are subject to urinary or, in some cases, biliary excretion. Metabolism of the BTEXs can represent both a detoxification process (e.g., enhancement of the formation and excretion of hippuric acid can counteract the acute neurotoxicity of toluene in animals) and a toxification process (e.g., cancer and hematopoietic effects from chronic exposure to benzene appear to be caused by reactive metabolic intermediates) (see ATSDR 1994, 1995d, 1997a, 1999a).

Aromatic $EC_{>9}$ –EC_{16} Fraction. Studies with animals following oral, intraperitoneal, or subcutaneous administration of naphthalene or 2-methyl naphthalene indicate that ring oxidation occurs via an initial epoxide intermediate that subsequently is converted to alcohol, dihydrodiol and quinone derivatives, some of which are conjugated to glutathione, glucuronic acid, or glycine, and that the presence of alkyl side groups presents another site for oxidation and conjugation (ATSDR 1995e). Naphthol and naphthoquinone derivatives have been detected in the urine of humans following exposure to naphthalene (ATSDR 1995e). Studies with animals exposed to isopropylbenzene (cumene), and with *in vitro* animal preparations, indicate that cumene is predominately oxidized at the l- or 2-carbon of the propyl side group to form alcohol or carboxylic acid derivatives that are conjugated predominately to glucuronic acid (EPA 1987a, 1997b). A study that analyzed urinary metabolites in humans following acute inhalation exposure to cumene provided supporting data (EPA 1987a).

Aromatic $EC_{>16}$ –EC_{35} Fraction. *In vitro* studies with human tissues and *in vitro* and *in vivo* animal studies with benzo(a)pyrene and other PAHs indicate that compounds in this TPH fraction will undergo oxidative metabolism involving the production of arene oxides, phenols, quinones, dihydrodiols (i.e., diols),

phenol-diols, and diol-epoxides (catalyzed by enzyme systems including cytochrome P-450 oxidases and epoxide hydrolase), and the conjugation of these intermediates to glutathione, glucuronic acid, or sulfate (ATSDR 1995f). Metabolism of PAHs facilitates both the elimination of more water soluble metabolites and the production of reactive intermediates (e.g., stereospecific isomers of arene oxides and diol-epoxides) thought to be responsible for the mutagenic and carcinogenic activity of carcinogenic PAHs (ATSDR 1995f).

Aliphatic EC_5 –EC_8 Fraction. Examination of urinary metabolites in humans and rats after exposure to *n*-hexane indicates that hydrocarbons in this fraction may be oxidatively metabolized via cytochrome P-450 oxidases to several alcohol, ketone, and carboxylic acid derivatives. Based on studies of urinary metabolites after exposure to *n*-hexane, proposed metabolites include l-, 2-, and 3-hexanol, 2-hexanone, 5-hydroxy-2-hexanone, 2,5-hexanedione, and hexanoic acid (ATSDR 1999b).

Aliphatic $EC_{>8}$ –EC_{16} Fraction. Hydrocarbons in this fraction are oxidatively metabolized to fatty acids and alcohols, apparently mediated by cytochrome P-450 isozymes (see Miller et al. 1996 for review). Studies regarding the metabolism of hydrocarbons in this fraction in humans or animals provide suggestive evidence that metabolism may be slow. In a study of humans exposed to 100 ppm white spirit 6 hours/day for 5 days (white spirit is a mixture comprised predominately of C_{10}-C_{12}, linear and branched alkanes), only minor differences were observed in the GC-MS spectrum of hydrocarbons in biopsied fatty tissue, than in the spectrum of hydrocarbons in the test material (Pedersen et al. 1984). In rats exposed by inhalation to single C_6-C_{10}, alkanes, cycloalkanes, or aromatic hydrocarbons at 100 ppm, 12 hours/day for 3 days, concentrations of alkanes and cycloalkanes were 2- to 3-fold higher than concentrations of aromatics 12 hours after cessation of exposure, suggesting that aliphatic hydrocarbons in this fraction may be metabolized more slowly than aromatic hydrocarbons of equivalent molecular weight (Zahlsen et al. 1992).

Aliphatic $EC_{>16}$ –EC_{35} Fraction. Aliphatic hydrocarbons in this fraction are not expected to undergo extensive metabolism in animals or humans. In monkeys, 2 days after intramuscular injection of a mineral oil emulsion with a radiolabeled C_{16} hydrocarbon (*n*-hexanedecane), substantial portions (30-90s) of radioactivity in various tissues existed as unmetabolized *n*-hexanedecane. The remainder of the radioactivity was found as phospholipids, free fatty acids, triglycerides, and sterol esters. No radioactivity was found in water-soluble fractions (ATSDR 1997b). The common presence of lipogranulomata in

human autopsies and the widespread dietary exposure to mineral oils and waxes (Wanless and Geddie 1985) are consistent with the concept that aliphatic hydrocarbons in this fraction are slowly metabolized.

6.4.4 Elimination and Excretion

Aromatic EC_5 –EC_9 Fraction. Studies with humans and animals exposed by various routes to BTEXs, indicate that compounds in this fraction may be expected to be eliminated predominately by urinary excretion of metabolites and to lesser degrees by exhalation of unchanged parent compound or biliary excretion of metabolites (see ATSDR 1994, 1995d, 1997a, 1999a).

Aromatic $EC_{>9}$–EC_{16} Fraction. Data from studies with animals exposed by several routes to naphthalene, monomethyl naphthalenes and isopropylbenzene (cumene) indicate that urinary excretion of metabolites represents the predominant pathway of elimination for these compounds. Detection of urinary metabolites in humans exposed to naphthalene or cumene provide supporting evidence (ATSDR 1995e; EPA 1987a, 1997b).

Aromatic $EC_{>16}$ –EC_8 Fraction. Studies with animals exposed by inhalation, and by oral, dermal, or parenteral administration, indicate that PAHs are eliminated by urinary and biliary excretion of metabolites (ATSDR 1995f).

Aliphatic EC_5 –EC_8 Fraction. Studies with humans and animals exposed to *n*-hexane suggest that hydrocarbons in this fraction, under low-exposure conditions, may be eliminated predominately as urinary metabolites and to a lesser extent in exhaled air as unchanged compound. Studies with rats indicate that the importance of exhalation of unchanged hexane as an elimination pathway increased from about 12% to 62% of body burden after inhalation exposure to 500 ppm and 10,000 ppm, respectively (ATSDR 1999b).

Aliphatic $EC_{>8}$ –EC_{16} Fraction. Results from studies with humans exposed by inhalation to white spirit (a mixture of C_{10}-C_{12} aliphatic hydrocarbons) suggest that hydrocarbons in this fraction are slowly eliminated following distribution to fatty tissues (Pedersen et al. 1984). Immediately after 5 consecutive days of 6-hour daily exposure to 100 ppm white spirit, the mean concentration of white spirit in fatty tissue was 41.1 mg/kg fat; approximately 60 exposure-free hours later, mean fatty tissue concentrations had declined by only 23% to 3 1.7 mg/kg fat. No studies were located regarding the routes of excretion for hydrocarbons in this fraction in humans or animals.

Aliphatic $EC_{>16}$ –EC_{35} Fraction. Hydrocarbons in this fraction may be expected to be eliminated predominately in the feces, based on experiments with rats given oral or intraperitoneal doses of tritiated mineral oil. With oral exposure, 90% of administered radioactivity appeared rapidly (within 2 days) in the feces, predominately as unchanged mineral oil; less than 10% of administered radioactivity appeared in the urine within 2 days of administration. With intraperitoneal exposure, radioactivity appeared more slowly in the feces (11% of administered radioactivity appeared in the feces within 8 days of dosing); urinary excretion of metabolites, within 8 days of dosing, represented about 8% of administered radioactivity (ATSDR 1997b).

6.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

No studies were located regarding the development of PBPK/PD models for complex mixtures of TPH in general.

Verhaar et al. (1997), however, recently reported on progress in developing PBPK/PD models for use in assessing human health risks from exposure to JP-5, a Navy Jet petroleum fuel containing a complex mixture of hydrocarbons in the C_9C_{18}, range. Verhaar et al. (1997) noted that their in-progress development of a PBPK/PD model for JP-5 is focused on the prediction of kinetics of JP-5 components in relevant tissues after acute inhalation exposure and the resultant toxicity (neurological effects linked to the dissolution of xenobiotic chemicals in the membrane of nerve cells). Verhaar et al. (1997) discussed how the development of PBPK/PD model(s) for complex mixtures involves:

(1) determining a lumping scheme to be used (in which similar mixture components are grouped [i.e., lumped] into a *pseudocomponent* for which necessary chemical parameters such as tissue partition coefficients are estimated), based on knowledge of the mixture's chemical composition, the route and duration of exposure that is of interest, and the mixture's toxicological effect(s) and mechanism of action (a lumping scheme based on the octanol-water partition coefficients of components was chosen for JP-5);

(2) formulating PBPK/PD model(s) with physiological compartments, reaction kinetic equations, and mass transfer equations that are appropriate to the toxicological effect(s) of concern (a brain compartment, including a pharmacodynamic subroutine, was proposed to be included in the PBPK/PD model for JP-5);

(3) determining whether there is enough information to include interactive effects between *pseudocomponents* in the model(s); and

(4) using quantitative structure-activity relationships (QSAR) to estimate necessary model parameters for *pseudocomponents* such as tissue-blood and air-blood partition coefficients, and metabolic rate constants.

The approach discussed by Verhaar et al. (1997) suggests that development of PBPK/PD models to use in assessing health risks from TPH will require similar focusing on relevant lumping schemes, exposure pathways and durations, and toxicological effects and mechanisms of action. Thus, it is likely that a PBPK/PD model developed to aid in the assessment of potential cancer risk from chronic exposure to TPH may substantially differ from a PBPK/PD model for assessing risk for potential neurological effects from acute exposure to TPH.

6.5 MECHANISM OF ACTION

Because TPH is a broadly defined entity consisting of complex mixtures of hydrocarbons of varying chemical composition (due to differences in original petroleum products and differential, time-dependent, fate and transport of components within any particular TPH mixture), this section discusses available information for components and petroleum products corresponding to the transport fractions of TPH. Limited additional information regarding the more heterogenous whole petroleum products can be found in the ATSDR toxicological profiles and other assessments of these products referenced in Section 6.3. In general, however, there is little information regarding mechanisms for these heterogenous products. The discussions of mechanisms in these documents often deal with the individual constituents, including additives and impurities that are not petroleum hydrocarbons, and with hydrocarbon mixtures that are similar to portions of the product.

6.5.1 Pharmacokinetics Mechanisms

Absorption. Available data suggest that hydrocarbons in the aliphatic EC_5-EC_5 and aromatic EC_5-EC_9 fractions may be more readily absorbed by the lungs, gastrointestinal tract, and skin than hydrocarbons in the aliphatic or aromatic hydrocarbons in larger molecular weight fractions. This

difference is due to their smaller molecular size and the presumed dependence of absorption of hydrocarbons on diffusion or facilitated diffusion.

Distribution, Storage and Excretion. Hydrocarbons in each of the aliphatic and aromatic fractions are expected to be distributed throughout tissues and organs following absorption. Preferential distribution to fatty tissues occurs especially with aliphatic hydrocarbons. Ingested or inhaled volatile aliphatic and aromatic hydrocarbons in the EC_5-EC_8 and EC_5-EC_9 fractions can be eliminated in exhaled breath as unchanged parent compound. Metabolic elimination of aromatic hydrocarbons in each EC fraction predominately occurs via oxidative metabolic pathways involving initial oxidation by cytochrome P-450 isozymes and conjugation to more water-soluble compounds such as glutathione and glucuronic acid. Some studies in animals suggests that aliphatic hydrocarbons (especially in the $EC_{>8}$-EC_{16} and $EC_{>16}$-EC_{35} fractions) may be metabolized more slowly than aromatic hydrocarbons. Metabolites of both aliphatic and aromatic hydrocarbons are excreted in urine and in feces via biliary excretion.

Route-dependent Toxicity. Ingested aliphatic hydrocarbons in the EC_5-EC_8 and $EC_{>8}$-EC_{16} fractions are aspirated to the lungs and can lead to pulmonary irritation, edema, and pneumonia. Materials with low viscosity (in the range of 30-35 centipoise) present an extreme aspiration risk, whereas those with high viscosity (150-250 centipoise) present very low aspiration risk (Snodgrass 1997).

6.5.2 Mechanisms of Toxicity

Central nervous system (CNS) depression caused by acute inhalation exposure to volatile aliphatic and aromatic petroleum hydrocarbons is generally thought to occur when the lipophilic parent hydrocarbon dissolves in nerve cell membranes and disrupts the function of membrane proteins by disrupting their lipid environment or by directly altering protein conformation. Oxidative metabolism of CNS-depressing hydrocarbons reduces their lipophilicity and represents a process that counteracts CNS-depression toxicity. More detailed information on this mechanism of toxicity can be found in ATSDR profiles on toluene (ATSDR 1994), ethylbenzene (ATSDR 1999a), and xylene (ATSDR 1995d).

Pulmonary irritation and pneumonia from inhalation and oral exposure to complex mixtures of petroleum hydrocarbons such as gasoline and kerosene are thought to involve direct parent hydrocarbon interaction with nerve cell membranes resulting in bronchoconstriction and dissolution into membranes of lung

parenchyma resulting in a hemorrhagic exudation of proteins, cells, and fibrin into alveoli (ATSDR 1998b; Klaassen 1996).

In contrast, metabolic bioactivation, mediated by pathways involving cytochrome P-450 isozymes, is thought to be responsible for hemolytic anemia and leukemia from exposure to benzene (ATSDR 1997a) genotoxic effects and cancer from exposure to carcinogenic PAHs (ATSDR 19950; hemolytic anemia, ocular effects, and lung effects from naphthalene and methyl naphthalenes (ATSDR 1995e); peripheral neuropathy from *n*-hexane (ATSDR 1999b); lung effects from ethylbenzene (ATSDR 1999a); and $\alpha_{2\mu}$-globulin nephropathy (which is unique to male rats) from hydrocarbons in gasoline (ATSDR 1995a).

6.5.3 Animal-to-Human Extrapolations

Rats and mice are much less sensitive than humans to the hemolytic effects of naphthalene. The dog appears to be a better model for humans for this effect (ATSDR 1995e).

Inhalation or oral exposure to a number of the individual constituents of the TPH fractions (particularly branched-chain alkanes) and also the petroleum products whose composition is similar to these fractions (e.g., JP-5, JP-7, and the dearomatized streams) induces a hydrocarbon-related nephropathy unique to male rats (ATSDR 1995c, 1995g, 1998b; TPHCWG 1997c). This lesion involves the formation of hyaline droplets in the cytoplasm of the proximal tubule cells of the cortex. The hyaline droplets contain high concentrations of the protein $\alpha_{2\mu}$-globulin, a protein found in male rats but not in humans. A likely mechanism for this accumulation is the slowing of the degradation of $\alpha_{2\mu}$-globulin as a result of binding with specific substances, such as petroleum hydrocarbons or their metabolites. Single cell necrosis and exfoliation of the proximal tubular epithelium occurs, and the tubules near the cortico-medullary junction become dilated and are eventually filled with coarsely granular casts and necrotic debris. Regenerative tubule cell proliferation and mineralization of the renal papillar tubules occurs with continued exposure. The nephropathy induced by accumulation of this protein has not been noted in female rats, in male rats that lack the ability to synthesize $\alpha_{2\mu}$-globulin, or in other species. Thus, it does not appear that the nephrotoxicity attributable to the $\alpha_{2\mu}$-globulin syndrome observed in male rats is relevant to humans.

Food grade and medicinal mineral oils which correspond to the aliphatic $EC_{>16}$-EC_{35} fraction of TPH produce liver granulomas in F344 rats. These granulomas are reactive, with associated inflammation and occasional parenchymal cell necrosis. The inflammatory effects are not seen in dogs, mice, or Long-Evans

or Sprague-Dawley rats fed comparable doses of similar mineral oils, according to TPHCWG (1997c). In addition, humans, who are exposed to mineral oils in the diet and by intentional ingestion of medicinal mineral oils, develop granulomas, but without evidence of inflammation or significant liver dysfunction. Whether the exposure levels for humans are comparable to those tested in experimental animals is not known. Nevertheless, the issue has been raised that F344 rats may be uniquely predisposed to the development of inflammatory granulomatous lesions, and that this difference in sensitivity may justify use of a smaller uncertainty factor in extrapolating from the F344 rat to humans (TPHCWG 1997c).

6.6 SELECTION OF FRACTION-SPECIFIC HEALTH EFFECTS CRITERIA

6.6.1 Overview

The focus of this section is the selection, when possible, of appropriate MRLs for the assessment of health effects of the aromatic and aliphatic fractions of TPH. Approaches to cancer assessment are also discussed. The TPH fractions are environmental transport fractions, as suggested by the TPHCWG (1997c), with a slight modification to include all the BTEXs in a redefined aromatic EC_5-EC_9 fraction.

Other agencies have addressed the problem of selection of health effects criteria for fractions or representative constituents of TPH (ASTM 1995; Hutcheson et al. 1996; TPHCWG 1997c), and their approaches were carefully evaluated during the preparation of this profile, as discussed in Sections 6.1 and 6.2. Nevertheless, ATSDR's concerns and mandate encompass a broader range of exposure periods than those of the other agencies, and ATSDR health criteria are developed somewhat differently and for a slightly different purpose. These issues were discussed in Section 6.1 and 6.2.

Tables 6-l and 6-2 summarize the suggested fraction-specific MRLs for inhalation and oral exposure. These fraction-specific MRLs are provisional values, reflecting the uncertainty inherent in this approach (see Section 6.6.2 for a more complete discussion). As with any ATSDR MRL, the MRLs in Tables 6-l and 6-2 are intended to serve as health guidance values and are not to be used to define clean-up or action levels. Information listed in brackets in Table 6-2 is from sources other than ATSDR toxicological profiles. This information indicates potentially sensitive end points but does not have the same level of confidence as information from the ATSDR toxicological profiles. Additional details and tables listing all the candidate MRLs and relevant cancer assessments are presented in Section 6.6.2. Chapter 7 also

Table 6-1. Fraction-Specific Provisional Inhalation MRLs and Critical Effects

Fraction	Indicator or surrogate compound or mixture	Acute MRL		Intermediate MRL		Chronic MRL	
		ppm	Effect	ppm	Effect	ppm	Effect
Aromatic							
EC_5–EC_9: Indicator Compounds	Benzene	0.05	Immunological/ lymphoreticular	0.004	Neurological	—	—
	Toluene	3	Neurological	—	—	1	Neurological
	Ethylbenzene	—	—	0.2	Developmental	—	—
	Xylene	1	Neurological	0.7	Developmental (neurological)	0.1	Neurological
$EC_{>9}$–EC_{16}	Naphthalene	—	—	—	—	0.002	Respiratory
$EC_{>16}$–EC_{35}	No data	—	—	—	—	—	—
Aliphatic							
EC_5–EC_8	n-Hexane	—	—	—	—	0.6	Neurological
$EC_{>8}$–EC_{16}	JP-5 and 8 JP-7	—	—	3 mg/m^3	Hepatic	0.3 mg/m^3	Hepatic
$EC_{>16}$–EC_{35}	No data	—	—	—	—	—	—

EC = Equivalent Carbon Number Index; MRL = minimal risk level

Source: Appendix A. MRLs and critical effects are summarized in Appendix A of this profile. Additional information is available in the profile for each compound (e.g., ATSDR. 1999b. Toxicological profile for hexane).

Table 6-2. Fraction-Specific Provisional Oral MRLs and Critical Effects[a]

Fraction	Indicator or surrogate compound or mixture	Acute MRL		Intermediate MRL		Chronic MRL	
		mg/kg/day	Effect	mg/kg/day	Effect	mg/kg/day	Effect
Aromatic							
EC_5–EC_9: Indicator Compounds	Benzene	—	—	—	—	—	—
	Toluene	0.8	Neurological	0.02	Neurological	—	—
	Ethylbenzene	—	—	—	—	—	—
	Xylene, mixed	—	—	0.2	Renal	—	—
	Xylene, *m*-	—	—	0.6	Hepatic	—	—
	Xylene, *p*-	1	Neurological	—	—	—	—
$EC_{>9}$–EC_{16}	Naphthalene	0.05	Neurological	0.02	Hepatic	—[a]	—
$EC_{>16}$–EC_{35}	Fluorene, fluoranthene	—	—	0.4	Hepatic	—	—
Aliphatic							
EC_5–EC_8	No data	—	—	—	—	—	—
$EC_{>8}$–EC_{16}	No ATSDR MRLs [Dearomatized petroleum streams][b]	—	—	——	[Hepatic][b]	—	—
$EC_{>16}$–EC_{35}	No ATSDR MRLs [Mineral oils C_{15}–C_{37}][b]	—	—	—	[Hepatic][b]	—	—

[a] No chronic MRL appears suitable for the assessment of health effects of the aromatic $EC_{>9}$-EC_{16} fraction as a whole, but a chronic MRL of 0.07 mg/kg/day is available for 1-methylnaphthalene.

[b] Critical effects are listed in brackets for mixtures that are not the subjects of ATSDR toxicological profiles, but have been evaluated by other agencies for the purpose of deriving health effects criteria. These health effects are shown only to indicate potentially sensitive endpoints of exposure to that fraction, and do not have the same level of confidence as an ATSDR assessment.

EC = Equivalent Carbon Number Index; MRL = minimal risk level

Source: Appendix A. MRLs and critical effects are summarized in Appendix A of this profile. Additional information is available in the profile for each compound (e.g., ATSDR. 1999b. Toxicological profile for hexane).

presents MRLs for constituents and whole petroleum products and health effects criteria developed by other agencies (EPA and TPHCWG RfDs and RfCs).

6.6.2 Minimal Risk Levels, Critical Effects, and Cancer Assessments for Fractions of TPH

The information in the following text is taken from the references cited in the tables that accompany the text. For the sake of readability, the references will not be cited in the text. Additional health effects information is available in the pertinent toxicological profiles (ATSDR 1994, 1995c, 1995d, 1995e, 1995f, 1995g, 1997a, 1998b, 1999a, 1999b), TPHCWG (1997c), EPA references cited in the tables including EPA (1998b), and in Section 6.2. In order to fill data gaps, some compounds, representative mixtures, or studies that have not been assessed in ATSDR toxicological profiles are listed, with the critical or sensitive effects as evaluated by other agencies (EPA and TPHCWG) shown in brackets. This was done to give a more complete picture of the potential health effects of fraction constituents, to aid in judging whether the available MRLs may be useful in assessing health effects of the entire fraction.

Aromatic EC_{5-9} Fraction: Indicator Compounds. This fraction consists of benzene, toluene, ethylbenzene and the xylenes (the BTEXs).

Inhalation Exposure. The available inhalation MRLs for each of the BTEXs, and the EPA cancer risk for benzene, can be used to assess the potential for health effects for each of these indicator compounds individually. This is consistent with current practice. These MRLs and their associated effects, as well as the EPA cancer assessments, are summarized in Table 6-3. Health effects that are common to the BTEXs are neurological effects. Developmental effects appear to be a sensitive effect of inhalation exposure to ethylbenzene and xylene. Benzene has hematological and immunological/lymphoreticular effects and is classified in EPA Group A (human carcinogen).

Oral Exposure. The oral MRLs for each of the BTEXs, and the EPA cancer risk for benzene, can be used to assess the potential for health effects for each of these compounds individually. No oral MRLs exist for ethylbenzene, but the limited oral data for this compound are reasonably similar to those for toluene. These MRLs and their associated effects, and the available EPA cancer assessments, are summarized in Table 6-4. Effects of oral exposure to these compounds are similar to those of inhalation exposure. In addition, renal and hepatic effects appear to be sensitive effects of xylene exposure.

Table 6-3. Inhalation MRLs, Critical Effects, and EPA Cancer Assessments for Aromatic EC_5–EC_9 Fraction

C	EC	Compound	ATSDR Toxicological Profile	Acute		Intermediate		Chronic		
				MRL		MRL		MRL		EPA Cancer WOE, risk per 1 ppm[a]
				ppm	Effect	ppm	Effect	ppm	Effect	
6	6.5	Benzene	1997a	0.05	Immunological/ lymphoreticular	0.004	Neurological	–	–	A, $2.7x10^{-2}$
7	7.58	Toluene	1994	3	Neurological	–	–	1	Neurological	D, NA
8	8.5	Ethylbenzene	1999a	–	–	0.2	Developmental	–	–	D, NA[b]
8	8.6–8.81	Xylene, mixed	1995d	1	Neurological	0.7	Developmental (neurological)	0.1	Neurological	D, NA

[a] EPA cancer WOE and risk are from the cited ATSDR toxicological profile and/or IRIS (EPA 1998b).

[b] EPA Classification in Group D (EPA 1998b) occurred prior to publication of chronic inhalation study of ethylbenzene (NTP 1996). ATSDR (1999a) notes that this classification is likely to change in the near future because the NTP study provides evidence of carcinogenicity (renal and testicular) in male rats and suggestive evidence in female rats and male and female mice.

C = carbon number; EC = Equivalent Carbon Number Index; MRL = minimal risk level; NA = not applicable; WOE = weight-of-evidence classification for carcinogenicity

Table 6-4. Oral MRLs, Critical Effects, and EPA Cancer Assessments for Aromatic EC_5 - EC_9 Fraction

C	EC	Compound	ATSDR Toxicological Profile	Acute		Intermediate		Chronic		
				MRL		MRL		MRL		EPA Cancer WOE, risk per mg/kg/day[a]
				mg/kg/day	Effect	mg/kg/day	Effect	mg/kg/day	Effect	
6	6.5	Benzene	1997a	–	–	–	–	–	–	A, $2.9x10^{-2}$[b]
7	7.58	Toluene	1994	0.8	Neurological	0.02	Neurological	–	–	D, NA
8	8.85	Ethylbenzene	1999a	–	–	–	–	–	–	D, NA[c]
8	8.6–8.81	Xylene, mixed	1995d	–	–	0.2	Renal	–	–	D, NA
8	8.6	Xylene, *-m*	1995d	–	–	0.6	Hepatic	–	–	–
8	8.61	Xylene, *p-*	1995d	1	Neurological	–	–	–	–	–

[a] EPA cancer WOE and risk are from the cited ATSDR toxicological profile and/or IRIS (EPA 1998b).

[b] Dose levels associated with excess cancer risks of 10^{-4}, 10^{-5}, 10^{-6}, and 10^{-7} have been calculated to be $3x10^{-3}$, $3x10^{-4}$, $3x10^{-5}$, and $3x10^{-6}$ mg/kg/day, respectively.

[c] EPA Classification in Group D (EPA 1998b) occurred prior to publication of a chronic inhalation study of ethylbenzene (NTP 1996). ATSDR (1999a) notes that this classification is likely to change in the near future because the NTP study provides evidence of carcinogenicity (renal and testicular) in male rats and suggestive evidence in female rats and male and female mice.

C = carbon number; EC = Equivalent Carbon Number Index; MRL = minimal risk level; NA = not applicable; WOE = weight-of-evidence classification for carcinogenicity

Aromatic $EC_{>9}$-EC_{16} Combined Fraction. The combined fraction consists of the following three fractions:

$EC_{>9}$-EC_{10} : a variety of alkylbenzenes (propyl-, methylethyl, trimethyl, and branched-chain butyl)

$EC_{>10}$-EC_{12}: a few alkylbenzenes (*n*-butyl-, *n*-pentyl-, a trimethyl-, and other multisubstituted), indans, and naphthalene

$EC_{>12}$-EC_{16}: a few longer chain and multi-substituted alkylbenzenes; biphenyls, methyl naphthalenes, and some smaller PAHs.

Inhalation Exposure. A chronic inhalation MRL is available for naphthalene; this MRL is listed in Table 6-5. There are no other inhalation MRLs for this fraction. All of the compounds in this fraction that have EPA carcinogenicity assessments have been classified in group D (not classifiable as to human carcinogenicity). Given the few health effects benchmarks available for the constituents of this fraction, and the general paucity of inhalation data for this fraction (see Section 6.2.2.1), selection of surrogate values for the combined fraction is problematic. Health effects that appear to be common to the compounds in this fraction are respiratory irritant effects, neurological effects, and renal effects, but it is not clear that they are common to all, or even that adequate investigation of respiratory or neurological effects was conducted for all compounds in the table. Based on some commonality of effect, the chronic MRL of 0.002 ppm for naphthalene could be adopted as a surrogate value for the combined fraction as a provisional measure. Great uncertainties are attendant on this selection, but the alternative is to disregard the potential for health effects of much of the mass of this fraction.

Oral Exposure. The only MRLs available for this fraction are acute and subchronic MRLs for naphthalene, an intermediate MRL for acenaphthene, and a chronic MRL for l-methyl naphthalene; these MRLs are listed in Table 6-6. Although more health effects data are available for oral exposure than for inhalation exposure to the constituents of this fraction, selection of surrogate values to use for oral exposure to this fraction is problematic. The acute and intermediate MRLs for naphthalene, 0.05 and 0.02 mg/kg/day, are equivalent to or lower than any other MRLs for this fraction, including the chronic MRL for l-methyl naphthalene. The compounds in this fraction tend to cause hepatic and renal effects. Naphthalene and l-methyl naphthalene have respiratory effects following oral exposure; it is expected that

Table 6-5. Inhalation MRLs, Critical Effects, and EPA Cancer Assessments for Aromatic $EC_{>9}$–EC_{16} Fraction

C	EC	Compound or mixture	ATSDR Toxicological Profile	Acute		Intermediate		Chronic		
				MRL		MRL		MRL		EPA Cancer WOE, risk per ppm[a]
				ppm	Effect	ppm	Effect[a]	ppm	Effect	
$EC_{>9}$-EC_{10}										
9	9.13	Isopropylbenzene (cumene)	–	–	–	–	[Renal and endocrine][b]	–	–	D, NA[b]
9 (8-10)	9.47–9.84 (8.81–0.52)	C_9 Aromatics: High flash aromatic naphtha[c]	–	–	–	–	–	–	[Hepatic and renal][c]	–
$EC_{>10}$-EC_{12}										
10	11.69	Naphthalene	1995e	–	–	–	–	0.002	Respiratory	D, NA[d]
$EC_{>12}$-EC_{16}										
12	15.06	Acenaphthylene	1995f	–	–	–	–	–	–	D, NA

[a] EPA cancer WOE and risk are from the cited ATSDR toxicological profile and/or IRIS (EPA 1998b). Critical effects are listed in brackets for mixtures or compounds that are not the subjects of ATSDR toxicological profiles, but have been evaluated by other agencies for the purpose of deriving health effects criteria. These health effects are shown only to indicate potentially sensitive endpoints of exposure to that fraction, and do not have the same level of confidence as an ATSDR assessment.

[b] EPA (1998b) concluded that the listed effect, which occurred in a 13-week inhalation study in rats (Cushman et al. 1995), was the critical effect.

[c] A mixture composed primarily of C_9 alkylbenzenes, with approximately 80% in the EC_9–EC_{10} range and the entire mixture (identified constituents) within the ranges shown in parentheses in the table. The major constituents of the mixture are trimethylbenzenes and methylethylbenzenes. According to the TPHCWG (1997b) the listed critical effect was seen in a 1-year inhalation study in rats (Clark et al. 1989).

[d] EPA Classification in Group D occurred prior to publication of a chronic inhalation study of naphthalene in mice (NTP 1992). A 1995 note added to the carcinogenicity file on IRIS indicates naphthalene may be more appropriately classified in Group C (EPA 1998b).

C = carbon number; EC = Equivalent Carbon Number Index; MRL = minimal risk level; NA = not applicable; WOE = weight-of-evidence classification for carcinogenicity

Table 6-6. Oral MRLs, Critical Effects, and EPA Cancer Assessments for Aromatic $EC_{>9}$–EC_{16} Fraction

C	EC	Compound	ATSDR Tox. Profile	Acute		Intermediate		Chronic		
				MRL		MRL		MRL		EPA Cancer WOE, risk per mg/kg/day[a]
				mg/kg/day	Effect	mg/kg/day	Effect[a]	mg/kg/day	Effect[a]	
$EC_{>9}$-EC_{10}										
9	9.13	Isopropylbenzene (cumene)	–	–	–	–	[Renal][b]	–	–	D, NA
9	9.62	1,3,5-Trimethyl-benzene	–	–	–	–	[Hepatic, renal, other][c]	–	–	–
$EC_{>10}$-EC_{12}										
10	11.69	Naphthalene	1995e	0.05	Neurological	0.02	Hepatic	–	–	D, NA[d]
10-11	11.69-12.99	Naphthalene/ methylnaphtha-lene mixture[e]	–	–	–	–	[Hepatic, endocrine, other][e]	–	–	–
$EC_{>12}$-EC_{16}										
11	12.99	1-Methyl-naphthalene	1995e	–	–	–	–	0.07	Respiratory	–
12	14.26	Biphenyl	–	–	–	–	–	–	[Renal][f]	D, NA
12	15.06	Acenaphthylene	1995f	–	–	–	–	–	–	D, NA
12	15.5	Acenaphthene	1995f	–	–	0.6	Hepatic	–	–	–

[a] EPA cancer WOE and risk are from the cited ATSDR toxicological profile and/or IRIS (EPA 1998b). Critical effects are listed in brackets for mixtures or compounds that are not the subjects of ATSDR toxicological profiles, but have been evaluated by other agencies for the purpose of deriving health effects criteria. These health effects are shown only to indicate potentially sensitive endpoints of exposure to that fraction, and do not have the same level of confidence as an ATSDR assessment.

[b] EPA (1997a, 1998b) concluded that the listed effect, which occurred in a 194-day oral study of isopropylbenzene in rats, was the critical effect.

[c] EPA (1996b) concluded that the listed effect, seen in a 90-day oral study in rats, was the critical effect.

[d] EPA Classification in Group D occurred prior to publication of chronic inhalation study of naphthalene in mice (NTP 1992). A 1995 note added to the carcinogenicity file on IRIS indicates naphthalene may be more appropriately classified in Group C (EPA 1998b).

[e] The TPHCWG (1997b) concluded that the listed effect, observed in an unpublished 13-week oral study of a mixture of naphthalene and methylnaphthalenes, was the critical effect. The composition of the mixture was not further specified. The above C and EC values assume the mixture contained naphthalene and *mono*methylnaphthalenes).

[f] According to EPA (1998b), the listed effect, seen in a lifetime oral study of 1,1,-biphenyl in rats, was the critical effect.

C = carbon number; EC = Equivalent Carbon Number Index; MRL = minimal risk level; NA = not applicable; WOE = weight-of-evidence classification for carcinogenicity

2-methyl naphthalene will as well. Neurological effects have been seen from acute exposure to naphthalene, and would also be expected with the alkyl benzenes, based on the inhalation data. Thus, there is some commonality in the health effects. Naphthalene appears to be one of the more toxic constituents of this fraction, so adoption of the MRLs for naphthalene as surrogate values for the entire mass of this fraction should be relatively protective. There is no chronic MRL for naphthalene, however, and the chronic MRL for l-methyl naphthalene (0.07 mg/kg/day) is similar to, but slightly higher than the intermediate MRL for naphthalene.

Aromatic $EC_{>16}$- EC_{35} Combined Fraction. The combined fraction consists of the following two fractions:

$EC_{>16}$- EC_{21}: anthracene, fluorene, phenanthrene, pyrene and other less well-known PAHs

$EC_{>21}$- EC_{35}: benz(a)anthracene; benzo(b)-, benzoCj)- and benzo(k)fluoranthene; benzo(g,h,i)perylene; benzo(a)- and benzo(e)pyrene; chrysene; dibenz(a,h)anthracene; fluoranthene; and indeno(1,2,3-c,d)pyrene, and other less well-known PAHs.

Inhalation Exposure. Very few health effects data for inhalation exposure and no inhalation MRLs are available for this fraction. Given the nonvolatile nature of these compounds, inhalation exposure as a result of contamination at hazardous waste sites would be anticipated to occur only through exposure to dust or particles containing PAHs.

Oral Exposure. The limited oral data for these PAHs indicate that hepatic effects are a common sensitive effect; renal effects have been seen with some. Intermediate MRLs of 0.4 mg/kg/day have been derived for fluorene and fluoranthene and of 10 mg/kg/day for anthracene; these are listed in Table 6-7. All of the commonly studied PAHs in the $EC_{>16}$-EC_{21} portion of the combined fraction have been classified in Group D (not classifiable as to human carcinogenicity). Many of the commonly studied PAHs in the $EC_{>21}$-EC_{35} portion of the combined fraction have been classified in Group B2 (probable human carcinogen). An intermediate MRL of 0.4 mg/kg/day was selected as a surrogate value for the combined fraction and should be applied to the non-carcinogenic PAHs in this fraction. A method for assessing the potential carcinogenic effects of these PAHs would be to use the EPA cancer risk levels for benzo(a)pyrene and the relative potency factors for the individual PAHs (Table 6-7).

Table 6-7. Oral MRLs, Critical Effects, and EPA Cancer Assessments for Aromatic $EC_{>16}$–EC_{35} Fraction[a]

C	EC	Compound	Acute		Intermediate		Chronic		
			MRL		MRL		MRL		EPA Cancer WOE, risk per mg/kg/day[b]
			mg/kg/day	Effect	mg/kg/day	Effect[b]	mg/kg/day	Effect	
$EC_{>16}$-EC_{21}									
13	17	Fluorene	–	–	0.4	Hepatic	–	–	D, NA
14	19	Phenanthrene	–	–	–	–	–	–	D, NA
14	19	Anthracene	–	–	10	Hepatic	–	–	D, NA
16	21	Pyrene	–	–		[Renal][c]	–	–	D, NA
$EC_{>21}$-EC_{35}									
16	22	Fluoranthene	–	–	0.4	Hepatic	–	–	D, NA
18	26	Benz[a]anthracene	–	–	–	–	–	–	B2, RP=0.145
18	27	Chrysene	–	–	–	–	–	–	B2, RP=0.0044
20	30	Benzo[b]fluoranthene	–	–	–	–	–	–	B2, RP=0.167
20	30	Benzo[k]fluoranthene	–	–	–	–	–	–	B2, RP=0.020
20	31	Benzo[a]pyrene	–	–	–	–	–	–	B2, 7.3[d]; RP=1
22	34	Dibenz[a,h]anthracene	–	–	–	–	–	–	B2, RP=1.11
22	34	Benzo[g,h,i]perylene	–	–	–	–	–	–	D, NA
22	35	Indeno[1,2,3-cd]pyrene	–	–	–	–	–	–	B2, RP=0.055

[a] All the compounds in this table are PAHs, and are included in the ATSDR toxicological profile on PAHs (ATSDR 1995f).

[b] EPA cancer WOE and risk are from the cited ATSDR toxicological profile and/or IRIS (EPA 1998b). Critical effects are listed in brackets for mixtures, compounds, or studies that are not the subjects of ATSDR toxicological profiles, but have been evaluated by other agencies for the purposes of deriving health effects criteria. These health effects are shown only to indicate potentially sensitive endpoints of exposure to that fraction, and do not have the same level of confidence as an ATSDR assessment.

[c] EPA (1997a, 1998b) concluded that the listed effect was the critical effect of pyrene, based on an unpublished oral 13-week study in mice (EPA 1995f). Although pyrene is included in the ATSDR toxicological profile on PAHs, this study was not cited (ATSDR 1995f). Therefore, it appears the study was not available to ATSDR for evaluation as a potential basis for an MRL.

[d] Dose levels associated with excess cancer risks of 10^{-4}, 10^{-5}, 10^{-6}, and 10^{-7} have been calculated to be $1x10^{-5}$, $1x10^{-6}$, $1x10^{-7}$, and $1x10^{-8}$ mg/kg/day, respectively.

C = carbon number; EC = Equivalent Carbon Number Index; MRL = minimal risk level; NA = not applicable; RP = Relative potency factor = the carcinogenic potency of this compound, relative to benzo[a]pyrene, as estimated by EPA (1993c) and reported by ATSDR (1995f). EPA (1993c) also reported relative potencies rounded to an order of magnitude and recommended that these rounded potencies be used because the quality of the data and the analysis do not support greater precision; WOE = weight-of-evidence classification for carcinogenicity

Aliphatic EC_5-EC_8 Combined Fraction. The combined fraction consists of the following two fractions:

EC_5- EC_6: *n*-pentane, *n*-hexane, dimethylbutanes, and methylpentanes, cyclopentane, some alkenes

$EC_{>6}$- EC_8: *n*-heptane, *n*-octane, some branched chain C_6-C_9 alkanes including trimethylpentanes, cyclohexane, methylcyclohexane, other cycloalkanes, some alkenes.

Inhalation Exposure. Only one inhalation MRL, a chronic MRL for *n*-hexane, is available for this combined fraction; this is listed in Table 6-8. *n*-Hexane produces a characteristic peripheral nephropathy in humans and animals; the chronic MRL is based on this effect in humans. Commercial hexane, which contains *n*-hexane plus other C_6 branched chain and cyclic alkanes (see Table 6-8), also has been shown to cause this effect in animals, due to its content of *n*-hexane (IRDC 1981) (see Section 6.2.4.1). The non *n*-hexane portion of the mixture does not. In addition, the non *n*-hexane constituents of this combined fraction do not appear to cause peripheral neuropathy when tested singly although, like *n*-hexane, they do cause neurological effects (depression of the central nervous system). *n*-Hexane and commercial hexane are respiratory irritants. Commercial hexane has undergone extensive recent testing as part of an EPA Test Rule under TSCA Section 4. However, until the database for commercial hexane can be more fully evaluated, the chronic MRL for *n*-hexane has been determined to be the most appropriate surrogate for a health guidance value for this fraction.

Oral Exposure. Health effects data regarding oral exposure to this fraction are limited and available mainly for *n*-hexane. *n*-Hexane caused peripheral neuropathy in two species of animals, indicating that effects by the oral route may be similar to those by the inhalation route. ATSDR concluded that the incompleteness of the oral database precluded derivation of oral MRLs for this compound.

Aliphatic $EC_{>8}$-EC_{16} Combined Fraction. The combined fraction consists of the following three fractions:

$EC_{>8}$- EC_{10}: *n*-nonane, *n*-decane, branched chain C_9C_{10} alkanes, substituted cycloalkanes, a few alkenes

Table 6-8. Inhalation MRLs, Critical Effects, and EPA Cancer Assessments for Aliphatic EC_5–EC_8 Fraction

C	EC	Compound	ATSDR Toxicological Profile	Acute		Intermediate		Chronic		
				MRL		MRL		MRL		EPA Cancer WOE, risk per ppm[a]
				ppm	Effect	ppm	Effect	ppm	Effect[a]	
EC_5-EC_6										
6	6	*n*-Hexane	1999b	–	–	–	–	0.6	Neurological	D, NA[b]
6	5.68–6.59	Commercial hexane[c]	(1999b)[c]	–	–	–	–	–	[Respiratory, reproductive?][c]	–[d]
$EC_{>6}$-EC_8										
7	7	n-heptane	–	–	–	–	–	–	–	D, NA
7	7.22	Methylcyclohexane	–	–	–	–	–	–	[Renal?][e]	D, NA[e]
8	6.89	2,2,4-Trimethyl-pentane	–	–	–	–	–	NV	–	–

[a] EPA cancer WOE and risk are from the cited ATSDR toxicological profile and/or IRIS (EPA 1998b), unless otherwise specified. Critical effects are listed in brackets for mixtures or compounds that are not the subjects of ATSDR toxicological profiles, but have been evaluated by other agencies for the purposes of deriving health effects criteria. These health effects are shown only to indicate potentially sensitive endpoints of exposure to that fraction, and do not have the same level of confidence as an ATSDR assessment.

[b] The WOE was determined by EPA (1989a).

[c] A mixture of C_6 alkanes, including ≈50% *n*-hexane. ATSDR (1999b) presented some toxicological data on commercial hexane, but did not consider the derivation of MRLs for this mixture. The TPHCWG (1997b) concluded that the above-listed effects were the critical effects, based on abstracts of unpublished 2-year inhalation studies of commercial hexane in rats and mice (Daughtrey et al 1994; Kelly et al 1994), which were not cited by ATSDR (1999b). The commercial hexane contained 53% n-hexane, 16% 3-methylpentane, 14% methylcyclopentane, 12% 2-methylpentane, 3 % cyclohexane, 1% 2,3-dimethylbutane, and <1% other constituents. The NOAELs chosen by the TPHCWG as the basis for the RfCs appear to be higher than the LOAELs for maternal toxicity in mice and rats in inhalation developmental toxicity studies (Bushy Run 1989a, 1989b). In addition, unpublished 26-week inhalation studies of a mixture of C_6 hexanes of approximately the same composition reported histopathologic evidence of peripheral neuropathy at a duration-adjusted LOAEL lower than the LOAELs in the 2-year studies (IRDC 1981). Thus, the conclusions of the TPHCWG regarding the critical effect need additional evaluation.

[d] Abstracts of unpublished chronic inhalation carcinogenicity studies of commercial hexane in rats and mice report evidence of carcinogenicity in female mice (Daughtrey et al. 1994; Kelly et al. 1994).

[e] Although EPA (1989c, 1997a) concluded that the critical effect of inhalation exposure methylcyclohexane was renal effects in male rats in a 1-year inhalation study with a postexposure observation period (Kinkead et al 1985), the effects appear to have been associated with $\alpha_{2\mu}$-globulin nephropathy, and thus may not be relevant to human health. The WOE was determined by EPA (1989c).

C = carbon number; EC = Equivalent Carbon Number Index; MRL = minimal risk level; NA = not applicable; NV = not verifiable; the health effects data for this compound were reviewed by the EPA RfD/RfC Work Group and determined to be inadequate for the derivation of an RfC (EPA 1998b); WOE = weight-of-evidence classification for carcinogenicity

$EC_{>10}$- EC_{12} and $EC_{>12}$- EC_{16}: longer chain *n*-alkanes; probably larger branched and cyclic alkanes, but EC values not provided (TPHCWG 1997a).

Inhalation Exposure. Health effects data are available for inhalation exposure to some petroleum products corresponding to this combined fraction. Intermediate MRLs of 3 mg/m^3 for JP-5 and JP-8 and 0.01 mg/m^3 for kerosene, and a chronic MRL of 0.3 mg/m^3 for JP-7 have been derived; these are listed in Table 6-9. These four fuels are similar in composition, consisting primarily of aliphatics in the C_9-C_{16} range. All contain some significant aromatic components. In addition, health effects data from studies of two dearomatized petroleum streams have been evaluated by the TPHCWG (1997c). The sensitive effect for exposure to all these products is hepatic. The effect for kerosene, however, was a decrease in blood glucose levels, attributed to hepatic effects. The MRL for kerosene, based on this effect, appears to involve greater uncertainty as to the toxicological significance of the effect. As a result, the intermediate MRL of 3 mg/m^3 and chronic MRL of 0.3 mg/m^3 for the jet fuels have been determined to be the most appropriate surrogate values for the assessment of health effects due to exposure to this fraction.

Oral Exposure. Limited data are available for health effects of oral exposure to this combined fraction. Three studies of dearomatized petroleum streams have been evaluated by the TPHCWG (1997c) for use in RfD derivations, but these studies are unpublished and unreferenced. In addition, a study of JP-8 (Mattie et al. 1995) was used for RfD derivation by the TPHCWG (1997c). The critical effects are listed in Table 6-10. There are no MRLs relevant to this fraction. The sensitive effect of the dearomatized streams was hepatic. Some slight indications of hepatic effects were also seen in the study of JP-8, but no histopathological effects or changes in absolute organ weight.

Aliphatic $EC_{>16}$- EC_{35} Combined Fraction. The combined fraction consists of the following fractions:

$EC_{>16}$- EC_{21}: *n*-hepta-, *n*-octa-, and *n*-nonadecane, *n*-eicosadecane, and probably branched and cyclic alkanes

$EC_{>21}$- EC_{35}: longer chain *n*-alkanes and probably branched and cyclic alkane

Table 6-9. Inhalation MRLs, Critical Effects, and EPA Cancer Assessments for Aliphatic $EC_{>8}$–EC_{16} Fraction

C	EC	Compound or Mixture	ATSDR Toxicological Profile	Acute		Intermediate		Chronic		
				MRL		MRL		MRL		EPA Cancer WOE, risk per mg/m^{3a}
				mg/m^3	Effect	mg/m^3	Effect[a]	mg/m^3	Effect	
10–11	–	C_{10}–C_{11} Iso-paraffinic solvent[b]	–	–	–	–	[Hepatic, adaptive][b]	–	–	–
7–11	–	Dearomatized white spirit[c]	–	–	–	–	[Hepatic, adaptive][c]	–	–	–
≈9–16	–	JP-7	1995c	–	–	–	–	0.3	Hepatic	–
9–16	–	JP-5, JP-8[d]	1998b	–	–	3[d]	Hepatic	–	–	–
9–16	–	Kerosene	1995g	–	–	0.01	Metabolic (hepatic)	–	–	–

[a] EPA cancer WOE and risk are from the cited ATSDR toxicological profile and/or IRIS (EPA 1998b). Critical effects are listed in brackets for mixtures or compounds that are not the subjects of ATSDR toxicological profiles, but have been evaluated by other agencies for the purposes of deriving health effects criteria. These health effects are shown only to indicate potentially sensitive endpoints of exposure to that fraction, and do not have the same level of confidence as an ATSDR assessment.

[b] A mixture composed of C_{10}–C_{11} branched-chain alkanes. According to the TPHCWG (1997b), the listed effect, seen in a 12-week inhalation study in rats (Phillips and Eagan 1984), was adaptive rather than adverse.

[c] A mixture composed of C_7–C_{11} branched, straight, and cyclic alkanes. According to the TPHCWG (1997b), the listed effect, seen in a 12-week inhalation study in rats (Phillips and Eagan 1984), was adaptive rather than adverse.

[d] The intermediate inhalation MRL was derived for JP-5 and JP-8 based on a study of JP-5.

C = carbon number; EC = Equivalent Carbon Number Index; MRL = minimal risk level; NA = not applicable; WOE = weight-of-evidence classification for carcinogenicity

Table 6-10. Oral MRLs, Critical Effects, and EPA Cancer Assessments for Aliphatic $EC_{>8}$–EC_{16} Fraction

C	EC	Compound or mixture	ATSDR Toxicological Profile	Acute		Intermediate		Chronic		
				MRL		MRL		MRL		EPA Cancer WOE, risk per mg/kg/day[a]
				mg/kg/day	Effect	mg/kg/day	Effect[a]	mg/kg/day	Effect	
9–12	–	C_9–C_{12} Dearomatized aliphatic[b]	–	–	–	–	[Hepatic][b]	–	–	–
10–13	–	C_{10}–C_{13} Dearomatized aliphatic[c]	–	–	–	–	[Hepatic][c]	–	–	–
11–17	–	C_{11}–C_{17} Isoparaffinic solvent[d]	–	–	–	–	[Hepatic][d]	–	–	–

[a] EPA cancer WOE and risk are from the cited ATSDR toxicological profile and/or IRIS (EPA 1998b). Critical effects are listed in brackets for mixtures or compounds that are not the subjects of ATSDR toxicological profiles, but have been evaluated by other agencies for the purposes of deriving health effects criteria. These health effects are shown only to indicate potentially sensitive endpoints of exposure to that fraction, and do not have the same level of confidence as an ATSDR assessment.

[b] A mixture composed of C_9–C_{12} branched, straight, and cyclic alkanes. The TPHCWG (1997c) concluded that the listed effect, which occurred in an unpublished and unreferenced 90-day oral study of this mixture in rats, was the critical effect.

[c] A mixture composed of C_{10}–C_{13} branched, cyclic, and straight alkanes. The TPHCWG (1997b) concluded that the listed effect, which occurred in an unpublished and unreferenced 13-week oral study of this mixture in rats, was the critical effect.

[d] A mixture composed of C_{11}–C_{17} branched and cyclic alkanes. The TPHCWG (1997b) concluded that the listed effect, seen in an unpublished and unreferenced 90-day oral study of this mixture in rats, was the critical effect.

C = carbon number; EC = Equivalent Carbon Number Index; MRL = minimal risk level; NA = not applicable; WOE = weight-of-evidence classification for carcinogenicity

Inhalation Exposure. No information was located on the health effects of inhalation exposure to compounds or mixtures of petroleum hydrocarbons that fall within this fraction.

Oral Exposure. No pertinent assessments by ATSDR exist, but studies of mixtures of mineral oil hydrocarbons have been evaluated by the TPHCWG (for use in deriving RfDs for this fraction). Table 6-l 1 summarizes the pertinent information. The critical effect of these mineral oils was judged to be hepatic.

6.7 RELEVANCE TO PUBLIC HEALTH

This profile covers total petroleum hydrocarbons (TPH), which is defined as the measurable amount of petroleum-based hydrocarbon in an environmental medium (Chapter 2). TPH is measured as the total quantity of hydrocarbons without identification of individual constituents. Sources of TPH contamination in the environment range from crude oil, to fuels such as gasoline and kerosene, to solvents, to mineral- based crankcase oil and mineral-based hydraulic fluids. These products contain not only a large number and variety of petroleum hydrocarbons, but also other chemicals that, strictly speaking, are not the subject of this profile, such as non-hydrocarbon additives and contaminants. The TPH issue is further complicated by the number of petroleum-derived hydrocarbons that have been identified-more than 250-and the variability in composition of crude oils and petroleum products (see Section 3.2 and Appendices D and E for details).

Following a spill, leak, or other release of a petroleum product into the environment, changes occur in the location and composition of the released hydrocarbons, as described in Section 5.3. The smaller molecular weight hydrocarbons, which tend to have relatively high vapor pressures and/or water solubilities, tend to volatilize into the air, dissolve into infiltrating rainwater or groundwater and migrate away from the release area, and biodegrade. The larger molecular weight constituents tend to sorb to soil or sediment and remain relatively immobile.

Because TPH is a complex and highly variable mixture, assessment of health impacts depends on several factors, assumptions, and circumstances. Of prime importance is the specific exposure scenario. For example, immediately following a large release of a “lighter” petroleum product (e.g., automotive gasoline), central nervous system depression could occur in people in the immediate vicinity of the spill if

Table 6-11. Oral MRLs, Critical Effects, and EPA Cancer Assessments for Aliphatic $EC_{>16}$–EC_{35} Fraction

C	EC	Compound	ATSDR Toxicological Profile	Acute		Intermediate		Chronic		
				MRL		MRL		MRL		EPA Cancer WOE, risk per mg/kg/day[a]
				mg/kg/day	Effect	mg/kg/day	Effect[a]	mg/kg/day	Effect	
15–37	–	Low MW Mineral oils[b]	–	–	–	–	[Hepatic][b]	–	–	–
27–45	–	High MW Mineral oils[c]	–	–	–	–	[Hepatic][c]	–	–	–

[a] EPA cancer WOE and risk are from the cited ATSDR toxicological profile and/or IRIS (EPA 1998b). Critical effects are listed in brackets for mixtures or compounds that are not the subjects of ATSDR toxicological profiles, but have been evaluated by other agencies for the purposes of deriving health effects criteria. These health effects are shown only to indicate potentially sensitive endpoints of exposure to that fraction, and do not have the same level of confidence as an ATSDR assessment.

[b] Five mixtures of cyclic alkanes with the following carbon ranges (15–30, 17–30, 21–35, and 22–37) and one mixture of branched chain alkanes of carbon range 18–30 were tested in a 90-day oral study in rats (Smith et al. 1996). The TPHCWG (1997b) concluded that the listed effect was the critical effect. The conclusion that one of the observed effects (mesenteric lymph node histiocytosis) was not adverse may need further evaluation, as does the existence of a LOAEL for one of these mixtures (Firriolo et al 1995) at a dose slightly lower than the NOAEL in the selected study.

[c] Two mixtures of branched-chain alkanes with carbon ranges of 27–43 and 28–45 were tested in a 90-day oral study in rats (Smith et al. 1996). The TPHCWG (1997b) concluded that the listed effect was the critical effect. The conclusion that one of the observed effects (mesenteric lymph node histiocytosis) was not adverse may need further evaluation.

C = carbon number; EC = Equivalent Carbon Number Index; MW = Molecular weight; MRL = minimal risk level; NA = not applicable; WOE = weight-of-evidence classification for carcinogenicity

they inhaled the volatilized components. In a confined or poorly ventilated area, asphyxiation would even be a concern. Contamination of groundwater and surface water with the soluble components (e.g., the BTEXs) could impact drinking water sources. Exposure to a contaminated water supply may take place over a period of weeks or years, and raises concerns for more subtle nervous system effects, developmental effects, and cancer. The less volatile or soluble constituents (such as benzo(a)pyrene) may tend to remain in the area of the release for extended periods. Even during the early stages of this release scenario, exposures will tend to be to fractions of the product (the more volatile or more soluble compounds) rather than to the whole product. Therefore, public health assessments for TPH require knowledge of the specific fractions and/or chemicals at the point of exposure (e.g., drinking water well, soil, air). These data are summarized in this toxicological profile (particularly Sections 3.2 and 6.3) and provided in more detail in the toxicological profiles on the individual components and whole products.

A central tool in ATSDR assessment of public health impacts is the minimal risk level (MRL) health guidance value. MRLs have been developed by ATSDR for many hazardous waste constituents, though no new MRLs have been developed for TPH. A limited number of existing MRLs can be applied to TPH assessment. Most are MRLs for individual TPH components (e.g., benzene); however, a few MRLs are available for whole petroleum products. MRLs for substances that represent the fractions defined by the ATSDR approach to assessing TPH health impacts are provided and discussed in this profile. In recognition of the likelihood that even acute exposures to fresh releases will be to fractions of a product, the information on pertinent fractions of TPH should also be consulted (particularly Sections 2.3, 6.1, 6.2 and 6.6).

In the case of weathered releases, the fraction approach is likely to be the most useful. Analytical methods that support the fraction approach should be chosen to characterize exposures (Section 3.3, TPHCWG approach). The identity of the original contaminating product(s) need not be known. Health effects data for these fractions are discussed in Section 6.2 and recommendations for fraction-specific MRLs and for cancer assessment are presented in Section 6.6.

The issue of exposure to complex mixtures was introduced and briefly discussed in Section 6.1.1. In Sections 6.1.2 and 6.1.3 other related TPH approaches are discussed. The ATSDR fraction approach preferentially adopts MRLs for petroleum products that are similar in composition to the transport fraction. When no such data are available, a surrogate MRL from a representative constituent of the

fraction is adopted for the entire mass of the fraction, a practice which implicitly assumes that the toxicity of the constituents of a fraction is additive. This approach is consistent with existing ATSDR and EPA guidance (ATSDR 1992; De Rosa et al. 1996; EPA 1986; Johnson and De Rosa 1995; Mumtaz et al. 1994).

Additional refinements to the fraction approach for assessing health effects include estimation of an index of concern (IOC) for the indicator compounds (the BTEXs) of the aromatic EC_5-EC_9 fraction, or to account for exposure to more than one fraction. This approach is also based on the assumption of additivity, and is reasonable for compounds or fractions that affect the same system or target organ. The IOC is the sum of the ratios of the monitored level of exposure to the accepted level of exposure for each of the constituents of a mixture:

$$IOC = E_1,/AL_1 + E_2AL_{2...} + E_i/AL_i$$

where:

E_1 = the actual exposure level to the ith component
$AL,$ = the acceptable exposure level for the ith component

The accepted levels of exposure for ATSDR assessments would be inhalation MRLs, or soil or water concentrations calculated from oral MRLs. For example, the IOC method could be applied to acute oral exposures to the aromatic EC_5-EC_9 fraction (toluene, *p*-xylene) and the aromatic $EC_{>9}$-EC_{16} fraction, for which the critical effects are neurological (Table 6-2).

Other refinements could be provided by implementing the target-organ toxicity dose approach, which attempts to estimate the plausible critical effect and IOC that would have been calculated had the particular mixture been tested (Mumtaz et al. 1994, 1997). This approach is complicated, and would be suggested only when additional assessment is needed, perhaps to resolve differences between expected and actual health effects outcomes, or where critical effects are different across constituents or fractions that make up the “mixture.”

Another complicated mixtures assessment method under investigation by ATSDR is the weight-of- evidence method for interactions (De Rosa et al. 1996; Johnson and De Rosa 1995; Mumtaz et al. 1994;

Mumtaz and Durkin 1992). This method provides adjustments to the IOC to take into account interactions between the constituents of the mixture. Application to the BTEXs, particularly benzene and toluene, for which interactions have been reasonably well characterized, may be fruitful if needed to resolve issues in a health assessment.

Regardless of the circumstances and methods, TPH health assessments are limited by data gaps in the toxicology for many of the compounds, transport fractions, and mixtures of petroleum products and wastes. The limitations of the analytical method(s) used to generate the TPH data must be understood (e.g., whether the analytical method identified transport fractions or specific compounds) (see Section 3.3). As long as the uncertainties and data limitations are recognized, the method described in Section 6.1.3 and the health effects information in Sections 6.2 and 6.3 provide general guidance for health assessments for TPH.

6.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as

copper, zinc, and selenium). Biomarkers of exposure to total petroleum hydrocarbons are discussed in Section 6.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by total petroleum hydrocarbons are discussed in Section 6.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. Biomarkers of susceptibility are discussed in Section 6.10, Populations That Are Unusually Susceptible.

More information on biomarkers of exposure and effect to specific petroleum hydrocarbons can be found in ATSDR toxicological profiles on benzene (ATSDR 1997a), toluene (ATSDR 1994), ethylbenzene (ATSDR 1999a), xylenes (ATSDR 1995d), hexane (ATSDR 1999b), naphthalene (ATSDR 1995e) and polycyclic aromatic hydrocarbons (ATSDR 1995f); information for specific petroleum products can be found in ATSDR profiles on automotive gasoline (ATSDR 1995a), fuel oils (ATSDR 1995g), jet fuels (ATSDR 1995c 1998b), mineral-based crankcase oils (ATSDR 1997c), hydraulic fluids (ATSDR 1997b), and Stoddard solvent (ATSDR 1995b).

6.8.1. Biomarkers Used to Identify or Quantify Exposure to TPH

Because of the compositional complexity of TPH, detection of specific hydrocarbons or their metabolites in biological fluids or tissues cannot be expected to provide a reliable biomarker of exposure to petroleum-derived hydrocarbons in general. However, detection of specific hydrocarbons (or their metabolites) from several aromatic and/or aliphatic fractions in biological fluids or tissues can provide reliable evidence of exposure. Examples of proposed biomarkers of exposure to petroleum products include: benzene in

exhaled air and phenol in urine to indicate exposure to gasoline (IARC 1989a), the odor of kerosene on the breath or clothing to indicate oral or dermal exposure to kerosene, and radiological findings of lung infiltrations to indicate oral or inhalation exposure to kerosene or other petroleum products (ATSDR 199.58; Snodgrass 1997). Lipid granulomatas found in autopsied livers and spleens (i.e., lipoid droplets surrounded by lymphocytes and macrophages) are thought to be caused by dietary exposure to mineral oils and waxes (Wanless and Geddie 1985; Miller et al. 1996); their detection in autopsied tissues may be useful as an index of exposure to petroleum hydrocarbons, especially hydrocarbons in the aliphatic $EC_{>16}$-EC_{35} fractions.

6.8.2 Biomarkers Used to Characterize Effects Caused by TPH

Symptoms of neurological dysfunction, such as ataxia, poor coordination and gait irregularities, are potential biomarkers of effect from acute or repeated high-level exposure to petroleum-derived hydrocarbons in the aliphatic EC_5-EC_8 and aromatic EC_5-EC_9 fractions (see ATSDR 1994, 1995a, 1995c, 1995d, 1995f, 1997a, 1998b, 1999a, 1999b). Such symptoms, while shared by many hydrocarbons in these fractions, are not specific to petroleum hydrocarbons and could indicate exposure to other substances such as halogenated hydrocarbons or neurotoxic metals. Such symptoms, however, are not expected from the low-level exposure to hydrocarbons in these fractions that is likely to be experienced by people residing in the vicinity of disposal sites contaminated with petroleum hydrocarbons.

Measurements of motor and sensory nerve conduction velocities and action potential amplitudes have been proposed as sensitive preclinical biomarkers of peripheral neuropathy in workers repeatedly exposed to *n*-hexane (ATSDR 1999b), but this effect is specific to *n*-hexane (and perhaps a few other aliphatic hydrocarbons in the EC_5-EC_8 fraction) among petroleum hydrocarbons.

Many, but not all, PAHs (aromatic $EC_{>16}$-EC_{35} hydrocarbons) are genotoxic in various test systems and carcinogenic in animal test systems. The measurement of benzo(a)pyrene-DNA adducts in human body tissues or fluids has been proposed as a biomarker of effect from exposure to combustion or pyrolytic products containing genotoxic and carcinogenic PAHs, of which benzo(a)pyrene is the most extensively studied (see ATSDR 1995f). These measurements, however, are specific to benzo(a)pyrene and do not identify the source of the benzo(a)pyrene (PAHs are ubiquitous in the environment because they are produced by the pyrolysis or combustion of any material containing hydrocarbons).

Hematological effects from exposure to hydrocarbons in the aromatic EC_5-EC_9 and $EC_{>9}$-EC_{16} fractions include hemolytic anemia from naphthalene exposure and decreased hematopoiesis and leukemia from benzene exposure. Because these effects are not specific to these hydrocarbons, frequent monitoring of blood cell counts in benzene-exposed workers has been used as a biomarker of hematotoxic effects (see ATSDR 1997a).

6.9 INTERACTIONS WITH OTHER SUBSTANCES

Individuals exposed to TPH in the environment are exposed to complex mixtures that are not generally restricted to hydrocarbons alone. It is reasonable to expect that components of such complex mixtures may interact to produce additive effects that do not influence the toxicity of individual components, and synergistic or antagonistic effects that do. Studies with the BTEXs (see ATSDR 1994, 1995d, 1997a, 1999a), with naphthalene and methylnaphthalenes (see ATSDR 1995e), with PAHs (ATSDR 1995f), and with hexane (ATSDR 1999b) indicate that competitive or non-competitive inhibitory interactions with active sites of cytochrome P-450 isozymes, epoxide hydrolases, or other enzymes can influence metabolism of individual hydrocarbons. This can lead to antagonism of toxic effects mediated by metabolic intermediates (e.g., hematopoietic and cancer effects from benzene, cancer, or genotoxic effects from carcinogenic PAHs such as benzo(a)pyrene or dibenz(a,h)anthracene; peripheral neuropathy from hexane) or synergism or potentiation of toxic effects mediated by the parent hydrocarbon (e.g., acute CNS depression from the BTEXs). In addition, inductive or enhancing effects on enzyme activities can increase metabolic rate or capacity leading to potential non-additive interactive effects on hydrocarbon toxicities: potential synergism or potentiation toxic effects with induction of enzymes catalyzing the production of toxic intermediates, and potential antagonism of toxic effects with induction of detoxifying enzymes. Given the compositional complexity of TPH mixtures that may be found in the environment, it is difficult, if not impossible, to make reliable statements predicting the magnitude and direction of specific interactions that may occur. In the face of such large uncertainty, assuming that chemicals in complex mixtures interact in an additive manner at a particular target organ may be the most reasonable approach because it is the most simple.

6.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to petroleum hydrocarbons than will most people exposed to the same level of petroleum hydrocarbons in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of petroleum hydrocarbons, or compromised function or organs affected by petroleum hydrocarbons.

Factors that inhibit or alter the activity of the mixed function oxidase enzymes may increase the risk from exposure to the indicator compounds in the aromatic EC_5-EC_9 fraction (the BTEXs), the aromatic $EC_{>16}$-EC_{35} fraction (the carcinogenic PAHs in this fraction) and a constituent of the aliphatic EC_5-EC_8 fraction (*n*-hexane). For example, concurrent alcohol consumption may increase the risk of central nervous system depression from the BTEXs, ototoxicity from toluene, and hematotoxicity from benzene. Acetone exposure may increase the risk of peripheral neuropathy of *n*-hexane. People who take haloperidol, acetaminophen, or aspirin, or who have a nutritionally inadequate diet, may also be more susceptible to the toxicity of these agents. ATSDR (1995f) noted that a substantial percentage of children consume less than the recommended dietary allowances of certain nutrients.

Other populations are unusually susceptible to the aromatic EC_5-EC_9 fraction. People with l3-thalassemia may be at risk for benzene exposure because some forms of β-thalassemia may exacerbate the adverse effects of benzene on the hematopoietic system. Children and fetuses may be at increased risk to benzene toxicity because their hematopoietic cell populations are expanding and dividing cells are at a greater risk than quiescent cells. Developmental effects in animals are the basis for intermediate inhalation MRLs for ethylbenzene and mixed xylene, indicating that the embryo/fetus may be particularly sensitive to these two BTEXs. People with subclinical and clinical epilepsy are considered at increased risk of seizures from xylene because of its central nervous system effects.

Person with inherited erythrocyte G6PD deficiency have an enhanced susceptibility to the hemolytic effects of naphthalene, a constituent of the aromatic $EC_{>9}$-EC_{16} fraction. Infants appear to be more sensitive than adults to this effect, and infants are more prone to permanent neurological damage as a consequence of the jaundice that results from the hemolysis. Naphthalene has been shown to cross the human placenta to

cause hemolysis and hemolytic anemia in the newborn infants of mothers who consumed naphthalene during pregnancy (ATSDR 1995e).

People with aryl hydrocarbon hydroxylase (AHH) that is particularly susceptible to induction may be more susceptible to the carcinogenic PAHs found in the aromatic $EC_{>16}$-EC_{35} fraction. Individuals undergoing rapid weight loss that includes loss of body fat are anticipated to be at risk because of the systemic release and activation of PAHs that had been stored in fat. People with genetic diseases that are associated with DNA-repair deficiencies (e.g., xeroderma pigmentosum, ataxia telangiectasia, familial retinoblastoma, Down's syndrome) may be more susceptible to PAH-related malignancy. Individuals who have significant exposure to ultraviolet radiation, as from sunlight, may be at increased risk of developing skin cancer from PAH exposure. The human fetus may also be particularly susceptible to PAH toxicity because of increased permeability of the embryonic/fetal blood-brain barrier and a decreased liver-enzyme conjugating function. Based on studies of benzo(a)pyrene in animals, women may be at increased risk of reproductive dysfunction following exposure to high levels of PAHs.

Individuals with impaired pulmonary function may be more susceptible to the respiratory irritant effects of the volatile petroleum hydrocarbons (primarily the aromatic EC_5-EC_9 and aliphatic EC_5-EC_9 fractions).

Additional information regarding populations unusually susceptible to the aliphatic EC_5-EC_8, $EC_{>8}$-EC_{16}, and $EC_{>16}$-EC_{35}, fractions is limited. Factors that alter the function of mixed function oxidase enzymes may increase the risk of peripheral neuropathy from exposure to *n*-hexane, a constituent of the EC_5-EC_8 fraction. A single animal study indicates that susceptibility to the neuropathic effects of *n*-hexane was more severe in young adults than in weanlings. A single study of kerosene ($EC_{>8}$-EC_{16}) in rats showed that younger animals, and particularly preweanlings, were more susceptible than older rats to the lethality of kerosene, but whether these findings for *n*-hexane and kerosene can be extrapolated to humans is uncertain. Case reports of accidental poisoning through ingestion indicate that children 5 years old or younger often mistakenly drank kerosene because it was accessible. The applicability of this scenario to hazardous waste sites is questionable.

More detailed information regarding populations that are unusually susceptible to petroleum hydrocarbons can be obtained from the ATSDR toxicological profiles (ATSDR 1994, 1995d, 1995e, 1995f, 1997a,

1998b, 1999a, 1999b) on which this section was based. Other pertinent toxicological profiles (ATSDR 1995b, 1995c, 1995g) noted a lack of information on susceptible populations.

6.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to petroleum hydrocarbons. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to petroleum hydrocarbons. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to petroleum hydrocarbons:

Snodgrass, W.R. 1997. Clinical Toxicology. In: Cassarett and Doull's Toxicology. The Basic Science of Poisons. Fifth Edition. pp. 969-986. C.D. Klaassen, M.O. Amdur, and J. Doull, eds McGraw-Hill, New York.

Friedman, P.A. 1987. Poisoning and Its Management. In: Harrison's Principles of Internal Medicine. Eleventh Edition. pp. 838-850. J.D. Jeffers, E.J. Scott and M. Ramos-Englis, eds. McGraw-Hill. New York.

Klaasen, C.D. 1996. Nonmetallic Environmental Toxicants. Air Pollutants, Solvents and Vapors, and Pesticides. In: Goodman and Gilman's The Pharmacological Basis of Therapeutics. Ninth Edition. J.G. Hardman and L.E. Limbird, eds. McGraw-Hill, New York.

Information on methods that may be effective in reducing absorption, reducing body burdens, or interfering with mechanisms of toxic action of specific petroleum hydrocarbons can be found in ATSDR profiles on the BTEXs (ATSDR 1994, 1995d, 1997a, 1999a), hexane (ATSDR 1999b), naphthalene (ATSDR 1995f), and PAHs (1995f). Additional information for petroleum products can be found in ATSDR profiles on automotive gasoline (ATSDR 1995a), fuel oils (ATSDR 19958) jet fuels (ATSDR 199512, 1998b), mineral-based crankcase oils (ATSDR 1997c) hydraulic fluids (1997b), and Stoddard solvent (ATSDR 1995b).

6.11.1 Reducing Peak Absorption Following Exposure

It is commonly recognized that, in the treatment of poisoning from ingestion of low viscosity, aliphatic or aromatic hydrocarbons found in petroleum products such as gasoline and kerosene, care must be taken to prevent aspiration into the respiratory tract (Friedman 1987; Klaassen 1996; Snodgrass 1997). Emesis, gastric lavage, and treatment with activated charcoal are often avoided unless large amounts have been ingested (>l00 mL) or there is a known risk of absorption of non-hydrocarbon additives (e.g., metals, pesticides) that may produce systemic effects. If gastric lavage is applied, an endotracheal tube with inflatable cuff is often used to prevent aspiration. Viscous, large molecular weight aliphatic hydrocarbons such as those in mineral oil, heavy lubricants, and Vaseline are not aspirated to the lung and have cathartic properties; removal treatments are not usually used. Absorption of petroleum hydrocarbons by the skin following dermal exposure can be reduced by washing with a mild soap or detergent and water, taking care not to abrade the skin.

6.11.2 Reducing Body Burden

Petroleum-derived hydrocarbons and their metabolites (e.g., fatty acids), especially those in the aliphatic and aromatic $EC_{>16}$-EC_{35} fractions, tend to accumulate in the liver, spleen, and adipose tissues. There are no known clinical methods to facilitate or accelerate removal of petroleum hydrocarbons or their metabolites from these tissues.

6.11.3 Interfering with the Mechanism of Action for Toxic Effects

Acute inhalation or aspiration of ingested aliphatic or aromatic petroleum hydrocarbons of low viscosity can lead to pulmonary irritation and hydrocarbon pneumonia, an acute hemorrhagic necrotizing disease. To counteract secondary bacterial infections and pulmonary edema, antibiotics and oxygen therapy are often applied when indicated by symptoms in particular patients (Klaassen 1996; Snodgrass 1997).

Specific aliphatic and aromatic hydrocarbons found in petroleum products are known to be-metabolized via cytochrome P-450 pathways to reactive metabolic intermediates that are thought to cause non-cancer and cancer effects from chronic exposure (e.g., peripheral neuropathy from 2,5-hexadione, a metabolite of hexane, and cancer effects from various intermediary metabolites of benzene and carcinogenic PAHs). There are no known clinical methods to interfere with these mechanisms of action. However, current research programs are studying the basis of how the consumption of cruciferous vegetables may protect

against chemical carcinogenesis, and examining the protective role that may be played by dietary antioxidants and the induction of Phase II enzymes (enzymes involved in the detoxification of products of cytochrome P-450 enzymes) (see Prochaska and Talalay 1992; Zhang et al. 1992; Talalay 1992; Fahey et al. 1997). Results from this type of research may lead to clinical methods counteracting the toxic effects of chronic exposure to bioactivated hydrocarbons.

6.12 ADEQUACY OF THE DATABASE

The adequacy of the database for many of the constituents of TPH and for petroleum products has been fully discussed in the corresponding toxicological profiles. This section will briefly discuss adequacy of the database to support a fraction-based assessment of TPH.

The database for the aromatic EC_5-EC_9 fraction is that for the individual BTEXs; the recommendation in this profile is to assess each of these compounds individually as indicator compounds. The database for inhalation exposure is more adequate than for oral exposure. Details are provided in the respective ATSDR profiles (ATSDR 1994, 1995d, 1997a, 1999a).

The database for the aromatic $EC_{>9}$-EC_{16} fraction lacks information on a mixture or mixtures that could represent the entire combined fraction. Limited inhalation data are available on a mixture of C9 aromatics (high flash aromatic naphtha, primarily $EC_{9.47}$-$EC_{9.84}$). Health effects data from these mixtures and from potential representative chemicals, including naphthalene, suggest some commonality of effect among constituents of this fraction. MRLs are available for chronic inhalation exposure and all three periods of oral exposure. Surrogate MRL values are suggested for chronic inhalation exposure and acute and intermediate oral exposure to this fraction. Nevertheless, the data do not *strongly* support a surrogate approach. Additional information on the database for naphthalene, 1- and 2-methyl naphthalene, acenaphthylene and acenaphthene is discussed in ATSDR (1995e, 1995f).

The adequacy of the database for the aromatic $EC_{>16}$-EC_{35} fraction, which consists of PAHs, is discussed in ATSDR (1995f). Data for suitable mixtures were not identified. Inhalation data for the individual constituents were particularly limited; no MRLs were available. The oral data support the selection of a surrogate MRL for intermediate exposure to the noncarcinogenic constituents of this fraction, but it is uncertain whether this value is appropriate to represent the noncancer effects of the carcinogenic PAHs.

The database for inhalation exposure to the aliphatic EC_5-EC_8 fraction includes data for a representative mixture, commercial hexane, but many of the studies were performed under a TSCA test rule and have been published only as abstracts (TPHCWG 1997c). ATSDR (1999b) briefly discussed commercial hexane in the toxicological profile on *n*-hexane, but did not consider MRL derivation for commercial hexane, as it was not the subject of the profile. The only compound or petroleum product corresponding to this fraction that has been the focus of MRL derivation by ATSDR is *n*-hexane, for which a chronic inhalation MRL is available. The data were considered inadequate for the derivation of oral MRLs for this compound (ATSDR 1999b). Details of the adequacy of the database for *n*-hexane are provided by ATSDR (1999b).

For the aliphatic $EC_{>8}$-EC_{16} fraction, the database includes a number of studies of petroleum products whose major constituents fall within the EC range of this fraction. These included dearomatized petroleum streams and fuels (JP-5, JP-7, JP-8, kerosene). Studies of the dearomatized petroleum streams are largely unpublished, include oral studies in animals, and have been reviewed by the TPHCWG (1997c). The critical effects were judged to be hepatic. MRLs were available for intermediate and chronic inhalation exposure to JP-7 and JP-5 and JP-8; these are based on hepatic effects. The MRLs for these jet fuels appeared suitable to represent the health effects of the fraction. Detailed analyses of the adequacy of the database for the fuels are provided by ATSDR (1995c, 1995g), 1998).

Mineral oils, which are petroleum products similar in composition to the aliphatic $EC_{>16}$-EC_{35} fraction, have been tested by the oral route, as reviewed by the TPHCWG (1997c); the TPHCWG based its derivation of health effects criteria on these studies. Issues regarding the TPHCWG's derivation include the classification of histiocytosis as a nonadverse effect and the suitability of the F344 rat to serve as a model for humans for this class of compounds (Section 6.2.6.2). ATSDR has not considered the health effects of these products in a toxicological profile, and there are no other petroleum products or constituents corresponding to this fraction that have MRLs.

Ongoing studies of interest are the studies performed under a Section 4 TSCA test rule of commercial hexane and of cyclohexane mentioned by the TPHCWG (1997c). In addition, the Verhaar et al. (1997) describe a proposed approach and ongoing research to develop PBPK/PD models for use in assessing human health risks from exposure to JP-5.