TOXICOLOGICAL PROFILE FOR JP-5 AND JP-8

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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UPDATE STATEMENT

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

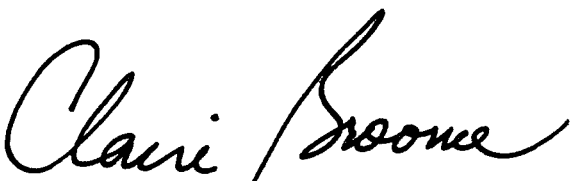
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). Section 211 of SARA also amended Title 10 of the U. S. Code, creating the Defense Environmental Restoration Program. Section 2704(a) of Title 10 of the U. S. Code directs the Secretary of Defense to notify the Secretary of Health and Human Services of not less than 25 of the most commonly found unregulated hazardous substances at defense facilities. Section 2704(b) of Title 10 of the U. S. Code directs the Administrator of the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare a toxicological profile for each substance on the list provided by the Secretary of Defense under subsection (b).

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures consistency with ATSDR policy.

2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

4. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for JP-5 and JP-8. The panel consisted of the following members:

1. Tim Borges, Ph.D., DABT, Technical Information Analyst, Clinton, TN
2. Lawrence Holland, D.V.M., Private Consultant, Los Alamos, NM
3. Edwin Kinkead, B.S., Private Consultant, Bonita Springs, FL
4. Wayne Landis, Professor, Bellingham, WA

These experts collectively have knowledge of JP-5 and JP-8's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(1)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about the jet fuels JP-5 and JP-8 and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for longterm federal cleanup activities. JP-5 and JP-8 have been found in at least 22 of the 1,445 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which JP-5 and JP-8 are found may increase. This information is important because exposure to these substances may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance or by skin contact.
If you are exposed to JP-5 and JP-8, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT ARE THE JET FUELS JP-5 AND JP-8?

Propellants are substances that move other objects or give thrust. JP-5 and JP-8 stand for jet propellant-5 and jet propellant-8. They are used by the military as aircraft fuels. JP-5 is the U.S. Navy's primary jet fuel, and JP-8 is one of the jet fuels used by the U.S. Air Force. Both JP-5 and JP-8 are colorless liquids and smell like kerosene. Kerosene is the primary substance in each. Although JP-5 and JP-8 are liquids at room temperature, they can also change into gas

vapor. Both JP-5 and JP-8 are flammable. JP-5 and JP-8 can be made from refining crude petroleum oil deposits found underground and under the ocean floor. They can also be made from shale oil found in rock. Because kerosene (which is also referred to as fuel oil no. 1) is the main part of JP-5 and JP-8, the profile sometimes uses the word kerosene and other names that it can be called instead of the words JP-5 and JP-8. In addition to kerosene, both JP-5 and JP-8 contain various additives according to standards specified by the U.S. Air Force and U.S. Navy. Other common names for JP-5, JP-8, and kerosene are these:

- fuel oil no. 1
- straight-run kerosene
- kerosine
- range oil
- Deobase (the trade name of a clear, white, deodorized kerosene)
- coal oil

In this profile, JP-5 and JP-8 are discussed together. More information on the chemical and physical properties of JP-5 and JP-8 is found in Chapter 3. More information on the production and use of JP-5 and JP-8 is found in Chapter 4.

1.2 WHAT HAPPENS TO JP-5 AND JP-8 WHEN THEY ENTER THE ENVIRONMENT?

JP-5 and JP-8 are made up of many different substances. Some of these chemicals easily evaporate into the air when jet fuels are spilled accidentally onto soils or surface waters (for example, streams, rivers, lakes, or oceans). Other chemical parts of JP-5 and JP-8 are more likely to dissolve in water following spills to surface waters or leaks from underground storage tanks. Some of the chemicals in jet fuels may slowly move down through the soil to the groundwater. Another group of chemicals in jet fuels readily attach to particles in the soil or water. Once attached in water, these particles may sink down into the sediment. The chemicals that evaporate may break down into other substances in air by reacting with sunlight (“photooxidize”) or other chemicals in the air. The chemicals that dissolve in water may also be

broken down into other substances by living organisms (primarily bacteria and fungi) in the soil or water. However, this may take many years to occur, depending on the environmental conditions. The breakdown products of JP-5 and JP-8 are not known, so it is not known whether they are toxic. Some chemicals that attach to soil or other matter (for example, marsh sediment) may remain in the environment for more than a decade. Although they make up only a tiny fraction of JP-5 and JP-8, benzene, toluene, and xylenes (single-ring aromatic compounds), as well as polycyclic aromatic hydrocarbons, are the components of JP-5 and JP-8 about which we have the greatest amount of information. These substances are toxic to humans. You can find this information in the Agency for Toxic Substances and Disease Registry's (ATSDR) toxicological profiles for these specific chemicals. See Chapters 4 and 5 for more information on what happens to JP-5 and JP-8 when they enter the environment.

1.3 HOW MIGHT I BE EXPOSED TO JP-5 AND JP-8?

It is unlikely that you will be exposed to JP-5 or JP-8 unless you work with jet fuels or live very close to where they are used or spilled. Exposure to JP-5 or JP-8 can occur if you have skin contact with soil or water contaminated from a spill or leak. You may also be exposed to JP-5 or JP-8 if you swim in waters where jet fuels have been spilled. If jet fuels have leaked from underground storage tanks and entered underground water, you may drink contaminated water from a well containing JP-5 or JP-8. You might breathe in some of the chemicals evaporating from a spill or leak site if you are in an area where an accident has occurred. Exposure to some of the components of JP-5 and JP-8 might occur from air releases if these components settle to the ground near populated areas. There are no data on the background levels of JP-5 and JP-8 that may be found in the environment.

Workers involved in making or transporting jet fuels or in refueling military aircraft that use JP-5 or JP-8 might breathe air containing these substances. Some workers may be exposed to JP-5 or JP-8 through their skin if they come into contact with them without adequate protection from gloves, boots, coveralls, or other protective clothing. For more information on how you might be exposed to JP-5 and JP-8, see Chapter 5.

1. PUBLIC HEALTH STATEMENT

1.4 HOW CAN JP-5 AND JP-8 ENTER AND LEAVE MY BODY?

JP-5 and JP-8 can enter and leave your body when you breathe them in the air, when you drink water or eat food containing them, and when your skin comes into contact with them. This can occur in the workplace or if you live near a facility where these fuels are made or near a military base. When you use kerosene or heating oil, you are exposed to some of the same substances that are found in JP-5 and JP-8. We do not know how much of these compounds might be taken up by your body if you inhale JP-5 and JP-8 vapor, drink contaminated water, or come in contact with JP-5 or JP-8. We have no information on what happens to these chemical mixtures once they enter your body. We do know that when animals were exposed to kerosene, small amounts were found in their brains, lungs, livers, spleens, and kidneys. It is not known whether kerosene would be found in these parts of the body in similarly exposed people. We do not know if JP-5 and JP-8 are broken down and leave the body primarily in the urine or the feces. The toxicological properties of JP-5 and JP-8 are very dependent upon the crude stock and batch lot. These compounds are complex and varied mixtures, and their composition may affect their toxicity. For more information on how JP-5 and JP-8 can enter and leave your body, see Chapter 2.

1.5 HOW CAN JP-5 AND JP-8 AFFECT MY HEALTH?

We know very little about the human health effects caused by JP-5 and JP-8, but some health effects might be predicted because of what we know about kerosene, the main chemical substance in these jet fuel mixtures. Many things will determine if you will be harmed by exposure to these substances, including how much you were exposed to; how long you were exposed; how you came in contact with them; and your age, sex, diet, family traits, and other factors described in the beginning of this section. Breathing in large amounts of JP-5 or JP-8 vapors or aerosol for a short time would cause you to have a suffocating feeling, and breathing would be painful. Numerous case studies have reported accidental poisoning in children as the result of drinking kerosene. Drinking kerosene may cause vomiting, diarrhea, swelling of the stomach, stomach cramps, drowsiness, restlessness, irritability, and loss of consciousness. Coughing, pneumonia, and difficult or painful breathing after drinking kerosene suggest that

kerosene has entered the lungs. In addition, drinking large amounts of kerosene can put you into a coma, cause convulsions, and may even cause death. When kerosene gets on your skin for short periods, it can make your skin itchy, red, and sore. Sometimes blisters may occur and your skin may peel.

Breathing kerosene or JP-5 vapors can also affect your nervous system. Some of the effects that have been noted in case studies include headache, lightheadedness, anorexia (loss of appetite), poor coordination, and difficulty concentrating.

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

Repeated contact with fuels such as JP-5 and JP-8 can cause skin cancer in mice. We do not know if JP-5 and JP-8 can cause cancer in humans. The International Agency for Research on Cancer (IARC) has concluded there is not enough information available to determine ifjet fuels or distillate (light) jet fuels cause cancer (Group 3 classification). However, IARC has determined that occupational exposures during petroleum refining are probably carcinogenic to humans (Group 2A classification). Exposure during petroleum refining includes exposures-to substances that are not found in JP-5 and JP-8. We do not know if JP-5 or JP-8 can cause birth defects or if they affect reproduction. See Chapter 2 for more information on the health effects of JP-5 and JP-8.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO JP-5 AND JP-8?

No medical test shows if you have been exposed to JP-5 or JP-8. Methods are available to determine if your blood contains JP-5 and JP-8 components such as benzene, toluene, and xylenes. However, the concentrations of these chemicals in fuels such as JP-5 and JP-8 are very low, and if they were detected in your blood it might not necessarily indicate that you had been exposed specifically to JP-5 and/or JP-8. In this case, it would be helpful for your doctor to know whether you might have been exposed to other chemicals. For information on tests for measuring exposure to individual components of JP-5 and JP-8, see the ATSDR toxicological profiles on benzene, toluene, xylenes, and polycyclic aromatic hydrocarbons. See Chapters 2 and 6 for information on medical tests and symptoms that suggest exposure to JP-5 and JP-8.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations a be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, Gater, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for JP-5 and JP-8 include the following:

The Department of Transportation regulates the transport of jet fuels such as JP-5 and JP-8 because they are classified as hazardous materials that are considered to pose a risk to health, safety, or property when moved. OSHA and the Air Force Office of Safety and Health (AFOSH) regulate levels of petroleum products in private sector workplaces and in Air Force workplaces, respectively. The maximum allowable amount of petroleum products in workroom air during an &hour workday, 40-hour workweek, is 400 milligrams per cubic meter (mg/m^3). ATSDR has derived an intermediate-duration inhalation minimal risk level (MRL) of 3 mg/m^3 for JP-5 and JP-8. An MRL is an estimate of daily human exposure to a substance over a specific period that is likely to be without an appreciable risk of adverse effects (noncarcinogenic). For more information on regulations and guidelines, see Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333

* Information line and technical assistance

Phone: l-800-447- 1544
Fax: (404) 639-6315 or 6324

1. PUBLIC HEALTH STATEMENT

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicolokal wofiles. contact:

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22 16 1
Phone: (800) 553-6847 or (703) 487-4650

2. HEALTH EFFECTS

2.1 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 of the toxicology of JP-5 and JP-8. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure-inhalation, oral, and dermal; and then by health effect-death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).
Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverseeffect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in

determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing no significant health risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Minimal Risk Levels or MRLs have been established for JP-5 and JP-8. 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 sufficient, reliable data exist to identify the most sensitive health effect(s) reported 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 1990), 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 may be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

There is no single formula for JP-5 and JP-8, but within certain limits the batch-to-batch differences are generally minor. The components of jet fuels are primarily aliphatic hydrocarbons of length C_8–C_{17} (NRC 1996). They are refined by a straight distillation of crude or shale oil, or by a distillation of crude or shale oil in the presence of a catalyst. The jet fuels are refined under more stringent conditions than kerosene and

contain various additives not found in kerosene. Typical additives to JP-5 and JP-8 include antioxidants (including phenolic antioxidants), static inhibitors, corrosion inhibitors, fuel system icing inhibitors, lubrication improvers, biocides, and thermal stability improvers. These additives are used in specified amounts only, as governed by commercial and military specifications. The exact composition of the jet fuel also varies depending on the crude from which it is refined. As a result of this variability, little information exists on the exact chemical and physical properties of jet fuels; however, the differences among these fuels are considered to be minor.

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to JP-5 or JP-8.

No deaths occurred in rats exposed to 5,000 mg/m^3 kerosene (physical form not specified) for 4 hours (Vemot et al. 199Oc), but only one concentration level was tested in this study. There was no treatment related lethality associated with exposure to JP-8 in an aerosol/vapor mixture when male Fischer-344 rats were exposed nose only to concentrations of either 520 mg/m^3 for 1 hour per day for 7 days or 495 mg/m^3 for 1 hour per day for 28 days (Pfaff et al. 1995). No rats died during 90-day inhalation exposures to 150 or 750 mg/m^3 JP-5 vapor (Air Force 1985; Cowan and Jenkins 1981a, 1981b; Gaworski et al. 1984). No mice died during a 90-day inhalation exposure to 150 or 750 mg/m^3 JP-5 vapor (Cowan and Jenkins 1981 a, 1981 b; Gaworski et al. 1984). One of 25 male rats exposed to 100 mg/m^3 deodorized kerosene vapor (the maximally achievable vapor concentration at standard temperature and pressure) for 6 hours per day, 5 days per week for 13 weeks, died of pneumonia (Carpenter et al. 1976). Male mice continuously exposed to airborne JP-8 for 90 days (500 or 1,000 mg/m^3) had a significantly higher mortality rate than the controls, although the study authors concluded that much of the mortality was due to necrotizing dermatitis that resulted from fighting (Mattie et al. 1991).

All LOAEL values from each reliable study for death in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2-l.

2.2.1.2 Systemic Effects

No studies were located regarding dermal effects in humans or animals after inhalation exposure to JP-5 or JP-8 fuels. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-1.

Respiratory Effects. There was no throat irritation in six volunteers following a 15minute exposure to a concentration reported to be 140 mg/m^3 of deodorized kerosene vapor (Carpenter et al. 1976). The study authors used a hot nichrome wire for the volatilization of the test material and reported that the concentration was probably the "highest attainable concentration at which vapor analysis is representative of liquid analysis." Air is substantially saturated with kerosene vapor at approximately 100 mg/m^3 (25 º C) although this is dependent upon the constituents of the mixture (Carpenter et al. 1976).

The effects of chronic exposure to jet fuels on Swedish factory workers were investigated by Knave et al. (1976,1978) and Struwe et al. (1983). They found a significant increase in coughing and a feeling of heaviness in the chests of exposed subjects when compared to unexposed controls from the same factory. The particular jet fuels to which the workers were exposed were not specified and may not have included JP-5 and JP-8, nor did the study adjust for the possible exposure to other chemicals. Inhalation exposure was likely since jet fuel vapor was detected by the authors; however, dermal and oral (i.e., from eating contaminated food) exposures could not be excluded. A jet fuel vapor concentration of 128-423 mg/m^3 and an estimated time-weighted average (WA) concentration of 250 mg/m^3 were detected in the breathing zones of the workers (Knave et al. 1978; Struwe et al. 1983). However, it was not possible to associate specific exposure concentrations with specific effects.

Limited epidemiological data suggest that chronic human inhalation exposure to kerosene vapor and/or combustion products from cooking with kerosene stoves does not induce respiratory illness. The presence of kerosene stoves in the homes of Malaysian children was not associated with chronic cough, persistent wheeze, asthma, or chest illness (Azizi and Henry 199 1). Asthmatic bronchitis and frequent common colds in 3-year-old Japanese children were not associated with the presence of kerosene stoves in their homes (Tominaga and Itoh 1985). The latter study corrected for exposure to passive smoke. These data are of limited usefulness because the duration of exposure was not reported and the levels of kerosene exposure could not be quantified. Finally, it is unclear whether kerosene exposure occurred in these individuals because it was used during cooking or because a kerosene stove was present in the home.

Table 2-1. Levels of Significant Exposure to JP-5 & JP-8 - Inhalation

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference (test substance)
					Less serious (mg/m3)	Serious (mg/m3)	
INTERMEDIATE EXPOSURE							
Systemic							
1	Rat (Harlan-Wistar)	13 wk 5 d/wk 6 hr/d	Resp	100 M			Carpenter et al. 1976 (FO1DOK)
			Cardio	100 M			
			Gastro	100 M			
			Hemato	100 M			
			Musc/skel	100 M			
			Hepatic	100 M			
			Renal	100 M			
			Other	100 M			
2	Rat (Wistar)	14 wk 6 d/wk 6 hr/d	Musc/skel	231 M			Starek and Vojtisek 1986 (Kerosene)
			Metabolic		58M (decreased blood glucose levels)		
			Other		231M (decreased metabolism of phenacetin)		

Table 2-1. Levels of Significant Exposure to JP-5 & JP-8 - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference (test substance)
3	Mouse (C57BL/6)	90 d 24 hr/d	Hepatic		150[b] F (hepatocellular fatty changes and vacuolization)		Gaworski et al. 1984 (FO1JP5)
			Other	750 F			
4	Dog (Beagle)	13 wk 5 d/wk 6 hr/d	Resp	100 M			Carpenter et al. 1976 (FO1DOK)
			Cardio	100 M			
			Gastro	100 M			
			Hemato	100 M			
			Musc/skel	100 M			
			Hepatic	100 M			
			Renal	100 M			
			Bd Wt	100 M			
	Neurological						
5	Rat (Harlan-Wistar)	13 wk 5 d/wk 6 hr/d		100 M			Carpenter et al. 1976 (FO1DOK)

Table 2-1. Levels of Significant Exposure to JP-5 & JP-8 - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference (test substance)
					Less serious (mg/m3)	Serious (mg/m3)	
6	Dog (Beagle)	13 wk 5 d/wk 6 hr/d		100 M			Carpenter et al. 1976 (FO1DOK)

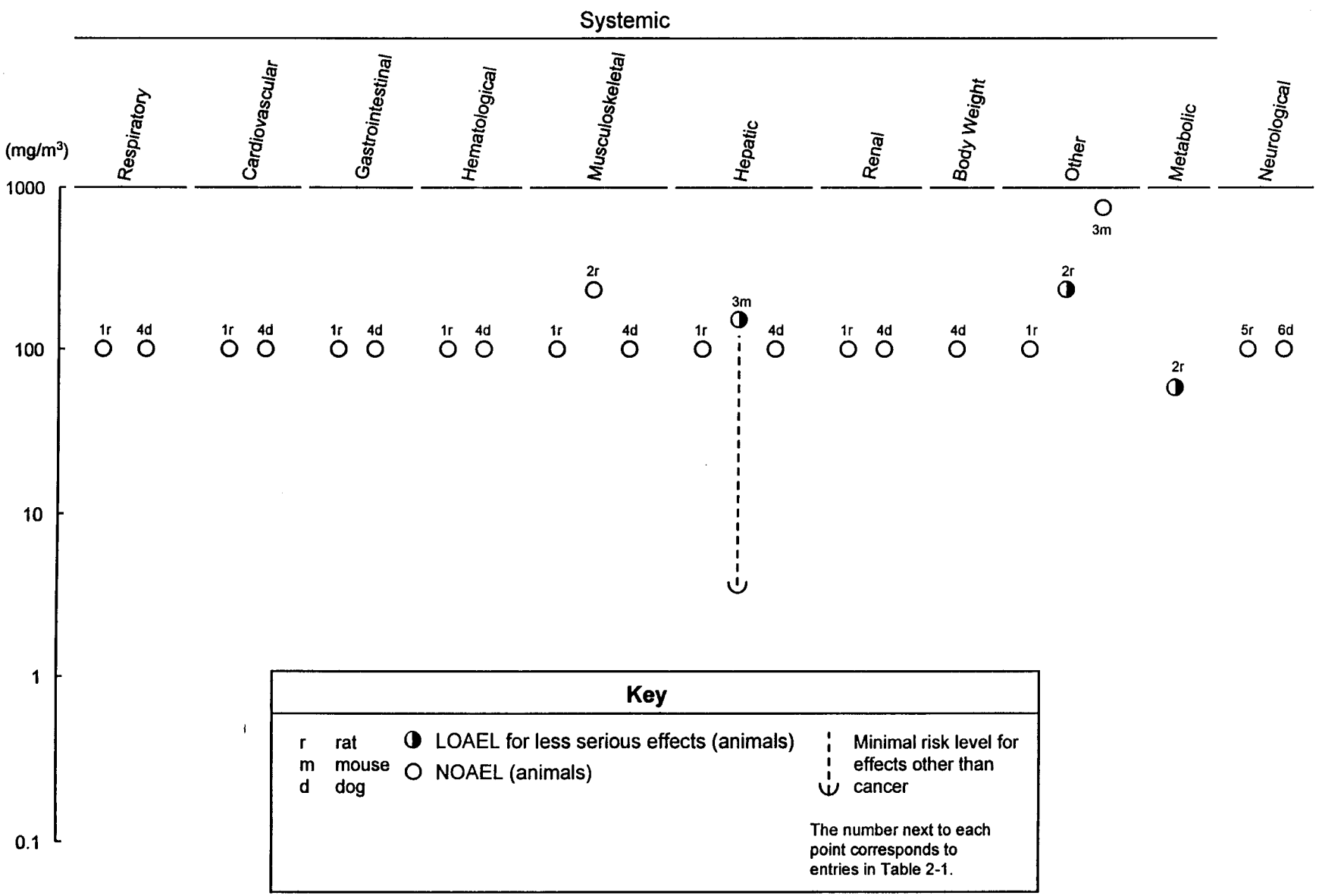
[a]The number corresponds to entries in Figure 2-1.

[b]Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 3 mg/m^3; a human equivalent exposure concentration (HEC) of 854 mg/m^3 was calculated by multiplying the mouse LOAEL by the ratio of the alveolar ventilation rate divided by the body weight of mice to the same parameters for humans ([0.04 m^3/day/0.0246 kg] / [20m^3/day/70kg]). The HEC was then divided by an uncertainty factor of 300 (10 for interspecies variability, 3 for intraspecies variability, and 10 for use of a LOAEL [less serious effect]).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); F = female; FO1DOK = deodorized kerosene; FO1JP5 = JP-5 (jet fuel); Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

Figure 2-1. Levels of Significant Exposure to JP-5 & JP-8 - Inhalation

Intermediate (15-364 days)



2. HEALTH EFFECTS

Animal data on respiratory effects following acute exposure to kerosene by inhalation are limited. Reductions in tidal volume and dynamic lung compliance, bronchoconstriction, and an increase in pulmonary resistance occurred in rabbits following inhalation of 32,500 mg/m3 kerosene aerosol for 4-9 minutes (Casaco et al. 1982). Bronchoconstriction was also induced in guinea pigs that were exposed to 20,400mg/m^3 kerosene aerosol for 5 minutes (Garcia et al. 1988b). No histopathological changes were noted in the respiratory system of rats or dogs following exposures of up to 100 mg/m3 deodorized kerosene vapor for 13 weeks (Carpenter et al. 1976).

Fischer rats exposed nose-only to approximately 497 or 520 mg/m^3 JP-8 (the physical form of the airborne JP-8 was not defined) for 1 hour per day for 7 or 28 days exhibited increased alveolar epithelial permeability,as measured by clearance of technetium-labeled diethylenetriamine pentaacetate (^{99m}TcDTPA) after 7 days. No appreciable increase occurred following further exposure (days 8-28) (Air Force 1994; Chen et al. 1992; Pfaff et al. 1995). Inspiratory dynamic compliance was also increased after 7 days, although no specific expiratory compliance or pulmonary resistance differences were found between the exposed and control rats after either 7 or 28 days (Air Force 1994; Pfaff et al. 1992a). In the same study, Fischer-344 rats exposed for 28 days exhibited significantly increased levels of substance P (a neuropeptide found in the central nervous system) and decreased levels of 6-keto-PGF_1, alpha (a stable metabolite of prostacyclin) in broncho-alveolar lavage fluid (Air Force 1994; Pfaff et al 1992b; Witten et al. 1992b). Lung epithelial permeability of Fischer-344 rats was also evaluated at two concentrations of JP-8 (500 and 800-1,100 mg/m^3; the physical form of the airborne JP-8 was not defined) for 7,28, and 56 days (Air Force 1994; Hays et al. 1994). The 56-day low-dose group had a significantly decreased ^{99m}TcDTPA clearance, while the 56-day high-dose group exhibited a significantly increased clearance. The study authors suggested that the increase at 56 days in the high-concentration group may represent an adaptive response that may include increased fibrosis of the lungs or repair to the alveolar capillary barrier (Hays et al. 1994). Pathological changes in rats exposed to 950 mg/m^3 (range, 813-1,094 g/m^3; the physical form of the airborne JP-8 was not defined) for 28 days included disruption of epithelial and endothelial structures, convoluted airways, and alveoli filled with red blood cells and fluid (Air Force 1994; Pfaff et al. 1993). Rats treated with capsaicin and subsequently exposed to 497 mg/m^3 JP-8 (the physical form of the airborne JP-8 was not defined) 1 hour per day for 7 days had a marked increase in sensitivity of the airways to histamine (Air Force 1994; Witten et al. 1992a). However, no useful information was provided on methods in these studies and the results should be viewed with caution (Air Force 1994; Chen et al. 1992; Hays et al. 1994; Pfaff et al. 1992a, 1992b, 1993; Witten et al. 1992a, 1992b).

2. HEALTH EFFECTS

Cardiovascular Effects. Mild hypertension was noted for 4 days in one of two individuals following a 1 -hour exposure to JP-5 vapor that occurred while flying a small airplane, although the concentration was not established (Porter 1990). Palpitations were noted in workers chronically exposed to jet fuel according to an epidemiological study in Swedish workers (Knave et al. 1976, 1978). The limitations of this study were discussed in detail under Respiratory Effects above.

Inhalation of kerosene aerosol by guinea pigs for 15 minutes daily for 2 1 days induced aortic plaques that resembled those seen in atherosclerosis in that species (Noa and Jllnait 1987a, 1987b). Significant increases in total serum cholesterol and decreases in high-density lipoprotein (HDL) were also noted. In these studies, only one concentration of kerosene aerosol, within a range of 20,400-34,000 mg/m^3, was tested. No significant or treatment-related microscopic or histopathological changes were noted in the heart tissue of rats or dogs exposed to up to 100 mg/m^3 deodorized kerosene (saturation concentration) for 6 hours per day, 5 days per week for 13 weeks (Carpenter et al. 1976).

Gastrointestinal Effects. One of two individuals that were exposed to JP-5 vapor for approximately 1 hour while flying a small airplane experienced nausea after landing (Porter 1990). The nausea subsided within 24 hours. Whether the nausea was related to the JP-5 exposure could not be determined. Nausea was also reported in Swedish workers chronically exposed to unspecified types of jet fuel (Knave et al. 1976).

No histopathological changes were noted in the gastrointestinal system of rats or dogs exposed to up to 100 mg/m^3 deodorized kerosene vapor for 6 hours per day, 5 days per week for 13 weeks (Carpenter et al. 1976).

Hematological Effects. No studies were located regarding hematological effects in humans after inhalation exposure to jet fuels.

No exposure-related hematological effects were noted in rats or dogs exposed to up to 100 mg/m^3 deodorized kerosene vapor for 6 hours per day, 5 days per week for 13 weeks (Carpenter et al. 1976). Beagle dogs continuously exposed to airborne JP-5 for 90 days (750 mg/m^3) exhibited a slight but statistically significant decrease in hemoglobin and red blood cell count, significant decreases in serum albumin levels, and sporadic changes in blood urea nitrogen (Air Force 1978b). Female rats exposed to 150 or 750 mg/m^3 and male rats exposed to 750 mg/m^3 had increased levels of creatinine and blood urea nitrogen (Air Force 1978b). Female beagles exposed to 750 mg/m^3 and male beagles exposed to 150 or 750 mg/m^3 exhibited an increase in red

blood cell fragility (Air Force 1978b). It should be noted that, at least at the high dose, a significant concentration of particulates was reported. This suggests that the exposure was to a combination of both vapor and aerosol.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to JP-5 or JP-8.

No histopathological changes were noted in the musculoskeletal system of rats or dogs exposed to up to 100 mg/m^3 deodorized kerosene vapor for 6 hours per day, 5 days per week for 13 weeks (Carpenter et al. 1976). Only one study of this effect was located.

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to JP-5 or JP-8.

Decreases in blood glucose levels were noted in rats after intermediate-duration inhalation exposures to a mean concentration of 58 mg/m^3 (range, 33-75 mg/m^3) kerosene vapor. Increases in blood lactate and pyruvate levels were noted at a mean concentration of 23 1 mg/m^3 (range, 183-256 mg/m^3) (Starek and Vojtisek 1986). Significant changes in blood lactate and pyruvate levels did not occur with exposures to 58 mg/m^3 kerosene. The study authors speculated that the decreased circulating glucose levels may be associated with both increased glycolysis and the inhibition of gluconeogenesis. Kerosene exposure affecting increased glycolysis is supported by the findings of increased concentrations of lactate and pyruvate in the blood and liver, as well as the increased lactate dehydrogenase activity in the liver. Further, the study authors suggest that the increased glycolysis may be the result of the inhibition of cellular respiration by kerosene. It was also noted that cellular respiration was inhibited in liver and kidney slices subsequent to the addition of kerosene to the incubation solution. Since the air saturating concentration of kerosene is approximately 100 mg/m^3, some of the exposure may have been to kerosene aerosol. Following exposure to up to 100 mg/m^3 deodorized kerosene vapor for 6 hours per day, 5 days per week for 13 weeks, no histopathological changes in the liver were noted in rats or dogs, and no liver weight changes were noted in dogs (Carpenter et al. 1976). Rats exposed to 1,100 mg/m^3 of airborne JP-5, 6 hours per day, 5 days per week for approximately 30 days, did not exhibit any significant changes in hepatic tissue morphology (Bogo et al. 1983). Significant lesions in the liver were noted in beagle dogs continuously exposed to airborne JP-5 for 90 days (150 or 750 mg/m^3). Diffuse, mild, and cloudy swelling of hepatocytes and “foamy” cytoplasm were seen microscopically. According to the study authors, the lesions were probably due to mild reversible

damage to the subcellular organelles (Air Force 1978b). Vacuolization and hepatocellular fatty changes were observed in the livers of mice exposed continuously to JP-5 at 150 mg/m^3 for 90 days (Gaworski et al. 1984). Based on this LOAEL, an intermediate-duration inhalation MRL of 3 mg/m^3 was calculated as described in the footnote to Table 2-l.

Renal Effects. Urinalyses values were within normal limits in two aviators who were exposed to JP-5 vapor for approximately 1 hour while flying a small airplane (Porter 1990).

Several studies have identified a nephropathy in male rats that is associated with exposure to hydrocarbon vapors, including some jet fuels (Air Force 1985; Bruner 1984; Cowan and Jenkins 1981a, 1981b; Gaworski et al. 1984). This hydrocarbon-induced nephropathy has only been demonstrated in adult male rats and has been linked to a specific protein, $\alpha_2\mu$-globulin, which is produced under hormonal control by the liver (Alden 1986). However, the $\alpha_2\mu$-globulin is unique to male rats and is not present in human kidneys. Hence this particular nephropathy has no significance for humans. When male rats are exposed to certain hydrocarbons, including JP-5, $\alpha_2\mu$-globulin accumulates in hyaline droplets, which can be visualized in proximal tubule cells. This buildup of $\alpha_2\mu$-globulin -containing hyaline droplets is thought to lead to cell necrosis; the cellular debris accumulates at the corticomedullary junction, causing tubule dilation and mineralization of the tubules.

Studies of 90-day continuous inhalation of 150 or 750 mg/m^3 JP-5 vapor (Air Force 1985; Bruner 1984; Cowan and Jenkins 1981 a, 1981 b; Gaworski et al. 1984) have shown that a dose-response relationship exists for multifocal tubular atrophy and focal tubular necrosis at the corticomedullary junction in male rats. Granular cysts form from the necrotic debris, which then plug and dilate the proximal tubules, resulting in chronic necrosis. In all cases of JP-5-induced male rat nephropathy, dose-dependent formation of cytoplasmic hyaline droplets in the proximal tubules of the renal cortex was prominent. Increased blood urea nitrogen and creatinine levels were found to be associated with this nephropathy in male rats following inhalation of 150 or 750 mg/m^3 JP-5 (Cowan and Jenkins 198la, 1981b). This nephropathy has also been identified in male rats exposed to JP-5 by the oral route (see the discussion of Renal Effects in Section 2.2.2.2).

The male rat nephropathy does not appear to be induced by subchronic exposures (i.e., go-day exposures) to deodorized kerosene. This lesion has not been noted in female rats, female mice (studies conducted on male mice were not located), or dogs of either sex when similarly exposed to JP-5 vapor (Air Force 1985; Bruner 1984; Cowan and Jenkins 198 1 a, 198 1 b; Gaworski et al. 1984). No histopathological changes were noted in

the renal system of rats or dogs exposed to up to 100 mg/m^3 deodorized kerosene vapor 6 hours per day, 5 days per week for 13 weeks (Carpenter et al. 1976). Rats exposed to 1,100 mg/m^3 of JP-5 vapor, 6 hours per day, 5 days per week for approximately 30 days, did not exhibit any significant changes in renal tissue morphology or urine chemistries (Bogo et al. 1983).

Male rats continuously exposed to JP-5 vapor for 90 days (150 or 750 mg/m^3) exhibited a nephropathy that was characterized by multifocal tubular atrophy and focal tubular necrosis. Tbe lesions were more severe at the 750-mg/m^3 exposure. The nephropathy was not seen in female rats or beagles similarly exposed (Air Force 1978b). It should be noted that, at least at the high dose, a significant concentration of particulates was reported. This suggests that the exposure was a combination of both vapor and aerosol.

Increased absolute and relative kidney weights were noted in male rats continuously exposed to airborne JP-8 for 90 days (500 or 1,000 mg/m^3); however, female kidney weights were unaffected. Male rats also exhibited an increase in urinary renal epithelial cell numbers. The exposed male rats developed three distinct renal effects: hyaline droplet formation, granular casts in the outer medulla, and an increase in severe lesions similar to chronic progressive nephrosis. After 2 weeks or 2 months of recovery subsequent to exposure, the hyaline droplets were no longer discernable; however, the granular casts and the nephrosis were still prominent. After 9 or 21 months of recovery, the granular casts were no longer discernable, but the nephrosis had increased in both severity and incidence, indicating that this lesion is progressive and irreversible (Mattie et al. 1991).

Ocular Effects. One case study describes eye irritation in two individuals exposed to JP-5 vapor for approximately 1 hour while flying a small airplane (Porter 1990). Although the exposure concentrations were not stated, the study author indicates that near the end of the flight, the “cockpit became overwhelmed with the odor of JP-5 fuel.” Both individuals experienced a burning sensation in their eyes, and one had itchy, watery eyes 1 day after the exposure. Hyperemic conjunctiva were also reported for one of the individuals; this effect subsided after 4 days. All effects appear to have been local in nature. Eye irritation was also noted in factory workers who were chronically exposed to jet fuel (Knave et al. 1978). The limitati&s of this study are discussed in detail in Section 2.2.1.2 (Respiratory Effects). Eye irritation was not induced in six volunteers by a 15minute exposure to 140 mg/m3 deodorized kerosene vapor (Carpenter et al. 1976).

No studies were located regarding ocular effects in animals after inhalation exposure to JP-5 or JP-8.

2. HEALTH EFFECTS

Body Weight Effects. No studies were located regarding body weight effects in humans after inhalation exposure to JP-5 or JP-8.

There was no change in body weight gain in rats exposed to up to 100 mg/m^3 deodorized kerosene vapor 6 hours per day, 5 days per week for 13 weeks (Carpenter et al. 1976). Body weight gain was decreased 57% in male mice exposed to 520 mg/m^3 JP-8 for 1 hour per day for 7 days and 37.5% in male mice exposed to 495 mg/m^3 for 1 hour per day for 28 days (Pfaff et al. 1995). There was no change in body weight gain in mice or female rats following go-day continuous inhalation exposure to 750 mg/m^3 JP-5 vapor (Air Force 1985; Gaworski et al. 1984). The growth of male rats was retarded, but that of beagles was unaffected, subsequent to continuous go-day exposure to 150 or 750 mg/m^3 of airborne JP-5 (Air Force 1978b). It should be noted that, at least at the high dose, a significant concentration of particulates was reported. This suggests that the exposure was to a combination of both vapor and aerosol. Male rats continuously exposed to airborne JP-8 for 90 days (500 or 1,000 mg/m^3) displayed a decrease in weight gain that persisted until the end of the study. Female body weights were unaffected (Mattie et al. 1991).

Metabolic Effects. There were no blood chemistry changes in either of two individuals following a 1 -hour exposure to JP-5 vapor while flying a small airplane (Porter 1990).

No significant metabolic changes in blood chemistry were noted in rats continuously exposed to airborne JP-8 for 90 days (500 or 1,000 mg/m^3) (Mattie et al. 1991). As indicated in the discussion of Hepatic Effects above, decreased blood glucose levels were noted in rats after intermediate-duration inhalation exposures to a mean concentration of 58 mg/m^3 kerosene vapor. Increases in blood lactate and pyruvate levels were noted at a mean concentration of 23 1 mg/m^3 (Starek and Vojtisek 1986).

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans after exposure to JP-5 or JP-8.

No significant or treatment-related microscopic or histopathological changes were noted in the spleen of rats or dogs exposed up to 100 mg/m^3 deodorized kerosene for 6 hours per day, 5 days per week, for 13 weeks (Carpenter et al. 1976).

2.2.1.4 Neurological Effects

Neurological effects in humans resulting from acute exposure to JP-5 vapor have been reported (Porter 1990). Coordination and concentration difficulties and fatigue were noted in two individuals following a lhour exposure to JP-5 in the cockpit of an unpressurized aircraft. The odor of JP-5 in the cockpit at the end of the flight was described as overwhelming. Other effects included headache, apparent intoxication, and anorexia. Neither experienced any sensory impairment. The effects subsided within 24 hours in one of the exposed individuals and within 4 days in the other (Porter 1990). In a study of six volunteers, slight olfactory fatigue was induced in three, and one reported "tasting something," following a 15-minute exposure to 140 mg/m^3 deodorized kerosene vapor (Carpenter et al. 1976). An epidemiological study reported the effects of chronic exposure to jet fuel in aircraft factory workers (Knave et al. 1976, 1978). This study found significant increases in neurasthenia (i.e., fatigue, depressed mood, lack of initiative, dizziness, and sleep disturbances) in the exposed subjects when compared to unexposed controls from the same factory. Neurasthenia was associated with a TWA concentration of 250 mg/m^3 of jet fuel, although exposure varied from 150 to 420 mg/m^3 (Struwe et al. 1983). Also, attention and sensorimotor speed were impaired in the exposed workers, but no effects were found on memory function or manual dexterity. Clinical signs and symptoms of polyneuropathy were also present in the majority of individuals examined. Based on Spectral Parameter Analysis of the electroencephalogram (EEG) signals, the study authors speculated that the effect of jet fuel may influence thalamic control of the cortical activity with an increased time variability, decreased frequency stability, and less widespread control of cortical neurons.

The neurotoxic effects of JP-8 exposure were examined in posture balance studies conducted on 27 U.S. Air Force employees who had been exposed to JP-8 for at least six months (Smith et al. 1997). Exposure concentrations could not be calculated in mg/m^3 because insufficient data were provided. Eight-hour breathing zone samples were collected for each employee. Mean exposure levels for employees in all job categories exposed to JP-8 fuel were: benzene (5.03±1.4 ppm); toluene (6.11±1.5 ppm); xylenes (6.04±1.4 ppm); and naphthas (419.6±108.9 ppm). The study authors noted that a statistical association between sway length and JP-8 benzene, which implied a subtle influence on vestibular/proprioception functionalities. The limitations of these studies, which include lack of specification of the type of jet fuel and no adjustment for possible exposure to other chemicals, were discussed in greater detail in the Respiratory Effects section above.

2. HEALTH EFFECTS

No histopathological changes were noted in the nervous system of rats or dogs exposed to up to 100 mg/m3 deodorized kerosene vapor 6 hours per day, 5 days per week for 13 weeks (Carpenter et al. 1975, 1976). An increase in water consumption was noted after 8 hours (lasting until the end of the study) in rats exposed to 1,100 mg/m^3 of airborne JP-5,6 hours per day, 5 days per week for approximately 30 days (Bogo et al. 1983). No significant clinical signs of toxicity were evident in mice exposed continuously to airborne JP-8 (500 or 1,000 mg/m3).for 90 days, except for an increased incidence of fighting (Mattie et al. 1991).

Mice receiving a single dose of 20 μL of kerosene placed in the pharynx (followed by aspiration) exhibited lack of coordination, drowsiness, and behavioral changes (Nouri et al. 1983). The study is limited because only one dose was tested and the actual dose entering the lungs by aspiration cannot be determined.

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after inhalation exposure to JP-5 or JP-8.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to JP-5 or JP-8.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to JP-5 or JP-8. Genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

There are limited epidemiological data regarding carcinogenicity in humans following chronic inhalation exposure to kerosene. No association between the use of kerosene stoves for cooking and bronchial cancer

was found among nonsmoking women (Chan et al. 1979). The concentrations and durations of exposures were not reported, and it could not be ascertained whether exposures were to kerosene vapor or kerosene aerosol. The association between the use of kerosene stoves and exposure to "petroleum products," and oral or pharyngeal cancer has been investigated (Zheng et al. 1992). Significantly ($p \leq 0.00l$) more male cases (27%) used kerosene stoves than controls (14.1%). A similar effect was not observed for females. This study is limited in that a wide range of fuels were used, the fuels were not adequately described, and no differentiation was made between effects potentially associated with kerosene vapor and effects possibly associated with the products of combustion.

A matched case-control study that examined risk factors for two common types of brain tumors in children, astrocytic glioma and primitive neuroectodermal tumor (POET), found a significant association (odds ratio [OR] = 8.9; 95% confidence interval [CI] 1.l-71.1; p=0.04) between astrocytoma and the use of kerosene during pregnancy by income-adjusted mothers (Bunin et al. 1994). The study used 321 control group individuals and monitored 321 cases, of which 155 were astrocytic glioma cases and 166 were PNET cases. Limitations in this study included possible selection bias, lack of information regarding exposure duration and concentrations, and exposure to other agents, such as alcohol, *N*-nitrosocompounds, and possibly pesticides.

A population-based case-referent study was conducted in Montreal, Canada, using a cohort of 3,726 cancer patients, of whom 43 individuals were exposed to jet fuel and 234 individuals were exposed to kerosene. A significant association between jet fuel and kidney cancer (OR = 3.1; 90% CI 1.5-6.6) was observed after an in-depth statistical analysis. However, some of the patients with kidney cancer who were exposed to jet fuel had also been exposed to aviation gasoline, which may have been responsible for the development of renal tumors (Siemiatycki et al. 1987). Limitations of this study included multiple chemical exposures and inadequate description of the jet fuels and exposure concentrations.

A historical prospective cohort study involving 2,176 men designed to examine the risk of lymphatic malignancies due to aircraft fuel exposure in the Swedish Air Force found no evidence of an association between aircraft fuel and lymphatic, or any of the other malignancies examined (Selden and Ahlborg 1991). Both cancer mortality and morbidity were examined in this study. This study was limited because the exposure concentrations and durations were not specified.

2. HEALTH EFFECTS

In a study conducted using rats, no renal tumors were observed during lifetime observation following a 90-day continuous exposure to 750 mg/ m^3 JP-5 vapor (Bruner 1984). This study, however, was not designed to specifically test carcinogenic potential.

2.2.2 Oral Exposure

2.2.2.1 Death

Numerous case studies have described death following the accidental ingestion of kerosene by children (usually under the age of 5, but as old as 15 years). The deaths were usually attributed to lipoidal pneumonia (Morrison and Sprague 1976; Santhanakrishnan and Chithra 1978; Zucker et al. 1986) that was probably induced by the aspiration of the kerosene. Specific respiratory effects associated with death from kerosene ingestion include pneumothorax (Lucas 1994; Mahdi 1988; Zucker et al. 1986), emphysema (Mahdi 1988), and pneumonitis (Singh et al. 1981). Cardiac arrhythmia was reported as the cause of death in one child; however, it was suspected that myocarditis and pulmonary edema may have been the cause of the rapid deterioration and death of the child (Dudin et al. 1991). Estimated ingested doses of kerosene associated with death are as low as 1,900 mg/kg based on the ingestion of 30 mL of kerosene by a 2-year-old child, and as high as 16,800 mg/kg based on the ingestion of 200 mL of kerosene by a 1-year-old child (Santhanakrishnan and Chithra 1978). An estimated oral dose of less than 5,300 mg/kg kerosene resulted in the death of a l0-month-old girl (Zucker et al. 1986). No lethality was reported for children from 10 months to 5 years old following ingestion of estimated doses ranging from 120 to 870 mg/kg and, in one instance, a dose as high as 1,700 mg/kg of kerosene (Dudin et al. 199 1). Although kerosene ingestion is the second leading cause of poisoning in rural Sri Lanka, accounting for 9.5% of the total cases, no deaths due to ingestion were reported (Hettiarachchi and Kodithuwakku 1989).

Death in rats occurred after a single dose (intragastric administration) of 12,000 mg/kg kerosene, but not after intragastric doses of 8,000-l 1,200 mg/kg kerosene or 12,150 mg/kg deodorized kerosene (Muralidhara et al. 1982). The study authors stated that the deodorized kerosene appeared to be safer than kerosene, but they did not indicate the component of kerosene that resulted in the greater toxicity. No treatment-related deaths occurred in pregnant rats treated once a day with up to 2,000 mg/kg JP-8 by gavage during gestational days 6-l 5 (Cooper and Mattie 1996). A single oral dose of 4,000 mg/kg kerosene was lethal to 10-day-old rats; however, this dose level was not tested in adult rats, and details of how the rats were treated were not provided (Deichmann et al. 1944). Death occurred in two out of six rats subsequent to a single gavage dose

of 47,280 mg/kg JP-5, but none died from single doses of 18,912-29,944 mg/kg JP-5 (Parker et al. 1981). One rat exposed to 37,824 mg/kg JP-5 died from a gavage accident. There were no other deaths in that treatment group. An LD_{50} of greater than 48,000 mg/kg was noted in rats receiving a single oral dose by gavage of 19,200,24,000,30,400,32,000, or 48,000 mg/kg of JP-5 (Bogo et al 1983). However, it should be noted that the volumes of the doses by gavage used here were extremely large and that any amount above 20 mL (lowest dose used in this study was 24 mL/kg) is probably too high a dose for rats.

The acute oral LD_{50} values for kerosene in guinea pigs and rabbits have been reported to be 16,320 and 22,720 mg/kg, respectively (Deichmann et al. 1944). In guinea pigs, 1 of 10 died at a single oral dose of 3,760 mg/kg, and 7 of 10 died at a single oral dose of 19,200 mg/kg. Death in rabbits did not occur after a single oral dose of 8,000 mg/kg, with 3 of 10 and 6 of 10 rabbits dying at single oral doses of 12,800 and 28,800 mg/kg, respectively. In guinea pigs, death occurred following a single oral dose of 3,760-19,200 mg/kg kerosene. These data for guinea pigs and rabbits are limited because the methodologies and experimental conditions of this study were poorly described. Oral gavage of 6,400 mg/kg/day kerosene administered for 7-10 days was lethal to 4 of 5 male calves; only one dose was tested in this study (Rowe et al. 1973).

Mortality in rats was induced by aspiration of 0.05-0.25 mL of kerosene; there was a dose-response relationship for death in this study (Gerarde 1963). Aspiration was induced by placing the test material into the back of the throat causing the animal to choke, which forced the test compound into the respiratory tract. The purpose of using aspiration as a route of exposure in animals was to mimic human respiratory exposure occurring during vomiting after ingestion of kerosene. Mortality in mice was noted following a single exposure to 20 μL kerosene by aspiration (Nouri et al. 1983). This latter study is limited because only one dose was tested. No treatment-related deaths were observed when groups of 10 male Sprague-Dawley rats were administered 0,750, 1,500, or 3,000 mg/kg neat JP-8 by gavage once a day for 90 days (Mattie et al. 1995).

All LOAEL values from each reliable study for death in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

No studies were located regarding ocular or metabolic effects in humans or animals after oral exposure to JP-5 or JP-8. The highest NOAEL and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. Even if kerosene is initially ingested (accidental ingestion of jet fuels is most often noted in children under 5 years of age), the respiratory toxicity is usually attributable to the aspiration of kerosene into the lungs during vomiting (Coruh and Inal 1966; Majeed et al. 1981; Nom-i and Al-Rahim 1970). Based on case studies that examined at least 50 cases of kerosene ingestion by children, the respiratory effects that primarily occur from kerosene ingestion are bronchopneumonia, bronchitis, pneumonitis, lung infiltrates and effusions, cough, dyspnea, and tachypnea (Akamaguna and Odita 1983; Aldy et al. 1978; Annobil1983; Annobil and Ogunbiyi 1991; Lucas 1994; Mahdi 1988; Santhanakrishnan and Chithra 1978; St. John 1982). Pneumonitis, pulmonary edema, and/or pneumonia were reported for children and adults who had ingested kerosene (Subcommittee on Accidental Poisoning 1962). Hypoxia has also been noted in some cases (Dudin et al. 1991). An epidemiological study found a significant increase in feelings of heaviness in the chests of workers who were chronically exposed to jet fuels by the inhalation, oral, and/or dermal exposure routes (limitations of the study are discussed in detail in Section 2.2.1.2 Respiratory Effects) (Knave et al. 1978). A follow-up study was conducted on children who 10 years earlier had been diagnosed with pneumonitis due to kerosene ingestion and who had abnormal chest radiographs at the time (Tal et al. 1984). Researchers found an increase in volume of isoflow, a decrease in change in flow while breathing helium compared to air at 50% vital capacity, and the continued presence of abnormal chest radiographs. The study suggests that there may be long-term respiratory effects following aspiration of ingested kerosene.

Several studies have reported estimated doses, usually based on the finding of an empty container near the poisoned child (Agarwal and Gupta 1974; Akamaguna and Odita 1983; Aldy et al. 1978; Coruh and Inal 1966; Dudin et al. 199 1; Nouri and Al-Rahim 1970; Saksena 1969; Santhanakrishnan and Chithra 1978). Although the effects associated with specific doses were not stated, kerosene was associated with pulmonary complications in 11 of the 422 cases studied (the incidence of the effects, ages associated with the effects, and doses were not reported). Pneumothorax, pneumomediastinum, and death were most frequently reported. The Subcommittee on Accidental Poisoning (1962) estimated that ingestion of 10-30 mL results in respiratory distress from aspiration of kerosene (Zucker et al. 1986). Respiratory distress was reported to

Table 2-2. Levels of Significant Exposure to JP-5 & JP-8 - Oral

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL			Reference (test substance)
					Less serious (mg/kg/day)		Serious (mg/kg/day)	
	ACUTE EXPOSURE							
	Death							
1	Rat (Wistar-CFTRI)	1 d (G)					12000 F (33% mortality; minimum lethal dose)	Muralidhara et al. 1982 (FO-1)
2	Rat (Sprague-Dawley)	1 d (G)					47280 M (33% mortality)	Parker et al. 1981 (FO1JP5)
	Systemic							
3	Rat (Sprague-Dawley)	10 d Gd 6-15 1x/d (G)	Bd Wt	500 F			1000 F (31% decreased maternal body weight gain)	Cooper and Mattie 1996 (FO1JP8)

Table 2-2. Levels of Significant Exposure to JP-5 & JP-8 - Oral (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference (test substance)
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
4	Rat (Wistar-CFTRI)	1 d (G)	Cardio	12000 F			Muralidhara et al. 1982 (FO-1)
			Gastro	12000 F			
			Hemato	12000 F			
			Hepatic	12000 F	NS F (cellular vacuolization; fatty infiltration)		
			Renal	12000 F	NS F (slightly dilated kidney tubules)		
			Bd Wt	12000 F	NS F (decreased body weight and food intake)		
5	Rat (Sprague-Dawley)	1 d (G)	Resp		NS M (congestion of the lung)		Parker et al. 1981 (FO1JP5)
			Cardio	NS M	NS M (epicardium congestion)		
			Gastro	18912 M	NS M (mottled liver; swollen liver; hepatocyte changes)		
			Hepatic		18912 M (hepatocyte necrosis)		
			Renal	37824 M	47280 M (hyaline droplets)		
			Derm		NS M (subcutis congestion; alopecia)		

Table 2-2. Levels of Significant Exposure to JP-5 & JP-8 - Oral (continued)

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL	LOAEL				Reference (test substance)
					Less serious		Serious		
	Neurological								
6	Rat (Sprague-Dawley)	10 d Gd 6-15 1x/d (G)		2000 F					Cooper and Mattie 1996 (FO1JP8)
7	Rat (Wistar-CFTRI)	1 d (G)		8000 F	9600 F	(unsteady gait; drowsiness)			Muralidhara et al. 1982 (FO-1)
	Developmental								
8	Rat (Sprague-Dawley)	10 d Gd 6-15 1x/d (G)		1000			1500	(decreased fetal body weight: 15% M, 13% F)	Cooper and Mattie 1996 (FO1JP8)

Table 2-2. Levels of Significant Exposure to JP-5 & JP-8 - Oral (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg)	LOAEL		Reference (test substance)
					Less serious (mg/kg)	Serious (mg/kg)	
	INTERMEDIATE EXPOSURE						
	Systemic						
9	Rat (Sprague-Dawley)	90 d 1 x/d (G)	Resp	3000 M			Mattie et al. 1995 (F01JP8)
			Cardio	3000 M			
			Gastro		750 M (stomach irritation)		
			Hemato		750 M (decreased lymphocytes)		
			Musc/skel	3000 M			
			Hepatic	3000 M			
			Renal	3000 M			
			Endocr	3000 M			
			Dermal		750 M (anal irritation and hyperplasia)		
			Bd Wt	750 M	1500 M (13% decrease body weight)	3000 M (43% decrease body weight)	
	Immunological/Lymphoreticular						
10	Rat (Sprague-Dawley)	90 d 1 x/d (G)		3000 M			Mattie et al. 1995 (F01JP8)

Table 2-2. Levels of Significant Exposure to JP-5 & JP-8 - Oral (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg)	LOAEL		Reference (test substance)
					Less serious (mg/kg)	Serious (mg/kg)	
	Neurological						
11	Rat (Sprague-Dawley)	90 d 1 x/d (G)		3000 M			Mattie et al. 1995 (F01JP8)
	Reproductive						
12	Rat (Sprague-Dawley)	90 d 1 x/d (G)		3000 M			Mattie et al. 1995 (F01JP8)

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an intermediate oral Minimal Risk Level (MRL) of 8 mg/kg/day calculated by dividing the NOAEL of 750 mg/kg/day by an uncertainty factor of 100 (10 for animal-to-human extrapolation and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Derm = dermal; F = female; FO-1 = fuel oil no. 1; FO1JP5 = JP-5 (jet fuel); FO1JP8 = JP-8 (jet fuel); (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; x = time(s)

Figure 2-2. Levels of Significant Exposure to JP-5 & JP-8 - Oral

Acute (≤14 days)

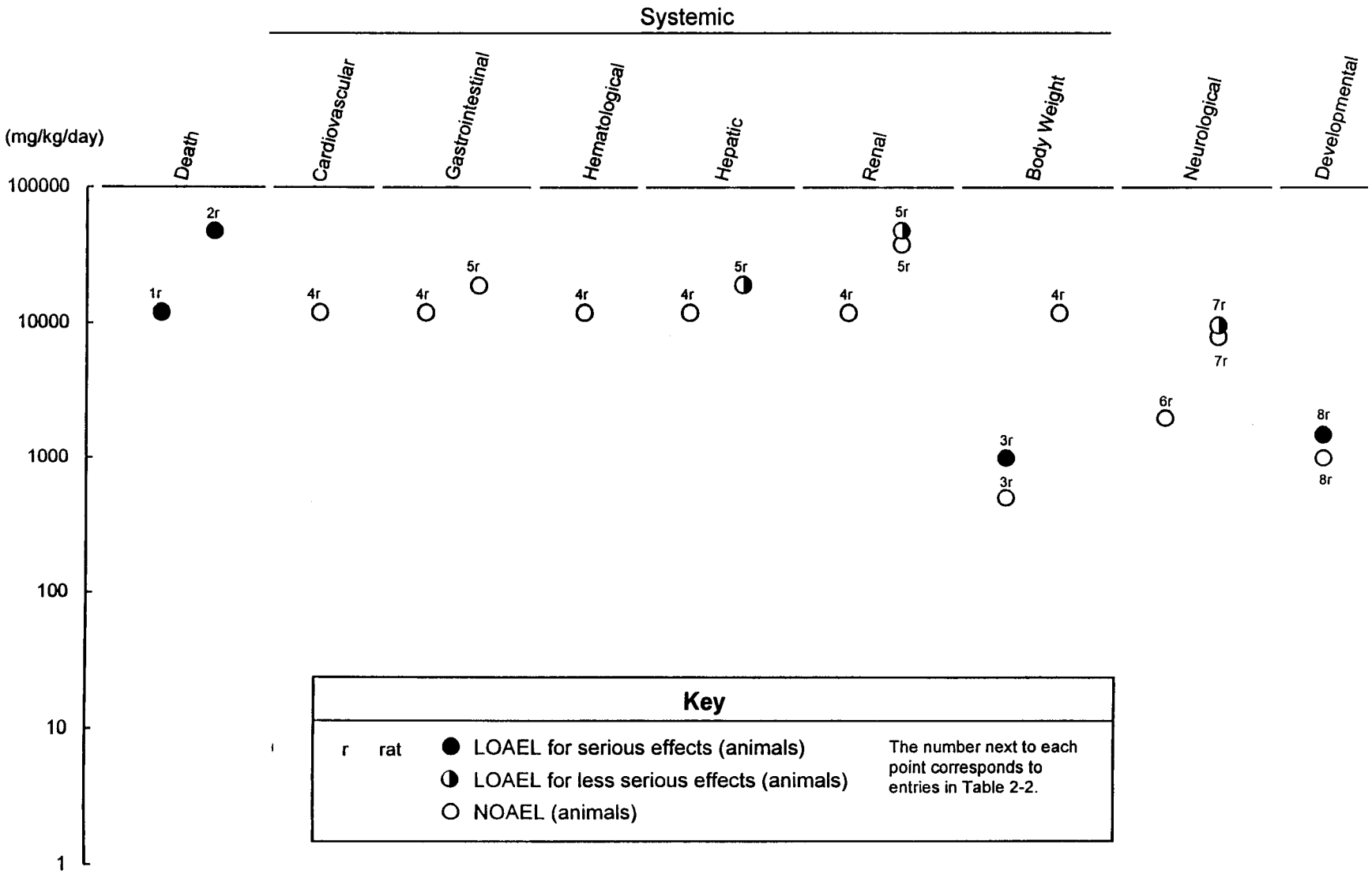
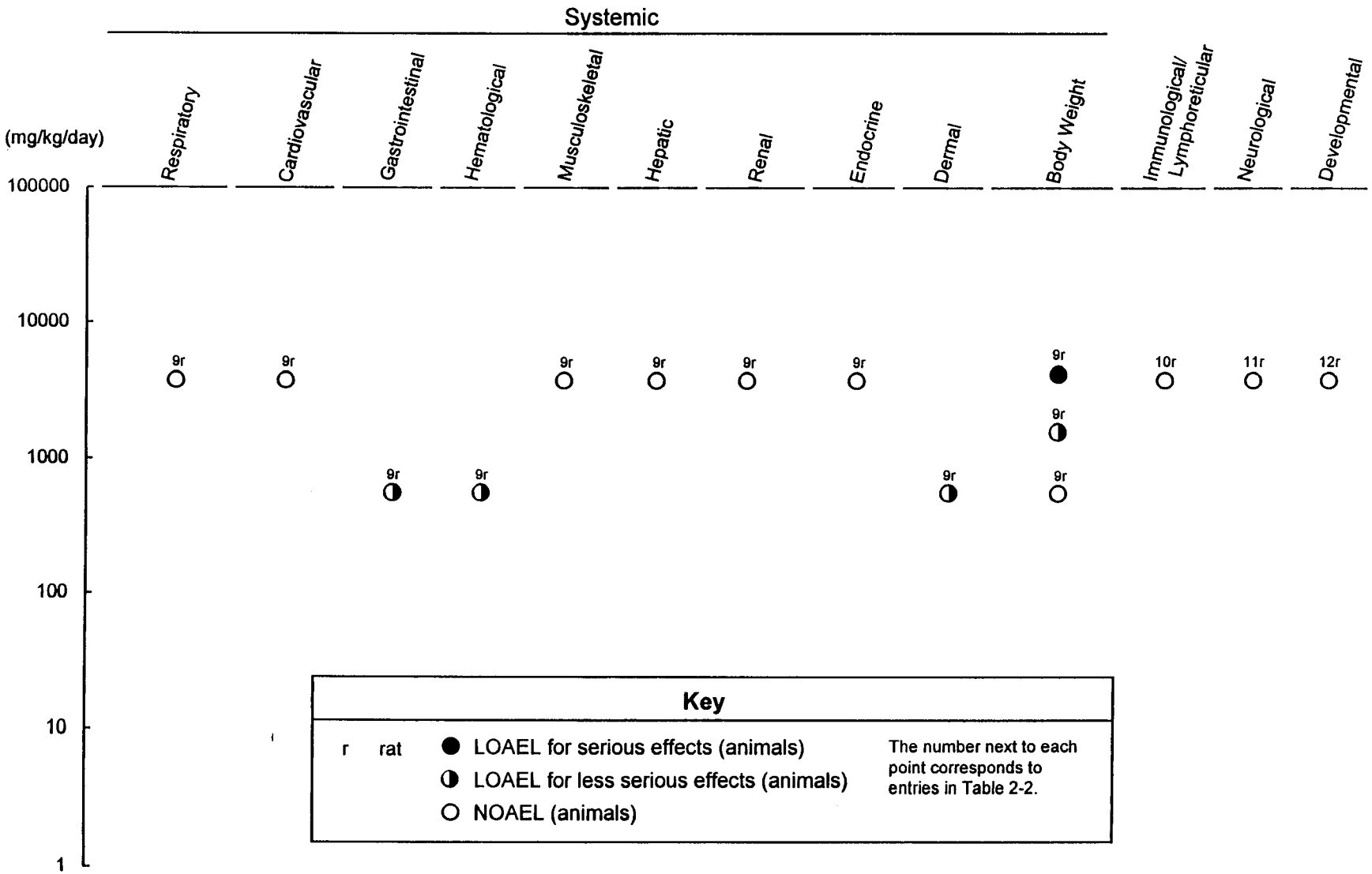


Figure 2-2. Levels of Significant Exposure to JP-5 & JP-8 - Oral

Intermediate (15-364 days)



have resulted in the deaths of a 2-year-old child and a l-year-old child after ingestion of 30 mL (1,900-2,000 mg/kg) and 200 mL (15,300-16,800 mg/kg) of kerosene, respectively (Santhanakrishnan and Chithra 1978).

Not all cases of kerosene ingestion result in toxicity. For instance, as many as 56% of the cases studied were asymptomatic in two study populations (Mahdi 1988; Santhanakrishnan and Chithra 1978). Also, 39% of one population of children had normal lung x-rays following kerosene ingestion (Annobil and Ogunbiyi 1991). No doses were reported in these cases, although the study authors estimated them as small. This reinforces the position that aspiration is the route of exposure when signs or symptoms of toxicity are seen following ingestion.

Mononuclear and polymorphonuclear cell infiltration and unspecified pathological lesions were noted in the lungs of guinea pigs after gavage administration of 3,200-8,000 mg/kg kerosene (Brown et al. 1974). In mice, aspiration of 20 μL of kerosene induced pulmonary consolidation and hemorrhage, pneumonitis, a decrease in pulmonary clearance of *Staphylococcus aureus,* and an increase in relative lung weight (Noari et al. 1983). Dogs exposed to 0.5 mL/kg kerosene by aspiration exhibited increases in oxygen utilization, intrapulmonary physiologic shunt fraction, respiratory rate, and decreases in arterial oxygen tension (Goodwin et al. 1988). In the aspiration studies, the actual dose entering the lungs could not be determined.

No treatment-related histopathological changes in the lung or nasal turbinates were reported in a study in which male Sprague-Dawley rats were administered up to 3,000 mg/kg neat JP-8 by gavage once a day for 90 days (Mattie et al. 1995).

Cardiovascular Effects. Tachycardia was noted in children following acute ingestion of kerosene (Akamaguna and Odita 1983; Coruh and Inal 1966). In one case study cardiomegaly, but not heart failure, occurred in 20% of the cases of kerosene poisoning (Akamaguna and Odita 1983). An epidemiological study found a significant increase in cardiac palpitations in workers who were chronically exposed to jet fuels by the inhalation, oral, and/or dermal exposure routes (Knave et al. 1978). The limitations of the study are discussed in detail in Section 2.2.1.2 (Respiratory Effects).

There were no histopathological changes and no change in relative heart weight in rats following exposure by gavage to single doses of up to 12,000 mg/kg kerosene or 12,150 mg/kg deodorized kerosene (Muralidhara et al. 1982). Data for deodorized kerosene are limited because effects were reported for only one dose.

Decreases in heart rate and mean arterial blood pressure occurred in dogs following aspiration of 0.5 mL/kg kerosene, and these values returned to the control values within 60 minutes (Goodwin et al. 1988). The actual dose entering the lungs by aspiration cannot be determined. This study is limited, however, because only one dose was tested.

No treatment-related histopathological effects on the heart were observed when male Sprague-Dawley rats were treated with neat JP-8 at doses of up to 3,000 mg/kg once a day for 90 days (Mattie et al. 1995).

Gastrointestinal Effects. The most commonly reported gastrointestinal effect in children following acute ingestion of kerosene is vomiting (Akamaguna and Odita 1983; Aldy et al. 1978; Lucas 1994; Mahdi 1988; Majeed et al. 1981; Nouri and Al-Rahim 1970; Saksena 1969; St. John 1982), including bloody vomit (Nom-i and Al-Rahmin 1970). Other effects noted have been abdominal pain and/or distension (Akamaguna and Odita 1983; Mahdi 1988; Majeed et al. 1981; Nouri and Al-Rahim 1970; Saksena 1969), gastroenteritis (Saksena 1969), and diarrhea (Majeed et al. 1981).

No diarrhea was noted in rats following exposure by gavage to single doses of up to 12,000 mg/kg kerosene or 12,150 mg/kg deodorized kerosene (Muralidhara et al. 1982). Stomach irritation and hyperplasia were observed in male Sprague-Dawley rats treated with 750, 1,500, or 3,000 mg/kg JP-8 by gavage once a day for 90 days (Mattie et al. 1995). The incidence and severity of the gastritis and hyperplasia were increased at all doses compared to controls, but there was an inverse relationship between these findings and dose. These effects may result from contact irritation of the JP-8, since it was administered to the animals without a vehicle. No histopathological changes in the intestine were observed in this study, but anal dermatitis and hyperplasia were also reported (Mattie et al. 1995).

Hematological Effects. Several case studies reported hematological effects in children following acute ingestion of kerosene. Increases in leukocyte counts were reported for 37-80% of the respective study populations (Dudin et al. 1991; Majeed et al. 1981; Nouri and Al-Rahim 1970). These studies do not state how long after exposure this effect was observed.

In rats exposed by gavage to single doses of up to 12,000 mg/kg kerosene or 12,150 mg/kg deodorized kerosene, there was no change in relative spleen weight, and no histopathological changes of the spleen occurred (Muralidhara et al. 1982). Rats had increased hematocrit, decreased white blood cell counts, and

increased erythrocyte counts following exposure by gavage to a single dose of 189 12 mg JP-S/kg (Parker et al. 1981). It has been suggested that dehydration might be the cause of hemoconcentration in these animals.

Hematological effects were observed in male Sprague-Dawley rats treated with 0,750, 1,500, or 3,000 mg/kg neat JP-8 by gavage for 90 days (Mattie et al. 1995). No significant changes were found in red blood cell count, but significant increases in neutrophils and significant decreases in lymphocytes were observed in all treated groups compared to controls. The increase in neutrophil count was probably a response to the renal nephropathy observed in this study, but the cause of the decrease in lymphocytes was unclear. Platelets were increased at high dose compared to controls.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to JP-5 or JP-8.

Male Sprague-Dawley rats treated with up to 3,000 mg/kg neat JP 8 for 90 days showed no histopathological changes in the sternum or in skeletal muscle (Mattie et al. 1995).

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to JP-5 or JP-8.

There was no change in the relative organ weight of the liver in rats following single doses (gavage) of up to 12,000 mg/kg kerosene or 12,150 mg/kg deodorized kerosene (Muralidhara et al. 1982). In the same study, histopathological examination revealed slight cellular infiltration and mild vacuolization of the liver, but the doses of kerosene and deodorized kerosene that induced these effects were not specified. A single gavage dose of 18,912–47,280 mg/kg JP-5 induced necrosis in the hepatocytes of rats (Parker et al. 198 1).
Similarly, a single dose of 18,912 mg JP-S/kg induced vacuolization of the periportal hepatocytes within 2 days of gavage, as well as statistically significant increases in serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), and lactate dehydrogenase levels (Parker et al. 1981). Rats that died subsequent to receiving a single oral dose by gavage of 24,30,38,40, or 60 mL/kg of JP-5 exhibited livers that were swollen and mottled. Liver lesions consisted of cytoplasmic vacuolization of hepatocytes and hepatocellular degeneration. Necrosis of individual hepatocytes was indicated by pyknosis and karyorrhexis (Bogo et al. 1983). Rats receiving a single dose of 24 mL JP-5/kg by gavage exhibited a transient increase in serum levels of SGOT and SGPT (Bogo et al. 1983; Mehm and Feser 1984). It was noted that the elevated levels of SGOT and SGPT occurred as early as 6 hours post-treatment and lasted up

to 5 days post-treatment (Mehm and Feser 1984). Liver sections revealed mitotic figures and increased numbers of binucleated cells. Normal tissue was observed after 5 days (Bogo et al. 1983; Mehm and Feser 1984). Male Sprague-Dawley rats that received 750, 1,500, or 3,000 mg/kg JP-8 without a vehicle by gavage once a day for 90 days showed significant increases in levels of aspartate aminotransferase and alanine aminotransferase compared to controls (Mattie et al. 1995). However, the changes were not dose related. Relative liver weight was increased and total bilirubin was increased in a dose-dependent manner at all doses compared to controls in this study. Triglycerides were significantly decreased at high dose. No effects were observed upon histopathological examination of the liver.

Renal Effects. Urinalysis tests in children were generally reported to be normal following acute ingestion of kerosene (Dudin et al. 1991; Mahdi 1988; Nouri and Al-Rahim 1970), although albuminuria was occasionally noted (Dudin et al. 1991; Nouri and Al-Rahim 1970).

No changes in relative kidney weights were noted in rats following single doses (gavage) of up to 12,000 mg/kg kerosene or 12,150 mg/kg deodorized kerosene (Muralidhara et al. 1982). Histopathological examination revealed slight cellular infiltration and mild vacuolization of kidney tissues and slight dilation of the kidney tubules in rats “poisoned” with kerosene and deodorized kerosene. From the study authors’ description of the results, it is not possible to determine at which dose the histopathological changes in the kidneys were observed.

Hyaline droplets were detected in the kidneys of two male rats that died 48 hours after a single exposure to 47,280 mg/kg JP-5 by gavage (Parker et al. 1981). This effect was not apparent in male rats that died less than 48 hours after exposure to 47,280 mg/kg or in rats that survived for 14 days following exposures to 18,912–37,824 mg/kg JP-5. However, hyaline droplets were apparent in rats that were killed within 2-3 days of exposure to 18,912 mg/kg JP-5. Thus, the effect appears to be induced within a specific period following exposure and also appears to be transient. A single gavage exposure to 18,912 mg/kg JP-5 also induced a statistically significant increase in creatinine levels (Parker et al. 1981). The most consistent renal change noted in rats that died subsequent to receiving a single oral dose by gavage of 19,200,24,000, 30,400, 32,000, or 48,000 mg/kg of JP-5 was the formation of eosinophilic hyaline droplets in the cytoplasm of epithehal cells in the proximal tubules (Bogo et al 1983). Renal tissue sections from rats receiving a single gavage dose of 19,200 mg/kg JP-5 exhibited cytoplasmic droplets in the proximal tubules. The presence of the droplets correlated with elevated levels of serum creatinine and blood urea nitrogen (Bogo et al 1983).

These effects are considered to be unique to male rats and are not expected to occur in humans (see discussion in Section 2.2.1.2 under Renal Effects).

A 90-day study using male Sprague-Dawley rats treated by gavage with 750, 1,500, or 3,000 mg/kg neat JP-8 also demonstrated this effect (Mattie et al. 1995). An $\alpha_{2\mu}$-globulin nephropathy was observed at all doses and a significant increase in the incidence and severity of chronic progressive nephrosis was observed in high-dose animals. Neither of these lesions is considered relevant for human health risk assessment. Values for urinalysis parameters were comparable to controls with the exception of urinary pH, which was significantly decreased at mid and high dose. Blood creatinine was significantly increased compared to controls only at low and mid dose. No treatment-related histopathological changes were found in the urinary bladder.

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to JP-5 or JP-8.

There were no histopathological changes in the adrenal glands and no changes in the relative adrenal gland weights in rats following the administration of single doses, by gavage, of up to 12,000 mg/kg kerosene or 12,150 mg/kg deodorized kerosene (Muralidhara et al. 1982). No histopathological changes were observed in the adrenal glands or pancreas of male Sprague-Dawley rats treated by gavage with up to 3,000 mg/kg JP-8 (Mattie et al. 1995).

Dermal Effects. Large blisters, erythema, and peeling skin were reported in two cases of apparent oral exposure to kerosene (Annobil1988). However, the strong odor of kerosene on one of the individuals and the kerosene-stained clothing of the other indicate that dermal exposure may have also occurred in these cases. Exposure levels were not reported.

Alopecia and congestion of the subcutis were noted in rats following gavage administration of single doses of 19,200 mg JP-S/kg (Parker et al. 1981). Anal irritation and hyperplasia were observed in a 90-day study in male Sprague-Dawley rats administered 750, 1,500, or 3,000 mg/kg undiluted JP-8 by gavage (Mattie et al. 1995). There was an increase in incidence and severity of anal hyperplasia and in the incidence of anal dermatitis in all treated groups compared to controls; the severity of the hyperplasia increased in a dose-dependent manner.

Male Sprague-Dawley rats that were treated with 750, 1,500, or 3,000 mg/kg neat JP-8 by gavage once a day for 90 days showed decreases in body weight compared to controls at low (6%), mid (13%), and high (43%) dose (Mattie et al. 1995). There is some question, however, regarding whether this effect was directly due to administration of JP-8 or whether it was due to decreased food consumption induced by gastric irritation.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to JP-5 or JP-8.

Maternal body weight gain was significantly decreased by 3 l%, 70%, and 85% (at 1,000,1,500, and 2,000 mg/kg, respectively) compared to controls when pregnant rats were treated with 0,500, 1,000, 1,500, or 2,000 mg/kg JP-8 once a day by gavage during gestational days 6–15 (Cooper and Mattie 1996).
Adjusted maternal body weight (the maternal body weight minus the gravid uterine weight) was significantly decreased compared to controls at 1,500 and 2,000 mg/kg.

Metabolic Effects. Fever has been reported in children following ingestion of kerosene (Akamaguna and Odita 1983; Aldy et al. 1978; Dudin et al. 1991; Lucas 1994; Mahdi 1988; Majeed et al. 1981; Nouri and Al-Rahim 1970; Saksena 1969; St. John 1982). In one study, fever and pulmonary complications were reported in children and adults who had ingested kerosene (Subcommittee on Accidental Poisoning 1962). It is not known whether the fever was secondary to the pulmonary effects.

No studies were located regarding metabolic effects in animals after oral exposure to JP-5 or JP-8.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans or animals after oral exposure to JP-5 or JP-8.

Gavage administration of up to 3,000 mg/kg of neat JP-8 to Sprague-Dawley rats once/day for 90 days caused no histopathological changes in lymph nodes or spleen, although relative spleen weight was increased at this dose, but not at 1,500 mg/kg, compared to controls (Mattie et al. 1995).

2.2.2.4 Neurological Effects

Lethargy, semicoma, and/or coma were reported in children and adults who had ingested kerosene. Estimated exposure levels of 10-30 mL kerosene were associated with complications of the central nervous system in 18 of 422 study participants (Subcommittee on Accidental Poisoning 1962). These effects also occurred at doses beyond this range, but the exact exposure levels are not known. Incidences of the effects, the ages associated with the effects, and the ingested doses were not reported. Several case studies have reported neurological effects in children following acute ingestion of kerosene. In studies that examined 50-205 kerosene poisoning cases, the neurological effects noted most frequently were unconsciousness or semiconsciousness, drowsiness, restlessness, and irritability (Akamaguna and Odita 1983; Aldy et al. 1978; Coruh and Inal 1966; Dudin et al. 199 1; Lucas 1994; Mahdi 1988; Majeed et al. 1981; Nouri and Al-Rahim 1970; Saksena 1969; Santhanakrishnan and Chithra 1978; St. John 1982). Coma and convulsions were also noted in numerous studies but were usually evident in only one or two individuals per study population (Coruh and Inal 1966; Dudin et al. 1991; Majeed et al. 198 1; Nouri and Al-Rahim 1970; Saksena 1969; Santhanakrishnan and Chithra 1978). Of 78 children (aged 1l-48 months) known to have ingested kerosene, 2 developed coma, convulsions, and then died after ingesting a quantity of kerosene estimated to be between 30 mL (1,890 mg/kg) and 50 mL (4,255 mg/kg) (Dudin et al. 1991). The cause of death was not neurological for these children, but death was attributable in one case to severe metabolic acidosis associated with hypoxia and in the second case to arrhythmia as well as myocarditis and pulmonary edema. Neither coma nor convulsions occurred in 76 children aged 10 months to 5 years after ingesting 3-20 mL of kerosene (equivalent to 126–l ,754 mg/kg). However, in the majority of the cases of kerosene ingestion, neurological effects were not associated with specific reported quantities. There are limited data that suggest that the central nervous system effects following ingestion of kerosene are due to hypoxia from kerosene-induced respiratory impairment (Majeed et al. 1981). Significant increases in neurasthenia (i.e., fatigue, depressed mood, lack of initiative, dizziness, and sleep disturbances) have been reported in workers who were chronically exposed to jet fuels by inhalation, oral, and/or dermal exposure. Also, attention and sensorimotor speed were impaired, but no effects were found on memory function or manual dexterity. The study authors speculated, based on Spectral Parameter Analysis of the EEG signal, that jet fuel may influence thalamiccontrol of the cortical activity with an increased time variability, decreased frequency stability, and less widespread control of cortical neurons (Knave et al. 1978). The limitations of this study are discussed in detail in Section 2.2.1.2 under Respiratory Effects.

Single exposures to 12,000 mg/kg kerosene and 12,150 mg/kg deodorized kerosene by oral gavage induced unsteady gait and drowsiness in rats; however, no neurological effects occurred from exposure to 8,000 mg!kg kerosene (Muralidhara et al. 1982). These data are limited since statistical analysis was not conducted and effects in the controls were not described. Also, a dose-response relationship cannot be identified from the deodorized kerosene data since only one dose was tested. For the first 2 days posttreatment, a significant reduction in food and water intake and a significant increase in cage activity were noted in rats that received a single dose (by gavage) of 19,200 mg/kg JP-5 (Bogo et al. 1983).

No clinical signs of neurotoxicity were found in pregnant Sprague-Dawley rats treated orally with 0,500, 1,000, 1,500, or 2,000 mg/kg JP-8 during gestational days 6–15 (Cooper and Mattie 1996). Similarly, no clinical signs of neurotoxicity and no treatment-related histopathological changes were found in the brain or sciatic nerve of male Sprague-Dawley rats administered 0,750, 1,500, or 3,000 mg/kg neat JP-8 by gavage for 90 days (Mattie et al. 1995).

The highest NOAEL and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to JP-5 or JP-8.

Male Sprague-Dawley rats were administered 0,750, 1,500, or 3,000 mg/kg undiluted JP-8 by gavage for 90 days (Mattie et al. 1995). Although relative testes weight was increased at high dose, no histopathological changes were observed in these organs.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to JP-5 or JP-8.

Pregnant Sprague-Dawley rats were treated orally by gavage with 0,500, 1,000, 1,500, or 2,000 mg/kg JP-8 during gestational days 6–l 5 (Cooper and Mattie 1996). Decreases were found in the body weight of fetuses of both sexes (15% males, 13% females) compared to controls at 1,500 mg/kg JP-8. These changes in fetal body weight were found in conjunction with significant decreases in maternal body weight gain at

1,000 m/kg and in adjusted maternal body weight at 1,500 mg/kg. No other signs of toxicity were observed in either dams or fetuses in this study.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to JP-5 or JP-8. Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding cancer in humans after oral exposure to JP-5 or JP-8.

A thymus sarcoma was found in 1 of 10 male Sprague-Dawley rats treated with 3,000 mg/kg neat JP-8 by gavage for 90 days (Mattie et al. 1995). No other tumors were observed in this study, which used doses of 0,750,1,500, or 3,000 mg/kg JP-8. Because this lesion may be incidental, it is not shown in Table 2-2 or Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to JP-5 or JP-8.

Daily dermal exposures to 0.1 mL kerosene for 1 week were not lethal to male mice. The skin at the exposure site was rough and swollen (Upreti et al. 1989). Death in mice occurred after dermal administration of 30,000–40,000 mg/kg JP-5 daily for 14 consecutive days, but not after daily dermal administration of 5,000–20,000 mg/kg JP-5 for 14 days (NTP/NIH 1986). Dermal application of 2,000–8,000 mg JP-5/kg 5 days per week for 13 weeks (NTPLNIH 1986), or 42.2 mg JP-5 three times per week for 40 weeks or twice weekly for 60 weeks (Schultz et al. 1981), was also lethal to mice. Conversely, dermal application of 500 or 1,000 mg JP-5/kg 5 days a week for 13 weeks (NTP/NIH 1986), or 21.1 mg JP-5 two or three times a week for 40 or 60 weeks (Schultz et al. 1981), was not lethal to mice. Statistically significant increases in mortality were noted in female mice following chronic exposure (five dermal applications per week for 103 weeks) to JP-5 at doses of 250 and 500 mg/kg when compared to controls. Incidence of death in females due to

treatment was 15/50 at 250 mg/kg and 33/50 at 500 mg/kg, compared to deaths in 4/50 controls. Excessive irritation and ulceration were seen at the site of the application (NTP/NIH 1986). Although the number of deaths in males under these conditions was increased over that of the controls, the increase in mortality was not statistically significant. This suggests that female mice may be more susceptible to exposure by this route. At 500 mg/kg, deaths were observed as early as week 2 of exposure to JP-5. It was not specified whether the animals were protected against oral exposure through grooming/fur licking behavior. In addition, the toxicity caused by the loss of skin integrity due to application of petroleum products at this level in mice can substantially affect the study results.

The highest NOAEL and all LOAEL values from each reliable study for death in each species and duration category are recorded in Table 2-3.

2.2.3.2 Systemic Effects

The highest NOAEL and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-3. No studies regarding metabolic effects in humans or animals following dermal exposure to JP-5 or JP-8 were located.

Respiratory Effects. A significant increase in feelings of "thoracic oppression" (no description provided) was found in workers who were chronically exposed to jet fuels by the inhalation, oral, and/or dermal exposure routes (Knave et al. 1976, 1978). The limitations of the study are discussed in detail in Section 2.2.1.2 (Respiratory Effects).

No histopathological or organ weight changes were noted in the respiratory system of male mice following daily dermal exposures to 0.1 mL kerosene for 1 week (Upreti et al. 1989), 13-week exposures to 2,000-8,000 mg JP-5/kg (five applications per week), or chronic exposures (five dermal applications per week for 103 weeks) to 250 or 500 mg JP-5/kg (NTP/NIH 1986).

Cardiovascular Effects. An epidemiological study found a significant increase in heart palpitations in workers who were chronically exposed to jet fuels by inhalation, oral, and/or dermal exposure routes (Knave et al. 1976, 1978). The limitations of the study are discussed in detail in Section 2.2.1.2 (Respiratory Effects).

Table 2-3. Levels of Significant Exposure to JP-5 & JP-8 - Dermal

Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL			Reference (test substance)
				Less serious (mg/kg/day)		Serious (mg/kg/day)	
ACUTE EXPOSURE							
Death							
Mouse (B6C3F1)	2 wk 7 d/wk					30000 F (100% mortality)	NTP/NIH 1986 (FO1JP5)
Systemic							
Mouse (B6C3F1)	2 wk 7 d/wk	Derm		NS	(scaly skin; hair loss; inflammation; acanthosis; hyperkeratosis)		NTP/NIH 1986 (FO1JP5)
		Bd Wt	5000	10000	(17% decrease in body weight gain)		
INTERMEDIATE EXPOSURE							
Death							
Mouse (B6C3F1)	13 wk 7 d/wk					2000 F (60% mortality)	NTP/NIH 1986 (FO1JP5)

Table 2-3. Levels of Significant Exposure to JP-5 & JP-8 - Dermal (continued)

Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference (test substance)
Mouse (BALB/c)	40 wk 3 x/wk				42.2 F (40% mortality) M (13% mortality)	Schultz et al. 1981 (FO1JP5)
Mouse (BALB/c)	40 wk 3 x/wk				41.5 F (27% mortality) M (7% mortality)	Schultz et al. 1981 (FO1JP8)
Systemic						
Mouse (B6C3F1)	13 wk 7 d/wk	Resp	8000			NTP/NIH 1986 (FO1JP5)
		Cardio	8000			
		Gastro	8000			
		Hemato		500 (splenic hematopoiesis)		
		Hepatic		500 (karyomegaly)		
		Renal	8000			
		Derm		500 (slight to moderate dermatosis)		
		Bd Wt	2000	4000 (decrease in body weight gain)		

Table 2-3. Levels of Significant Exposure to JP-5 & JP-8 - Dermal (continued)

Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference (test substance)
Mouse (BALB/c)	40 wk 3 x/wk	Hemato		21.1 (increased spleen weight)		Schultz et al. 1981 (FO1JP5)
		Hepatic	42.2			
		Renal		21.1 M (increased kidney weight) 21.1 F (decreased kidney weight)		
		Bd Wt		21.1 (7-11% decrease in body weight)		
Mouse (BALB/c)	40 wk 3 x/wk	Hemato		21.1 (increased spleen weight)		Schultz et al. 1981 (FO1JP8)
		Hepatic	41.5			
		Renal		21.1 F (increased kidney weight) 21.1 M (decreased kidney weight)		
		Bd Wt		21.1 (7-11% decrease in body weight)		

Table 2-3. Levels of Significant Exposure to JP-5 & JP-8 - Dermal (continued)

Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL		Reference (test substance)
				Less serious (mg/kg/day)	Serious (mg/kg/day)	
Neurological						
Mouse (B6C3F1)	13 wk 7 d/wk		8000M			NTP/NIH 1986 (FO1JP5)
Reproductive						
Mouse (B6C3F1)	13 wk 7 d/wk		8000			NTP/NIH 1986 (FO1JP5)
CHRONIC EXPOSURE						
Death						
Mouse (B6C3F1)	90-103 wk 5 d/wk				250 F (30% mortality) 250 M (34% mortality)	NTP/NIH 1986 (FO1JP5)

Table 2-3. Levels of Significant Exposure to JP-5 & JP-8 - Dermal (continued)

Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference (test substance)
Systemic						
Mouse (B6C3F1)	90-103 wk 5 d/wk	Resp	500			NTP/NIH 1986 (FO1JP5)
		Cardio	500			
		Gastro	500			
		Hemato	250	500 (amyloid deposits in spleen)		
		Musc/skel	500			
		Hepatic	250	500 (amyloid deposits in liver)		
		Renal	250	500 (amyloid deposits in kidney)		
		Derm			250 (ulcers; dermatitis)	
		Bd Wt	250	500 (12-25% decrease in body weight gain)		
Neurological						
Mouse (B6C3F1)	90 - 103 wk 5 d/wk		500			NTP/NIH 1986 (FO1JP5)

Table 2-3. Levels of Significant Exposure to JP-5 & JP-8 - Dermal (continued)

Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference (test substance)
Reproductive						
Mouse (B6C3F1)	90 - 103 wk 5 d/wk		500			NTP/NIH 1986 (FO1JP5)
Cancer						
Mouse (B6C3F1)	90-103 wk 5 d/wk				250 (malignant lymphomas)	NTP/NIH 1986 (FO1JP5)
Immuno/Lymphor						
Mouse (B6C3F1)	90-103 wk 5 d/wk		250	500 (granulocyte hyperplasia in the bone marrow; hyperplasia in the lymph nodes)		NTP/NIH 1986 (FO1JP5)

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Derm = dermal; F = female; FO1JP5 = JP-5 (jet fuel); FO1JP8 = JP-8 (jet fuel); Gastro = gastrointestinal; Hemato = hematological; Immuno/Lymphor = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = time(s)

No histopathological changes were noted in the cardiovascular system of mice dermally exposed to 2,000–8,000 mg JP-5/kg for 13 weeks (five applications per week) or mice chronically exposed (five applications per week for 103 weeks) to 250 or 500 mg JP-5/kg (NTP/NIH 1986).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after dermal exposure to JP-5 or JP-8.

No histopathological changes were noted in the gastrointestinal tract of mice subsequent to five dermal applications of JP-5 for 13 weeks (2,000-8,000 mg/kg) or in mice chronically exposed (five applications per week for 103 weeks) to 250 or 500 mg/kg JP-5 (NTP/NIH 1986).

Hematological Effects. No studies were located regarding hematological effects in humans after dermal exposure to JP-5 or JP-8.

A decrease in the splenic relative weight that was not accompanied by histopathological changes was noted in male mice following daily dermal exposures to 0.1 mL kerosene for 1 week (Upreti et al. 1989). In addition, decreases in hemoglobin concentration, increases in erythrocyte and white blood cell counts, and increased incidence of polymorphonuclear leukocyte concentrations were reported. Females were not tested in this study (Upreti et al. 1989). Hematopoiesis by the spleen (extramedullary hematopoiesis) was noted in mice receiving 500-8,000 mg JP-5/kg by dermal administration 5 days per week for 13 weeks (NTP/NIH 1986). Extramedullary hematopoiesis is indicative of a response to a hematological effect.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after dermal exposure to JP-5 or JP-8.

No histopathological changes were noted in the musculoskeletal system of mice following dermal application of 250 or 500 mg JP-5/kg 5 days per week for 103 weeks (NTP/NIH 1986).

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to JP-5 or JP-8.

No histopathological or organ weight changes were noted in the livers of male mice following daily dermal exposures to 0.1 mL kerosene for 1 week (Upreti et al. 1989). Slight hepatic karyomegaly was noted in mice

receiving 500-8,000 mg JP-5/kg dermally five times per week for 13 weeks. Amyloidosis of the liver occurred in mice following the dermal administration of 500 mg JP-5/kg, five times per week for 103 weeks, but not in those treated with 250 mg/kg (NTP/NIH 1986).

Renal Effects. No studies were located regarding renal effects in humans after dermal exposure to JP-5 or JP-8.

No histopathological or organ weight changes were noted in the kidneys of male mice following daily dermal exposures to 0.1 mL kerosene for 1 week (Upreti et al. 1989), or following exposure to 2,000–8,000 mg JP-5/kg five times per week for 13 weeks (NTP/NIH 1986). Renal lesions were produced in at least one sex and at one or both dose levels (100% or 50%) in mice dermally treated three times per week for 60 weeks with JP-5 (Easley et al. 1982). However, the lesions could not be duplicated in mice injected intraperitoneally with 100 mg/kg (using a corn oil vehicle) three times per week for up to 60 days or in mice injected intraperitoneally with 25 μL of JP-5 for 2-8 weeks (Easley et al. 1982). In contrast to the study reported by Barrientos et al. (1977) in which oliguria was manifested as a symptom of acute diesel fuel toxicity, the dermally treated test animals in the Easley et al. (1982) study demonstrated increased urine output, increased insensitive water loss, and increased water consumption. The inability to reproduce the lesions and the increased water consumption and loss led the study authors to speculate that dermal application may be the necessary route of exposure to cause the renal toxicity (Easley et al. 1982). It should be noted that only abbreviated results were reported. Intermediate and chronic exposures to petroleum oils were reported to induce a nodular appearance of the kidney as well as tubular atrophy of the renal cortex in mice (Schultz et al. 1981). However, it was not reported which petroleum fuels induced the kidney injury, although JP-5 was among those studied. From calculations of the kidney-to-body-weight ratios in mice exposed to 21.1 or 42.2 mg JP-5 for 40 weeks, dose-related trends were noted in female mice for increased relative kidney weights (right kidney only) (Schultz et al. 198 1). There were no dose-response trends for the changes in relative kidney weights in males exposed to JP-5. Statistical analysis was not conducted on the changes in kidney-to-body-weight ratios. Therefore, the significance of the dose-response trends cannot be confirmed. Amyloidosis of the kidney was found to be secondary to dermatitis in mice chronically exposed (five dermal applications per week for 103 weeks) to 500 mg JP-5/kg (NTP/NIH 1986).

Endocrine Effects. No studies were located regarding endocrine effects in humans after dermal exposure to either JP-5 or JP-8.

There were no histopathological changes, or changes in the weights of adrenal glands of male mice following daily dermal exposure to 0.1 mL kerosene for 1 week (Upreti et al. 1989).

Dermal Effects. Experimental data regarding dermal exposure of humans to jet fuels are limited. In one study, there was a dose-dependent increase in dermatitis from acute exposures to 55-85% solutions of kerosene (1.5 mL of a solution applied to "midback" for 24 hours) (Tagami and Ogino 1973). No effects were noted in these subjects from exposure to the 40% solution of kerosene. This study is limited because no vehicle controls were used. Also, each subject was exposed to all test solutions (i.e., four different concentrations of kerosene), but the chronological spacing of the four treatments is not known. Therefore, it is not known if some of the observed effects were a result of sensitization, rather than a direct effect of the kerosene. Topical application of 1.0 mL of kerosene impaired protein synthesis, but not deoxyribonucleic acid (DNA) replication or collagen synthesis in the epidermis (Lupulescu and Birmingham 1975). Hyperemia, cellular damage of the epidermis, and mild edema also occurred following acute exposure to 1.0 mL kerosene (Lupulescu and Birmingham 1976; Lupulescu et al. 1973). Histological changes included disorganization of the cells, cytolysis, and enlarged intercellular spaces in the stratum comeum and spinous cells of the epidermis (Lupulescu and Birmingham 1976). Effects had subsided within 72 hours in some individuals (Lupulescu et al. 1973). These studies are limited because each tested only one dose.

Dermal effects of jet fuels from known or suspected short-term dermal exposures are described in several case studies. Erythema, bullae, burning, and itching were reported in a 45-year-old man following a 20minute dermal exposure to kerosene (Mosconi et al. 1988). Three males (2-l 5 years old) and one female (2 years old) exhibited blisters, reddening, flaccid bullae, pustules, soreness, burning, swelling, and denudation of the skin following dermal exposures to unknown volumes of kerosene (Tagami and Ogino 1973). Large blisters, erythema, and peeling skin were reported in two cases of apparent oral exposure to kerosene (Annobil 1988); however, the strong odor of kerosene on one of the individuals and the kerosene-stained clothing of the other strongly indicate that dermal exposure may have also occurred in these cases. Exposure levels were not specified. Dermatosis and erythema were evident in factory workers who were exposed to kerosene for up to 5 hours daily by handling kerosene-soaked steel parts; exposure levels were not reported (Jee et al. 1985).

Male mice treated dermally daily for 1 week with 0.1 mL kerosene exhibited rough skin, edema, and inflammation at the exposure sites (Upreti et al. 1989). Females were not tested in this study. Female mice treated dermally for 6 weeks with middle distillates, including straight-run kerosene, developed hyperplasia and necrosis in the epidermis (Ingram et al. 1993) and increased sebocyte counts (Lesnik et al. 1992). Skin irritation was not induced in male rabbits following a single application (0.5 mL) of undiluted JP-5 or JP-8 (Schultz et al. 1981). Alternatively, New Zealand White rabbits that received JP-8 on both intact and abraded skin exhibited a slight irritation (Kinkead et al. 1992a), while JP-5 elicited no such response (Kinkead et al. 1992b). Acute dermal exposures to unspecified concentrations of JP-5 induced dermatitis (acanthosis, scaly skin, hair loss, inflammation, parakeratosis, and/or hyperkeratosis of the skin) in mice (NTP/NJH 1986). Intermediate exposure (five dermal applications per week for 14 weeks) to 500-8,000 mg JP-5/kg induced slight-to-moderate dermatosis, which increased with dose in mice. Chronic dermal application (five times per week for 103 weeks) of 250 or 500 mg JP-5/kg induced dermatitis and ulcerations of the skin in mice (NTP/NIH 1986). The severity, but not the incidence, of dermatitis induced by JP-5 was dose dependent; the doses were possibly too high and may have caused a chemical bum. Similarly, the incidence of ulcers induced by the chronic application of JP-5 was dose dependent. However, dose fractionation, which allows some recovery time, can alter the response of the total dose. In some cases, dose fractionation can cause more severe dermal effects than the same dose applied once. Dermatitis was noted in mice that were chronically exposed dermally to JP-5, although effective doses were not reported (Easley et al. 1982).

Ocular Effects. Eye irritation has been noted in factory workers who were chronically exposed to jet fuels (Knave et al. 1978). The limitations of this study are discussed in detail in Section 2.2.1.2 (Respiratory Effects).

Ocular irritation was not induced in rabbits by JP-5 in several studies (Cowan and Jenkins 1981 a, 1981 b; Schultz et al. 198 1). although Draize scores were not reported by some of the investigators (Cowan and Jenkins 198 la, 1981b). Similarly, neither JP-5 (Kinkead et al. 1992b) nor JP-8 (Kinkead et al. 1992b) induced ocular irritation in New Zealand White rabbits.

Body Weight Effects. No studies were located regarding body weight effects in humans after dermal exposure to JP-5 or JP-8.

There was no change in body weight of male mice following daily dermal exposures to 0.1 mL kerosene for 1 week (Upreti et al. 1989). Acute exposure to at least 10,000 mg JP-5/kg, but not 5,000 mg/kg, induced decreases in body weight in mice. Mice treated dermally with JP-5 (at 500, 1,000,2,000,4,000, or 8,000 mg/kg) five times per week for 13 weeks exhibited relatively small changes in weight gain. Male mice treated with 8,000 mg/kg displayed a 7% decrease in body weight, while a 3% increase was observed in females treated with 8,000 mg/kg (NTP/NIH 1986). Although an analysis of the weight data was not included, the data suggest that weight was unaffected by the dermal treatment with JP-5 in this study. Derrnal application three times per week for 40 weeks (total weekly doses of 126.6 and 63.3 mg of JP-5) produced significant weight reduction in mice (Schultz et al. 1981); however, the study authors failed to fully describe the methods and doses used. Chronic exposures (dermal application five times per week for 103 weeks) to 500 mg JP-5/kg induced decreases in body weight relative to controls (NTP/NIH 1986).

Other Systemic Effects. No studies were located regarding other systemic effects in humans after dermal exposure to JP-5 or JP-8.

No effects on food or water intake were observed in male mice following daily dermal exposures to 0.1 nL kerosene for 1 week (Upreti et al. 1989). Increases in daily water consumption were noted in mice exposed to JP-5; however, the doses were not reported (Easley et al. 1982). Similarly, dermal application of JP-5 increased water consumption and urine output (accompanied by a loss in osmolarity) in mice. Easley and coworkers (1982) speculated that the increased water consumption in these animals may have been the result of impaired renal function (see above discussion of Renal Effects, Section 2.2.3.2) or dehydration.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans after dermal exposure to JP-5 or JP-8.

Acute dermal treatment (“patch test”) with 1% JP-5 induced mild dermal sensitization in guinea pigs (Cowan and Jenkins 198 la, 1981b). Similarly, weak sensitization was noted in guinea pigs that were treated with 0.1 mL JP-8 four times over a 10-day period and subsequently challenged with 0.1 nL (Kinkead et al. 1992a). Dermal sensitization did not occur in guinea pigs that were dermally treated with nine doses of 0.1% JP-5 in propylene glycol over a 3-week period (Schultz et al. 1981). However, moderate sensitization was observed

when guinea pigs received seven injections of 0.1 mL of 0.01% JP-5 in peanut oil over a 15-day period and were then challenged with 0.05 mL of JP-5 (Kinkead et al. 1992b).

Decreases in the relative weights of the lymph nodes and thymus were noted in male mice following daily dermal exposures to 0.1 mL kerosene for 1 week (Upreti et al. 1989). In addition, thymocyte counts, bone marrow nucleated cell counts, thymic cortical lymphocytes, and the cellularity of the thymic lobules were decreased. Jncreases in the cellular populations of the popliteal lymph nodes and the axial lymph nodes were also present. This study is limited because females were not tested. Chronic dermal application of JP-5 (500 mg/kg, five times per week, for 103 weeks) induced granulocytic hyperplasia in the bone marrow in male and female mice and hyperplasia in the lymph nodes of female mice (NTP/NIH 1986). Amyloidosis of the spleen was found secondary to dermatitis in mice dermally treated (five times per week for 103 weeks) with 500 mg JP-5/kg; this effect was not noted following dermal application of 250 mg JP-5/kg (NTP/NIH 1986). This was most likely a result of chronic ulceration at the site of application.

The highest NOAEL and all LOAEL values from each reliable study for immunological effects in each species and duration category are recorded in Table 2-3.

2.2.3.4 Neurological Effects

A significant increase in neurasthenia (i.e., fatigue, depressed mood, lack of initiative, dizziness, and sleep disturbances) was found in workers who were chronically exposed to jet fuels by either inhalation, oral, or dermal exposure (Knave et al. 1978). Also, attention and sensorimotor speed were impaired in the exposed workers, but no effects were found on memory function or manual dexterity. Results of EEG tests suggest that the exposed workers may have had instability in the thalamocortical system. The limitations of the study were discussed in detail in Section 2.2.1.2 (Respiratory Effects).

Increased response to tactile stimuli and hyperactivity occurred in male mice at initiation of daily dermal exposures to 0.1 mL kerosene for 1 week (Upreti et al. 1989). Females were not tested in this study. No histopathological changes were noted in the nervous system of mice following dermal application of 2,000-8,000 mg JP-5/kg five times per week for 13 weeks or mice chronically exposed (five applications per week for 103 weeks) to 250 or 500 mg JP-5/kg (NTP/NIH 1986).

The highest NOAEL values for neurological effects in each species and duration category are recorded in Table 2-3.

2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after dermal exposure to JP-5 or JP-8.

No histological changes were noted in the reproductive system of mice dermally treated with 2,000-8,000 mg JP-5/kg (five times per week for 13 weeks) or in mice chronically exposed (dermal application five times per week for 103) to 250 or 500 mg JP-5/kg (NTPINJH 1986).

The highest NOAEL values for reproductive effects in each species and duration category are recorded in Table 2-3.

2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after dermal exposure to JP-5 or JP-8.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to JP-5 or JP-8. Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding cancer in humans after dermal exposure to JP-5 or JP-8.

Unspecified skin tumors were induced in C3HF/Bd mice following a 40-week exposure to 22.9 mg (but not 42.2 mg) JP-5 or a 60-week exposure to 5.7-42.2 mg JP-5 (the highest incidence was at 11.4 mg) (Schultz et al, 198 1). Tumors were more prevalent in females than males. None of the control animals developed skin tumors, and statistical analysis was not conducted The tumor incidence was not dose dependent, and historical control data for this strain of mouse were not provided No skin cancer was reported in $B6C3F_1$

mice dermally treated (five times per week for 103 weeks) with 250 or 500 mg JP-5/kg. Malignant lymphomas were noted in 39% of females treated with 250 mg JP-5/kg, 11% of females at 500 mg JP-5/kg, and 15% of females in the control group (NTP/NIH 1986). No dose-response relationship was apparent for this effect. A significant negative trend in the incidence of malignant lymphomas was noted in males of the high-dose group; rates dropped from 16% in the control group to 6% at 250 mg JP-5/kg and 2% at 500 mg JP-5/kg. Jet A (a kerosene fuel used by commercial airlines that is similar to JP-8 but does not contain certain additives) produced an increased incidence (26%) of tumors (primarily squamous cell carcinoma and fibrosarcoma) in C3HEleN mice receiving dermal applications three times per week. It was noted that Jet A produced inflammatory and degenerative changes at the application site that led to "early mortality" and that the nonneoplastic lesions and their attendant effects were so severe that the application of Jet A was discontinued at week 62 (Clark et al. 1988). The study authors suggested that epidermal degeneration may serve to mask tumor development. This phenomenon is often observed with chronic-duration carcinogenicity studies of petroleum and shale-derived fuels.

The dermal carcinogenicity of mixtures of petroleum products that have a boiling point range of .. approximately equal to or greater than 370º C is primarily related to the polycyclic aromatic hydrocarbon (PAH) content of the material (Biles et al. 1988). Some petroleum-derived materials contain cracked stocks that are known to contain biologically active PAHs; however, virgin distillate petroleum products (boiling range of approximately 177-370º C), which include various middle distillate jet fuels, primarily contain saturated species (Biles et al. 1988). Although these virgin petroleum materials contain low concentrations of PAHs, repeated application can induce dermal tumors. It has been reported that the tumorigenicity of three petroleum-derived liquids and four coal-derived liquids were not consistent with the PAH content of the test materials (Witschi et al. 1987). In the report of a 2-year skin-painting study of four petroleum middle distillates (including jet fuel), the authors suggested that the aromatic and sulfur heterocycles tested were not the source of tumorigenicity in middle distillates (Freeman et al. 1993). These results suggest that the tumorigenic potential of the middle distillates is not related to their PAH content.

It has been alternatively hypothesized that the carcinogenic activity of jet fuels is a secondary effect associated with dermal irritation (Biles et al. 1988; Clark et al. 1988; McKee et al. 1994). Biles et al. (1988) speculated that the irritating properties of middle distillate petroleum fuels played a role in the mechanism of dermal carcinogenesis in a lifetime skin-painting assay, although the data did not demonstrate such a relationship. In fact, they noted that the test groups with the most severe "degree of epidermal degeneration and necrosis" demonstrated the lowest tumor yields. Of course, if the skin is actually destroyed, then it would

be most unlikely that skin tumors would be formed. Repeated application of four petroleum-derived distillates (including Jet A and diesel) to mouse skin induced severe inflammation and degenerative changes; however, the severity and early onset of inflammation were not always predictive of tumorigenicity (Clark et al. 1988).

The role of chronic acanthosis and inflammation in tumor promotion by a middle distillate has been investigated (Skisak 1991). Male CD-l mice received a single dermal treatment of 50 μL of 7,12-dimenthylbenz[a]anthracene (DMBA) as an initiator and were subsequently treated with 25,50, or 100 μL of hydrodesulfurized kerosine (HK) twice weekly for 25 weeks. Washing after treatment and topical application of dexamethasone were used to control inflammation. The mice treated with 100 μL of HK had the greatest tumor incidence (35/53) and the highest degree of acanthosis throughout the study. While the tumor responses of the groups treated with 25 μL and 50 μL were similar (14/54 and 13/54, respectively), the degree of acanthosis was much more pronounced in the mice treated with 50 μL HK. Application of dexamethasone to animals treated with 50 μL reduced the tumor incidence to 0, although acanthosis was still observed. It is interesting to note that washing the mice (l-2 hours after treatment) with an Ivory soap solution after treatment with 50 μL of HK increased tumor incidence (22/53) compared to the group treated with 50 μL HK but left unwashed (13154). The group washed with the soap solution also had elevated levels of acanthosis relative to the unwashed group during several intervals during the study. The study authors concluded that although hyperplasia may play a role in the promoting activity, there are other factors involved.

In a 2-year skin-painting study designed to evaluate the role of skin irritation in the tumorigenicity of middle distillates, 37.5 μL of jet fuel and steam-cracked gas oil were applied two times per week, and jet fuel was also applied in an intermittent fashion (dosing was suspended for 2-3 weeks when irritation was noted in 20% of the group and resumed when it was resolved in all but 20%) (Freeman et al. 1993). The 2-3-week on/off treatment cycle produced irritation that was less severe than dosing two times per week, and only l/50 intermittently dosed animals developed tumors, compared with 22/50 in the twice-weekly dosed group. Freeman et al. (1993) indicate that, for jet fuel, a state of chronic irritation may be necessary for tumor development. Based on studies of substances that produce chronic irritation without producing tumors, there are other factors, in addition to chronic irritation, that may be necessary for tumor production in response to JP-5 or JP-8.

All LOAEL values from each reliable study for cancer effects in each species and duration category are recorded in Table 2-3.

2 .3 TOXICOKINETICS

Few data were available concerning the absorption, distribution, metabolism, and excretion of JP-5 or JP-8. Indirect evidence suggests that JP-5 and JP-8 may be absorbed through the respiratory tract, the gastrointestinal tract, and percutaneously in humans and laboratory animals (see Section 2.3.1). No data were located concerning the metabolism of JP-5 or JP-8 in humans or laboratory animals. No quantitative data were found regarding the excretion of JP-5 or JP-8.

2.3.1 Absorption

2.3.1 .l Inhalation Exposure

No studies were located specifically regarding the absorption of JP-5 or JP-8 in humans or laboratory animals after inhalation exposure. However, indirect evidence of gastrointestinal, cardiovascular, hematological, renal, dermal, and/or ocular effects from a case report in which two pilots were exposed to JP-5 vapor while flying a small aircraft indicate that it can be absorbed following inhalation exposure in humans (Porter 1990). Effects on animals acutely exposed to jet fuels by inhalation also provide indirect evidence for inhalation absorption (Casaco et al. 1985b; Garcia et al. 1988b).

2.3.1.2 Oral Exposure

No studies were located specifically regarding the absorption of JP-5 or JP-8 in humans after oral exposure. There is evidence, however, that absorption from the gastrointestinal tract occurs following ingestion of kerosene by humans (Subcommittee on Accidental Poisoning 1962). In a study of 760 cases of accidental ingestion of petroleum distillate products, including kerosene, it was concluded that patients-developed complications including pulmonary effects in the absence of vomiting and lavage, leading to the "inference that bloodstream absorption is a factor in the toxicity of these products to humans."

Limited animal data and indirect evidence indicate that kerosene is poorly absorbed from the gastrointestinal tract. Kerosene labeled with 3H-toluene or ^{14}C-hexadecane was administered to tracheotomized baboons (15

mL/kg) by nasogastric tube (Mann et al. 1977), and the isotopes were recovered after 6 hours from the brain, lung, liver, spleen, heart, and kidney.

The potential absorption of ingested kerosene by the lungs after aspiration was tested by comparing respiratory effects from oral exposures in nontracheotomized and tracheotomized monkeys (Wolfsdorf and Kundig 1972). The tracheotomized monkeys that received the kerosene via nasogastric tube could not aspirate the kerosene; thus, the potential for respiratory exposure by aspiration was prevented. Lung lesions were seen in the nontracheotomized monkeys, but no lesions were seen in the tracheotomized monkeys. These data suggest that aspiration of JP-5 or JP-8, not gastrointestinal absorption, is the underlying cause of the respiratory effects. Additionally, a lack of pulmonary toxicity was reported in dogs in which aspiration was prevented, supporting the supposition that pulmonary toxicity following kerosene ingestion is the result of aspiration of kerosene into the lungs, rather than absorption from the gastrointestinal tract (Dice et al. 1982).

2.3.1.3 Dermal Exposure

No studies were located on the absorption of JP-5 or JP-8 following dermal exposure in humans or laboratory animals. However, because dermal exposure to JP-5 in mice may induce renal damage (Easley et al. 1982), it may be assumed that dermal absorption does occur. It is possible that dehydration may have been responsible for the renal damage observed in this study, however, renal damage is described in Section 2.2.3.2 (Renal Effects). No studies were located that directly tested dermal absorption of JP-5 or JP-8 vapor.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding the distribution of JP-5 or JP-8 in humans or laboratory animals after inhalation exposure.

2.3.2.2 Oral Exposure

No studies were located regarding the distribution of JP-5 or JP-8 in humans after oral exposure.

Limited animal data indicate that kerosene is absorbed and distributed to various tissues (Mann et al. 1977). Kerosene, labelled with ^{3}H-toluene or ^{14}C-hexadecane, was given to tracheotomized baboons (15 mL,/kg) by nasogastric tube (Mann et al. 1977). Radioactivity was recovered from the brain, lung, liver, spleen, heart, and kidney after 6 hours. ^{3}H-Toluene was absorbed and taken up by most tissues to a greater extent than was ^{14}C-hexadecane; however, the amounts absorbed and distributed were minimal (Mann et al. 1977).

2.3.2.3 Dermal Exposure

No studies were located regarding the distribution of JP-5 or JP-8 in humans or laboratory animals after dermal exposure.

2.3.3 Metabolism

No studies were located regarding the metabolic pathway of JP-5 or JP-8 in humans or laboratory animals subsequent to inhalation, oral, or dermal exposure.

2.3.4 Elimination and Excretion

No studies were located regarding the excretion of JP-5 or JP-8 following inhalation, oral, or dermal exposure in humans or laboratory animals.

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

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species.
Figure 2-3 shows a conceptualized representation of a PBPK model.

If PBPK models for JP-5 and JP-8 exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

PBPK models for JP-5 or JP-8 in humans or animals were not identified.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

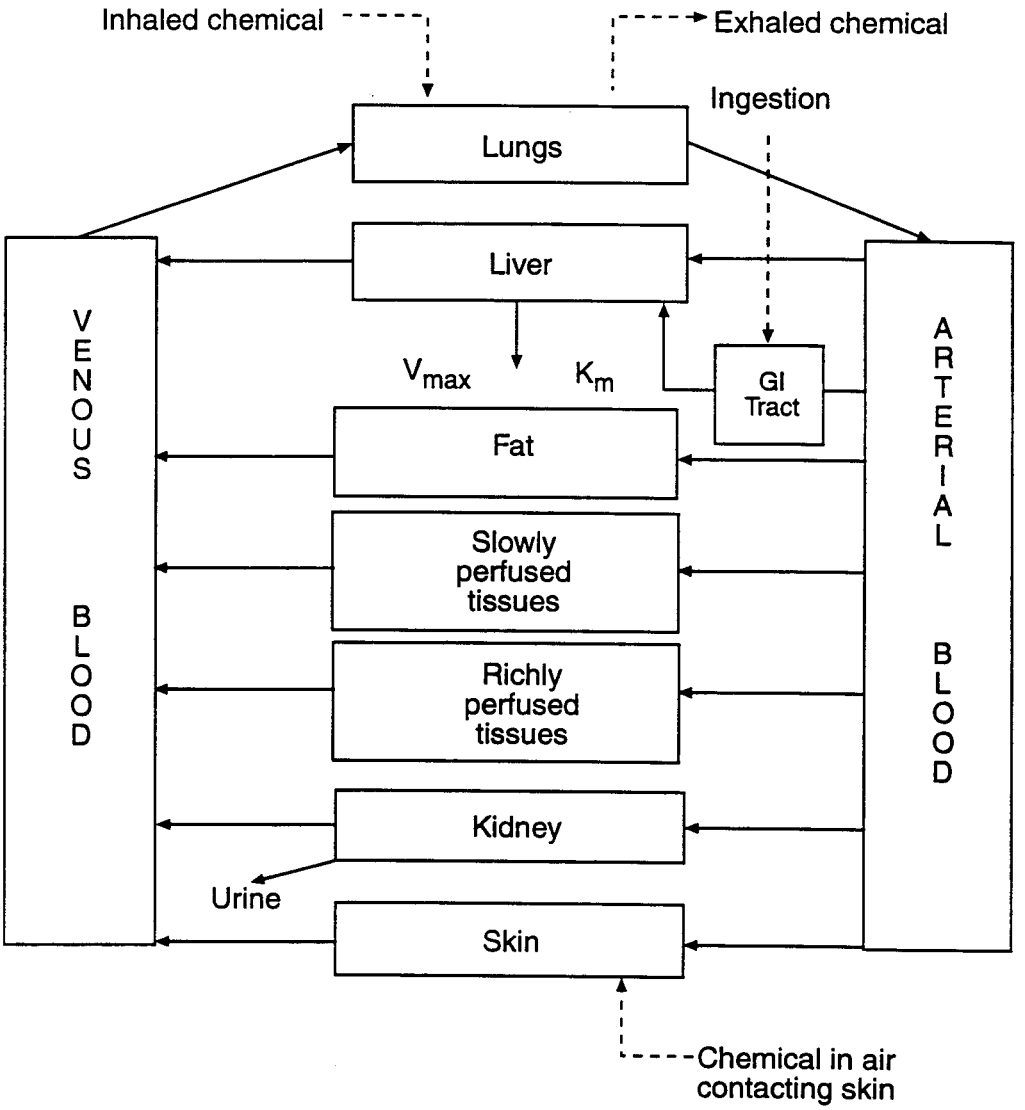
No studies were identified concerning the pharmacokinetic mechanisms of either JP-5 or JP-8.

2.4.2 Mechanisms of Toxicity

The primary risk from ingestion of kerosene is aspiration during emesis, which may cause pneumonitis. A number of studies have investigated the biochemical mechanism of the lung response to exposure to large concentrations of aerosolized kerosene (Casaco et al. 1982, 1985a, 1985b). The study authors speculated that kerosene may induce asthma-like symptoms by acting on the parasympathetic nervous system either through a direct effect on the vagus nerve or by inhibiting acetylcholinesterase. Garcia and Gonzalez (1985), based on their observation that kerosene caused an "increase in Ca^{2+}-dependent ATP hydrolysis without increase in the rate of net calcium accumulation," concluded that kerosene induced an effect on the membrane of the sarcoplasmic reticulum. They suggested that the mechanism of kerosene-induced bronchoconstriction may involve changes in the ionic flow across the cellular membranes to prolong muscle contraction. Although generalizations cannot be made regarding the hematological effects of JP-5 and JP-8 on humans, the effect of kerosene on the first two steps of the heme synthetic pathway has been studied in an animal model. Both hepatic α-aminolevulinic acid (α-ALA) dehydratase and α-ALA synthetase activities were decreased in female rats after intraperitoneal injection of kerosene, while heme oxygenase was unaffected (Rao and Pandya 1980). Since α-ALA synthetase is the rate-limiting enzyme of the heme biosynthesis pathway, hepatic heme biosynthesis may be inhibited by kerosene. It is conceivable that decreases in enzyme activities may be related to extramedullary hematopoiesis; however, there are no data to support this conjecture.

The biochemical mechanism of central nervous system depression seen with jet fuels and common to many organic solvents has not been elucidated. The mechanism of carcinogenesis associated with various formulations of middle distillate fuels is unknown.

Figure 2-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically-based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

2.4.3 Animal-to-Human Extrapolations

The animal models utilized in the available toxicological studies were the laboratory species commonly used in human health risk assessments. They had no species-specific peculiarities, with the exception of the $\alpha_{2\mu}$-globulin-related nephropathy that occurs in male rats.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview.

The basic composition of JP-5 and JP-8 is similar to that of kerosene. They are refined by a straight distillation of crude or shale oil, or a distillation of crude or shale oil in the presence of a catalyst. The jet fuels are, however, refined under more stringent conditions and contain various additives not found in kerosene. Typical additives to JP-5 and JP-8 include antioxidants (including phenolic antioxidants), static inhibitors, corrosion inhibitors, fuel system icing inhibitors, lubrication improvers, biocides, and thermal stability improvers. These additives are used in specified amounts as governed by commercial and military specifications. The exact composition of a jet fuel is also dependent upon the crude oil from which it is refined. Because of this inherent variability, little information exists on the exact chemical and physical properties of jet fuels. However, it is clear that the primary component of both JP-5 and JP-8 is kerosene, and any additives are quantitatively minor constituents of the mixtures.

Information regarding the health effects of jet fuels in humans and other animals is available for the inhalation, oral, and dermal routes of exposure. Most of the information in humans is from cases of accidental ingestion of kerosene that resulted in respiratory, neurotoxic, and to a lesser extent gastrointestinal effects. In addition, a few case studies have identified these effects as well as cardiovascular, hematological, and renal effects in humans after inhalation and/or dermal exposures. Jet fuels appear to be eye and skin irritants in both animals and humans following direct contact. Animal data exist for most systemic effects; however, the data are inconclusive for many of the end points. Further, a number of the animal studies utilized an aerosol for exposure. It should be noted that the toxicity from an aerosol varies from that of a vapor (the probable form of human exposure). The available epidemiological studies are generally inconclusive, since they cannot reliably associate exposures to jet fuels with the adverse effects reported.

2. HEALTH EFFECTS

Minimal Risk Levels for JP-5 and JP-8.

Inhalation MRLs.

- **An intermediate inhalation MRL of 3 mg/m^3 was derived for JP-5 and JP-8 from the study by Gaworski et al. (1984) in which hepatocellular fatty changes and vacuolization were observed in mice exposed to JP-5 vapor at 150 mg/m^3 continuously for 90 days. Based on the LOAEL of 150 mg/m^3, the MRL was calculated as described in the footnote to Table 2- 1. Similar effects 150 on the liver were also observed in mice at 750 mg/m^3. This study is supported by a study of deodorized kerosene in which no significant adverse effects were observed in rats or dogs exposed to 100 mg/m^3 6 hours per day, 5 days per week for 13 weeks (Carpenter et al. 1976).**

No acute or chronic inhalation MRLs were derived for JP-5 or JP-8 because available data were not suitable for MRL derivation. Studies that report lethality or subtle biochemical alterations without attendant pathology cannot be used for MRL determination.

Oral MRLs.

No acute, intermediate, or chronic oral MRLs were derived for either JP-5 or JP-8 because available data were not suitable for MRL derivation. Studies that report lethality or subtle biochemical alterations without attendant pathology cannot be used for MRL determinations. Dose-related hepatocyte necrosis (Parker et al. 1981) occurred at doses that were greater than or equal to dose levels at which more serious effects occurred; therefore, these data are unsuitable for the determination of an MRL.

Death. No quantitative lethality data for humans were located from studies of inhalation or dermal exposure to JP-5 or JP-8. Based on case studies reporting deaths in humans following ingestion of kerosene, estimated lethal doses of kerosene range from 1,900 to 16,800 mg/kg (Dudin et al. 1991; Santhanakrishnan and Chithra 1978). These lethal doses are based upon specific cases in which kerosene was ingested by a l-year-old child (30 mL) and a 2-year-old child (200 mL). No lethality was reported for children from 10 months to 5 years old following ingestion of 120-880 mg/kg of kerosene (Dudin et al. 1991). There are no human data that identify lethal oral doses in adults, and no dose-response data are available for humans. Therefore, it is not possible to approximate a threshold dose for lethality in humans.

Acute and intermediate exposures to moderate-to-high concentrations of JP-5, JP-8, and kerosene (Air Force 1985; Cowan and Jenkins 1981a, 1981b; Gaworski et al. 1984; Pfaff et al. 1995; Vemot et al. 1990c), ranging up to 5,000 mg/m^3 kerosene (aerosol), were not lethal to rats, including pregnant rats

vapor form at concentrations that occur at elevated temperatures or as the result of exposure to an aerosol. However, the data are not sufficient to draw generalizations concerning the lethal concentration or cumulative dose of jet fuels in humans.

The acute oral LD_{50} values for kerosene in guinea pigs and rabbits have been reported to be 16,320 mg/kg and 22,720 mg/kg, respectively (Deichmann et al. 1944). These data suggest that guinea pigs may be more sensitive to kerosene than rabbits. A lethal dose of kerosene of 6,400 mg/kg has been reported in calves (Rowe et al. 1973), and the lethal dose for rats is 12,000 mg/kg (Muralidhara et al. 1982). Comparison of these data is problematic because they suggest that species differences and age sensitivity may exist for oral kerosene toxicity, although such differences have not been established.

Jet fuels and petroleum products with similar compositions have differing oral lethality profiles in rats. Acute lethal doses in rats were reported to be 12,000 mg/kg for kerosene (Muralidhara et al. 1982) while lethal doses in 2 of 24 rats treated with a single oral dose of 18,900 mg/kg JP-5 were reported to be (Parker et al. 1981). However, an oral dose of 12,200 mg/kg of deodorized kerosene was not lethal in rats (Muralidhara et al. 1982). No treatment-related deaths were observed in rats administered up to 3,000 mg/kg JP-8 by gavage for 90 days (Mattie et al. 1995). Although differences in the oral toxicity of the various types of jet fuels and differences in species thresholds of toxicity may exist, the oral toxicity of JP-5 and JP-8 is relatively low. The intestinal absorption of jet fuels in humans is also relatively low. Aspiration and its resultant pulmonary effect would be the primary risk from ingestion of jet fuels.

Daily dermal exposures to 0.1 mL kerosene for 1 week were not lethal to male mice (Upreti et al. 1989). A minimum lethal dermal dose of 20,000 mg/kg (dose applied daily for 14 days) was reported for JP-5 from acute dermal exposure in mice, although this dose was decreased to 2,000 and 250 mg/kg following intermediate (five applications per week for 13 weeks) and chronic exposures (five applications per weeks for 103 weeks), respectively (NTP/NIH 1986). Conclusions cannot be drawn from the available data regarding dermal exposure to humans by JP-5 or JP-8 near hazardous waste sites, although the probability of death occurring from dermal exposures appears remote.

Systemic Effects.

Respiratory Effects. Epidemiological studies did not indicate any evidence of respiratory toxicity in children from exposure to kerosene vapor and combustion products from kerosene stoves used for cooking (Azizi and Henry 199 1; Tominaga and Itoh 1985). Another epidemiological study reported “thoracic

oppression" and cough in workers who were chronically exposed to jet fuels by the inhalation, oral, and/or dermal routes (Knave et al. 1976, 1978; Struwe et al. 1983). However, the specific jet fuels to which exposure occurred were not specified in this study, and it cannot be determined whether these exposures included JP-5 and/or JP-8. A low concentration of deodorized kerosene vapor did not cause respiratory irritation in humans (Carpenter et al. 1976). Animal data indicate that functional parameters of the lung may be affected (Casaco et al. 1982), and bronchoconstriction may occur (Casaco et al. 1982; Garcia et al. 1988b) from acute inhalation of kerosene aerosol. No histopathological evidence of respiratory toxicity was found in animals following relatively low-to-moderate intermediate inhalation or acute, intermediate, and chronic dermal exposures to compositional analogs of jet fuels (primarily kerosene) (Carpenter et al. 1976; NTP/NIH 1986; Upreti et al. 1989). These data suggest that bronchoconstriction or respiratory impairment may occur in humans at high inhalation or dermal exposure levels to kerosene or jet fuels. Relatively low or moderate exposure levels may also affect sensitive members of the population, but this cannot be conclusively determined from the data. The data also indicate that humans who are occupationally exposed may be at increased risk of developing respiratory lesions.

Ingestion of kerosene has been shown to induce respiratory effects in humans, although it appears that aspiration is the primary cause of the pulmonary toxicity and the most serious consequence of ingestion. Numerous studies in animals and humans have illustrated the introduction of kerosene into the lungs from vomitus and the subsequent manifestation of deleterious effects in the respiratory tract (Coruh and Inal 1966; Dice et al. 1982; Majeed et al. 1981; Nouri and Al-Rahim 1970; Wolfe et al. 1970; Wolfsdorf and Kundig 1972). Limited absorption of kerosene from the gastrointestinal tract may also occur (Mann et al. 1977). Specific effects that have occurred in humans following ingestion of kerosene include bronchopneumonia, bronchitis, pneumonitis, lung infiltrates and effusions, cough, dyspnea, hypoxia, and tachypnea (Akamaguna and Odita 1983; Aldy et al. 1978; Annobil1983; Annobil and Ogunbiyi 1991; Dudin et al. 1991; Lucas 1994; Mahdi 1988; Santhanakrishnan and Chithra 1978; St. John 1982). The animal data describing respiratory toxicity are limited but are consistent with the findings in humans. No histopathological effects were observed in the lungs of rats treated by gavage with JP-8 for 90 days (Mattie et al. 1995). Oral exposure data for humans are available only for kerosene. However, since jet fuels are composed primarily of kerosene, similar effects may be expected.

A number of studies have investigated the biochemical mechanism of lung response to concentrations of aerosolized kerosene ranging up to a mean of 32.5 mg/L. The studies suggest that kerosene may induce asthma-like symptoms by acting on the parasympathetic pathway through a direct effect on the vagus nerve. Alternatively, kerosene may inhibit acetylcholinesterase, resulting in bronchoconstriction from

increased concentration of acetylcholine in the trachea (Casaco et al. 1982, 1985a, 1985b). It has also been reported that kerosene can affect the calcium pump of the rabbit sarcoplasmic reticulum (Garcia and Gonzalez 1985). This suggests that the mechanism for kerosene-induced bronchoconstriction may involve changes in the ionic flow across the cellular membranes, thereby prolonging muscle contraction.

Cardiovascular Effects. Mild hypertension from acute inhalation of JP-5 vapor (Porter 1990) and palpitations from chronic inhalation, dermal, and/or oral exposures to unspecified jet fuels have been reported in humans (Knave et al. 1976, 1978; Struwe et al. 1983). Tachycardia and cardiomegaly were reported in children following acute ingestion of kerosene (Akamaguna and Odita 1983; Coruh and Inal 1966). It is not known how soon after accidental ingestion the cardiovascular effects were observed, although Akamaguna and Odita (1983) indicate that the interval between the accident and hospital arrival ranged from 1 hour to 14 days. Most of the available animal studies found no organ weight changes or histopathological changes of the cardiovascular system of rats and mice following inhalation, oral, or dermal exposures to kerosene (Carpenter et al. 1976; Mattie et al. 1995; Muralidhara et al. 1982; NTP/NIH 1986). However, there are some limited data regarding cardiac effects. Inhalation of kerosene aerosol (20,400-34,000 mg/m^3, 15 minutes daily for 21 days) or smoke (2 hours daily for 21 days) induced aortic plaques in guinea pigs (Noa and Illnait 1987a). Aspiration of kerosene decreased heart rate and mean arterial blood pressure in dogs (Goodwin et al. 1988). The effects in dogs were observed immediately after dosing and returned to normal by 60 minutes. Because the dogs were studied for only a short period after dosing, it is not known if later heart effects may have occurred. It is unlikely that cardiovascular effects will occur in humans exposed to low levels of JP-5 or JP-5 8 near hazardous waste sites by inhalation, or oral routes of exposure.

Gastrointestinal Effects. Inhalation of JP-5 vapor induced nausea in one individual (Porter 1990), while ingestion of kerosene induced more severe effects. These included vomiting, abdominal pain and/or distension, gastroenteritis, bleeding, and diarrhea (Akamaguna and Odita 1983; Aldy et al. 1978; Lucas 1994; Mahdi 1988; Majeed et al. 1981; Nouri and Al-Rahim 1970; Saksena 1969; St. John 1982). Nausea was also reported in workers chronically exposed by inhalation to unspecified types of jet fuel (Knave et al. 1976; Struwe et al. 1983). No histopathological changes in the gastrointestinal tract were reported in animals exposed to jet fuels by the inhalation or dermal routes of exposure (Carpenter et al. 1976; NTP/NIH 1986). Acute oral exposure to kerosene or deodorized kerosene at a dose of 12,150 mg/kg did not induce diarrhea in rats (Muralidhara et al. 1982), but intermediate-duration oral exposure to JP-8 caused gastric irritation and hyperplasia (Mattie et al. 1995). Although the data in humans are largely anecdotal, they strongly suggest that gastrointestinal effects are induced by both ingestion and inhalation

of JP-5 and kerosene. However, it is not believed that these effects will occur in humans exposed to the low levels found near hazardous waste sites.

Hematological Effects. Limited data in humans suggest that the ingestion of some aliphatic hydrocarbons may induce hematological effects in some individuals (Algren and Rodgers 1992), and it is not known whether these effects would occur in all individuals. However, of 12 patients admitted to the pediatric intensive care unit of a children's hospital during a 5-year period with respiratory distress associated with hydrocarbon aspiration, the only hematological effects observed were intravascular hemolysis in 3 individuals. A fourth patient who had ingested kerosene had clinically insignificant hemolysis (Algren and Rodgers 1992). Increases in leukocyte counts from acute ingestion of kerosene (Dudin et al. 1991; Majeed et al. 1981; Nouri and Al-Rahim 1970) have also been reported in humans. No hematological effects were noted in two individuals exposed to JP-5 by inhalation for a few hours (Porter 1990).

No hematological or splenic effects were reported in rats following oral exposure to kerosene (Muralidhara et al. 1982), in rats and dogs following inhalation of deodorized kerosene (Carpenter et al. 1976), or in rats following oral administration of deodorized kerosene (Muralidhara et al. 1982). Decreases in hemoglobin concentration (32%), increases in erythrocyte and white blood cell counts, and an increased incidence of polymorphonuclear leukocyte counts were noted in mice after acute dermal exposure to kerosene. A decrease in the relative spleen weight was noted, although histopathological changes were not found (Upreti et al. 1989). Oral exposure to JP-5 increased the hematocrit, decreased white blood cell counts, and increased erythrocyte counts in rats (Parker et al. 1981). Increased white blood cell and red blood cell counts and an increased incidence of polymophonuclear white blood cells were noted in mice after acute dermal exposure to kerosene. Significant decreases in lymphocytes were observed in male rats treated with 750, 1,500, or 3,000 mg/kg JP-8 by gavage for 90 days (Mattie et al. 1995).

The effect of kerosene on the first two steps of the heme synthetic pathway was studied in rats. The study showed that hepatic α-ALA dehydratase and α-ALA synthetase activities were decreased in female rats after intraperitoneal injection of kerosene (Rao and Pandya 1980). Since α-ALA synthetaste is the ratelimiting enzyme of the heme biosynthesis pathway, hepatic heme biosynthesis may be inhibited by kerosene. However, it is not known whether the low levels of JP-5 and JP-8 found near hazardous waste sites would induce changes.

Musculoskefetd Effects. No studies were located regarding musculoskeletal effects in humans after inhalation, oral, or dermal exposure to JP-5 and JP-8. No histopathological changes were noted in the

musculoskeletal systems of rats and dogs exposed by inhalation to up to 100 mg/m^3 deodorized kerosene vapor for 13 weeks (Carpenter et al. 1976) or rats exposed by gavage to up to 3,000 mg/kg JP-8 for 90 days (Mattie et al. 1995). Mice treated dermally with marine diesel fuel and JP-5 (up to 500 mg/kg, 5 days per week for 90 or 103 weeks) did not develop adverse musculoskeletal effects (NTP/NIH 1986). The limited information available from animal studies is not sufficient to assess its relevance to the human musculoskeletal system.

Hepatic Effects. No human data are available for inhalation, oral, or dermal exposures to JP-5 and JP-8 with regard to hepatic toxicity. Inhalation of 231 mg/m^3 kerosene vapor induced increases in blood lactate and pyruvate levels in rats, and exposure to 58 mg/m^3 kerosene vapor induced decreases in blood glucose levels (Starek and Vojtisek 1986). Neither rats nor dogs developed histopathological changes in the liver following inhalation exposure to 20,48, or 100 mg/m^3 deodorized kerosene vapor (Carpenter et al. 1976). Histopathological examination did reveal slight cellular infiltration and mild vacuolization of the livers of rats following gavage with kerosene or deodorized kerosene, although liver weight was not affected (Muralidhara et al. 1982). Gavage with JP-5 induced increases in serum hepatic enzyme activities, hepatocyte necrosis, and vacuolization of the periportal hepatocytes in rats (Parker et al. 1981). No histopathological changes were noted in the livers of mice following acute dermal exposures to 0.1 mL kerosene (Upreti et al. 1989). Rats administered 750 mg/kg JP-8 by gavage for 90 days had significant increases in aspartate aminotransferase and alanine aminotransferase levels compared to controls, but no histopathological changes in the liver were evident (Mattie et al. 1995). Slight hepatic karyomegaly was noted in mice exposed to 500-8,000 mg/kg JP-5 through five dermal applications per week for 13 weeks (NTP/NIH 1986). Although the data from animal studies are not sufficient to assess the relevance to human health, they suggest that jet fuels may cause hepatic effects in humans. It is not known whether these effects could be caused by the low levels of JP-5 or JP-8 found near hazardous waste sites.

Renal Effects. Urinalysis was normal following inhalation of JP-5 by two individuals and following ingestion of kerosene by numerous individuals (Dudin et al. 1991; Mahdi 1988; Nom-i and Al-Rahim 1970; Porter 1990).

Renal lesions have been produced in mice by dermal application of JP-5. However, the inability to duplicate these lesions with intraperitoneal injections suggests that the renal effects were secondary to skin injury (Easley et al. 1982). Lymphocytic inflammation has been induced in the urinary bladder of mice with chronic dermal application of JP-5 (NTP/NIH 1986). However, acute and intermediate dermal

exposures to kerosene and JP-5, respectively, did not induce any renal toxicity in mice (NTP/NIH 1986; Upreti et al. 1989).

Inhalation or oral exposure to JP-5 or JP-8 induces a hydrocarbon-related nephropathy unique to male rats (Air Force 1985; Bruner 1984; Cowan and Jenkins 1981a, 1981b; Gaworski et al. 1984; Mattie et al. 1995; Parker et al. 1981). The progression of this lesion has been noted in several studies, including studies conducted on the hydrocarbon decalin (decahydronaphthalene) (Air Force 1985; Alden 1986; Bruner 1984; Cowan and Jenkins 1981a, 1981b; Gaworski et al. 1984; Parker et al. 1981). Specifically, hyaline droplets are formed 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 not found in humans. It is believed that this protein accumulates in the cytoplasm of the renal tubule cells because the degradation of $\alpha_{2\mu}$-globulin is slowed as a result of binding with specific substances, such as jet fuels, or their metabolites. The tubules near the corticomedullary junction become dilated and are eventually filled with coarsely granular casts and necrotic debris. This results in nephron obstruction and chronic necrosis. The nephropathy induced by accumulation of this protein has not been noted in female rats, female mice (studies conducted on male mice were not located), or dogs of either sex when exposed in similar conditions to JP-5 or JP-8 vapor (Air Force 1985; Bruner 1984; Cowan and Jenkins 198 la, 1981b; Gaworski et al. 1984). It does not appear that the nephrotoxicity attributable to the $\alpha_{2\mu}$-globulin syndrome observed in male rats is relevant to humans (Olson et al. 1990). There is no evidence of renal necrosis in humans acutely exposed to JP-5 vapor (Porter 1990). It appears unlikely that renal effects would be observed in humans exposed to JP-5 or JP-8 near hazardous waste sites.

Dermal Effects. Cellular destruction at the site of administration was noted in humans after dermal exposure to kerosene (Lupulescu and Birmingham 1976; Lupulescu et al. 1973). Oral and/or dermal exposure to kerosene induced blisters, erythema, and peeling skin in two cases (Annobil 1988). Case studies describe numerous effects in or on the skin following dermal exposure to kerosene. These effects include itching, blisters, reddening, flaccid bullae, pustules, soreness, burning, swelling, and denudation (Annobil 1988; Jee et al. 1985; Mosconi et al. 1988; Tagami and Ogino 1973). There are limited data suggesting that epidermal damage may be induced by kerosene at the site of application by impairing protein synthesis in the epidermis (Lupulescu and Birmingham 1975). However, these data are insufficient to identify the toxic effects that may occur in humans following dermal exposure to kerosene at levels found near hazardous waste sites.

Anal dermatitis and hyperplasia were observed in rats following oral treatment with undiluted JP-8 in a 90-day study (Mattie et al. 1995). Acute, intermediate, and chronic dermal exposures to JP-5 have induced various degrees of dose-dependent dermatitis in mice (Easley et al. 1982; NTP/NIH 1986). The dermal effects included acanthosis, inflammation, parakeratosis, and hyperkeratosis (NTP/NIH 1986). JP-5 also induced skin irritation in guinea pigs (Cowan and Jenkins 198 la) and rabbits (Kinkead et al. 1992a), but JP-8 did not induce dermal irritation in rabbits (Kinkead et al. 1992b). Dermal irritation was induced in mice by acute dermal exposure to kerosene (Upreti et al. 1989).

Endocrine Effects. Very limited acute-duration oral (Muralidhara et al. 1982) and dermal (Upreti et al. 1989) studies in animals indicate that kerosene does not adversely affect the adrenal glands. No adverse effects on the adrenal glands or pancreas were found upon histopathological examination of these organs in an intermediate-duration oral study using JP-8 (Mattie et al. 1995). But, the data from animal studies are not sufficient to assess whether humans may develop endocrine effects following exposure to JP-5 and JP-8 at levels found near hazardous waste sites.

Ocular Effects. JP-5 vapors were reported to be irritating to the eyes of two individuals and were associated with hyperemic conjunctiva in one of the two (Porter 1990). Eye irritation was also reported in workers who were chronically exposed to unspecified jet fuels (Knave et al. 1978). Deodorized kerosene vapors were shown to induce eye irritation in some persons (Carpenter et al. 1976). These data indicate that jet fuels may induce eye irritation in humans, although no ocular irritation was reported when JP-5 or JP-8 was instilled into the eyes of rabbits (Kinkead et al. 1992a, 1992b). However, data are insufficient to determine whether ocular effects would be expected to occur in humans exposed to low levels found near hazardous waste sites.

Body Weight Effects. Decreased body weight gain was found in rats exposed to JP-8 by inhalation for acute- or intermediate-duration exposures (Pfaff et al. 1995). Body weight gain was also decreased when pregnant rats were treated orally with JP-8 during gestational days 6-15 (Cooper and Mattie 1996). There were also dose-dependent decreases in body weight observed in male rats treated orally with JP-8 in an intermediate-duration study (Mattie et al. 1995). However, the effects on body weight observed in this study may have been due to gastric irritation induced by administration of undiluted JP-8. Dose-dependent decreases in body weight were induced in mice by acute and intermediate dermal exposures to JP-5 (NTP/NIH 1986; Schultz et al. 1981) or JP-8 (Schultz et al. 1981). Decreases in food or water consumption were not noted subsequent to acute dermal exposure to kerosene (Upreti et al. 1989). After rats received a single dose of 24 mL JP-5/kg, a 7% weight loss was noted by the 2nd day (Bogo et al.

1983). Data are insufficient to determine whether these effects might be expected in humans exposed to low levels of JP-5 or JP-8 near hazardous waste sites.

Metabolic Effects. There were no blood chemistry changes in either of two individuals following a 1 -hour exposure to JP-5 vapor while flying a small airplane (Porter 1990). Several case studies reported fever in children following acute ingestion of kerosene (Akamaguna and Odita 1983; Aldy et al. 1978; Dudin et al. 1991; Mahdi 1988; Majeed et al. 1981; Nom-i and Al-Rahim 1970; Saksena 1969; St. John 1982; Subcommittee on Accidental Poisoning 1962). The anecdotal nature of the reports concerning the effects of ingestion of kerosene in children cannot be used to predict other possible outcomes.

No significant metabolic changes in blood chemistry were noted in rats continuously exposed to airborne JP-8 for 90 days (500 or 1,000 mg/m3) (Mattie et al. 1991). Changes in blood glucose, lactate, and pyruvate observed in rats exposed to kerosene vapor are discussed under hepatic effects.

Immunological and Lymphoreticular Effects. No studies were located regarding immunotoxicity or lymphoreticular effects in humans after inhalation, oral, or dermal exposure or in laboratory animals following inhalation exposure to jet fuels. No histopathological changes were observed in the spleen or lymph nodes of rats administered 3,000 mg/kg JP-8 for 90 days (Mattie et al. 1995). However, there was a decrease in relative spleen weight at this dose. Dermal application of JP-5 induced granulocytic hyperplasia in the bone marrow and hyperplasia in the lymph nodes of mice. Decreases in the relative weights of the lymph nodes and thymus were noted in mice following dermal exposure to kerosene (Upreti et al. 1989). In addition, thymocyte counts, bone marrow nucleated cell counts, thymic cortical lymphocytes, and the cellularity of the thymic lobules were decreased. Increases in the cellular populations of the popliteal lymph nodes and the cell population of the axial lymph nodes were also present. These data suggest that jet fuels may have an effect on the immune system of mice, although the toxicological significance of these effects cannot be determined. Whereas dermal exposure to jet fuels (liquid or vapor) would be expected to induce skin irritation or possibly dermatitis, there are also some data available to evaluate delayed skin sensitization. JP-5 induced a moderate sensitization reaction in guinea pigs (Kinkead et al. 1992b), although in another study the authors concluded that it was not a sensitizer according to their test criteria (Cowan and Jenkins 1981a). The lack of data in humans and the small amount of animal data are insufficient to determine whether jet fuels would induce immunological or lymphoreticular effects in humans exposed to low levels near hazardous waste sites.

Neurological Effects. Numerous neurological effects were reported after kerosene ingestion by children: unconsciousness or semiconsciousness, drowsiness, restlessness, irritability, and in fewer cases, coma and convulsions (Akamaguna and Odita 1983; Aldy et al. 1978; Coruh and Inal 1966; Dudin et al. 1991; Lucas 1994; Mahdi 1988; Majeed et al. 1981; Nouri and Al-Rahim 1970; Saksena 1969; Santhanakrishnan and Chithra 1978; St. John 1982; Subcommittee on Accidental Poisoning 1962). Neither coma nor convulsions occurred in children aged 10 months to 5 years that ingested 3-20 mL of kerosene (doses approximating 120-1,800 mg/kg) (Dudin et al. 1991). There are limited data that suggest that the central nervous system effects noted following ingestion of kerosene are due to hypoxia arising from kerosene-induced respiratory impairment (Majeed et al. 198 1).

Neurological effects have been reported following inhalation of JP-5 vapor. These included fatigue, coordination and concentration difficulties, headache, apparent intoxication, and anorexia. Effects subsided within 24 hours for one individual and within 4 days for the other. Sensory impairment did not occur in these individuals (Porter 1990). Experimental data indicate that olfactory fatigue and unusual taste sensation may occur in some individuals after a 15minute inhalation exposure to 140 mg/m^3 deodorized kerosene vapor (Carpenter et al. 1976). Neurasthenia (i.e., fatigue, depressed mood, lack of initiative, dizziness, sleep disturbances) and impairment of attention and sensorimotor speed were associated with chronic inhalation, oral, and/or dermal exposures to jet fuel by factory workers (Knave et al. 1978; Struwe et al. 1983). It is not known to which jet fuels the workers were exposed and it was not clear what other chemical exposures may have occurred. Subtle changes in posture balance were observed in workers exposed to JP-8 (Smith et al. 1997), but exposure concentrations could not be determined, and exposure to other chemicals was probable. Oral exposure to kerosene and deodorized kerosene induced ataxia and drowsiness in rats in one study (Muralidhara et al. 1982), but a study of pregnant rats treated orally with JP-8 during gestation days 6-15 reported no clinical signs of neurotoxicity (Cooper and Mattie 1996). Aspiration of kerosene induced drowsiness, lack of muscular coordination, and behavioral changes (Nouri et al. 1983), and dermal exposure induced an increased response to tactile stimuli and hyperactivity in mice (Upreti et al. 1989). No histopathological changes were noted in the nervous system of rats following oral exposure to JP-8 for 90 days (Mattie et al. 1995) or in mice following dermal exposures to JP-5 (NTP/NIH 1986). The information from human and laboratory animal studies indicates that neurotoxicity may occur by all routes of exposure and that all jet fuels may be neurotoxic. As is common with many hydrocarbons, the primary acute neurotoxic effect of jet fuels is central nervous depression that may be manifest in a number of symptoms. However, it is not known whether these effects might occur in humans after exposure to low levels of JP-5 or JP-8 found near hazardous waste sites.

Reproductive Effects. No studies were located regarding reproductive effects in humans after inhalation, oral, or dermal exposure to jet fuels. Although relative testis weight was increased in rats exposed to JP-8 for 90 days, there was no evidence of histopathological change in this organ (Mattie et al. 1995). No histological changes were noted in the reproductive system of mice dermally exposed to JP-5 for 13 weeks or chronically exposed to JP-5 (NTP/NIH 1986). There is not enough information to assess the human reproductive toxicity to jet fuels following oral, inhalation, or dermal exposures.

Developmental Effects. No studies were located regarding developmental effects in humans after inhalation, oral, or dermal exposure to jet fuels or in animals after inhalation or dermal exposure to jet fuels.

Significant decreases in fetal body weight were found after pregnant rats were treated orally during gestational days 6-15 with 1,500 mg/kg JP-8 compared to controls (Cooper and Mattie 1996). These changes in fetal body weight were found in conjunction with significant decreases in maternal body weight gain at 1,000 mg/kg and in adjusted maternal body weight at 1,500 mgkg. The NOAEL for maternal body weight changes was 500 mg/kg. No other maternal or fetal signs of toxicity were observed at doses up to 2,000 mg/kg JP-8. Data are insufficient to assess the developmental toxicity to jet fuels after inhalation, oral, or dermal exposures.

Genotoxic Effects. No genotoxicity studies involving human or animal exposure to jet fuels were identified. The results from a study employing a human cell line showed that neither 5 nor 50 ppm petroleum-derived JP-5 (PD-JP-5) interfered with Snyder-Theilen feline sarcoma virus (ST-FeSV)-directed transformation of human foreskin fibroblastic cells (Blakeslee et al. 1983). Higher concentrations (≥ 100 ppm) were cytotoxic. The study authors consider this *in vitro* assay to be a useful predictor of carcinogenesis since several known carcinogens have been shown to suppress transformation in cells infected with the ST-FeSV by blocking a specific virus gene function.

Kerosene administered intraperitoneahy did not increase the frequency of chromosomal aberrations in bone marrow cells harvested from rats following a one-time exposure to 0.04,O. 13, or 0.4 mL or a 5-day exposure to 0.02,0.06, or 0.18 r&/day (Conaway et al. 1984). No rationale was provided for the selection of 0.4 mL (LD_5) as the high dose and no data were reported regarding cytotoxic effects on the target organ (i.e., bone marrow cells). The genotoxicity of kerosene was also evaluated with the mouse lymphoma $TK^{+/-}$ forward mutation assay. The data reported were insufficient to permit a full evaluation of the results; however, the study authors reported kerosene to be negative (Conaway et al. 1984).

JP-5 was not mutagenic in the Ames assay when activated with S9 (Aroclor-induced rat liver enzymes) (Schultz et al. 1981). Similarly, JP-5 was not mutagenic in well-conducted *Sulmonellu typhimurium* preincubation assays. Doses of each agent evaluated without S9 activation and with rat or hamster liver fractions ranged from 3 to 333 μg/plate without S9 and from 100 to 10,000 μg/plate both with and without S9 (JP-5) (NTP/NIH 1986). It was also reported that kerosene was negative in the *Salmonella*/mammalian microsome mutagenicity assay with the following conditions: 0.001-5 μL/plate +/-S9 (plate test) and 6.25-50 μL/rnL +/-S9 (preincubation assay) (Conaway et al. 1984).

JP-8 was subjected to a battery of tests to evaluate its genotoxic potential (Air Force 1978a). The battery of tests included the Ames assay, the mouse lymphoma assay, the unscheduled DNA synthesis assay, and dominant lethal assays. The Ames assay utilized five strains of *S. typhimurium* and was conducted with and without a metabolic activation system. JP-8 was not mutagenic in the Ames assay and was toxic to most of the bacterial strains at concentrations above 1 μL/plate. The mouse lymphoma assay was used to evaluate JP-8 for forward mutation induction. JP-8 did not induce mutation in mouse lymphoma cells and was considered moderately toxic to the assay at 0.16 μL/mL. Unscheduled DNA synthesis evaluates the ability of a material to react with DNA and is assessed by the incorporation of ^{3}H-thymidine. JP-8 induced the incorporation of significant levels of labeled thymidine. The activity was moderate and not dose related. Toxicity was evident at 5.0 μL/mL. The dominant lethal assay determines the capability of a material to induce genetic damage in germ cells. JP-8 did not induce effects either in mice at doses of 0.13,0.4, and 1.3 mL/kg or in rats at doses of 0.1, 0.3, and 1.0 rnL/kg.

These data suggest that the jet fuels do not present a genotoxic hazard to humans (refer to Table 2-4 and Table 2-5 for a further summary of these studies).

Cancer. Scherr and colleagues (1992) reported no additional relative risk for non-Hodgkin's lymphoma for subjects occupationally exposed to "gasoline or kerosene." No significant increased relative risk for any type of cancer was noted in Swedish Air Force personnel exposed to military aircraft fuels (including an "unleaded kerosene type jet fuel") (Selden and Ahlborg 1991). A significant association between the incidence of astrocytoma in children and the reported use of kerosene by their mothers during pregnancy, when adjusted for income, was reported by Bunin et al. (1994). However, these data should be interpreted with caution because of maternal exposure to other agents and lack of data on exposure duration and concentrations. Although a significant association was observed between exposure to jet fuel and kidney cancer in a population-based case-referent study, some individuals were also exposed to aviation gasoline (Siemiatycki et al. 1987). No definitive association was found between occupational exposure to kerosene

TABLE 2-4. Genotoxicity of Kerosene *In Vivo*

Species (test system)	End point	Results	Reference
Kerosene			
Mammalian cells:			
Rat (bone marrow)	Chromosome aberrations	–[a]	Conaway et al. 1984

[a]Negative after intraperitoneal exposure but study was compromised

– = negative result

TABLE 2-5. Genotoxicity of Kerosene and JP-5 *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
JP-5 Fuel				
Prokaryotic organisms:				
Salmonella typhimurium (TA1535, TA97, TA98, TA100)	Gene mutation	–	–	NTP/NIH 1986
S. typhimurium (TA98)	Gene mutation	–	–	Schultz et al. 1981
Mammalian cells:				
ST-FeSV-infected human foreskin fibroblasts	Inhibition of morphological transformation	No data	–	Blakeslee et al. 1983
Kerosene				
Prokaryotic organisms:				
S. typhimurium (TA98)	Gene mutation	+	No data	Blackburn et al. 1986
S. typhimurium (TA1535, TA1537, TA1538, TA98, TA100)	Gene mutations	–	–	Conaway et al. 1984
Mammalian cells:				
Mouse lymphoma (L5178Y)	Gene mutations	–	–	Conaway et al. 1984

– = negative result; + = positive result; ST-FeSV = Snyder-Theilen feline sarcoma virus

and cancer in this same study. Chan and coworkers (1979) examined exposure to kerosene from kerosene cooking stoves. Exposure to kerosene combustion products may have occurred instead of, or in addition to, inhalation of kerosene vapor. A thymus sarcoma was found in 1 of 10 male rats treated orally with JP-8 for 90 days (Mattie et al. 1995). Due to the small numbers of animals used and the short duration of the study, it is not possible to determine whether this tumor was incidental. Therefore, no firm conclusions regarding human health can be drawn from these data.

No dermal cancer was noted in B6C3F, mice following chronic dermal exposure to 250 or 500 mg/kg/day JP-5 (NTP/NIH 1986). Unspecified skin tumors were noted in C3HF/Bd mice, but the tumor incidence was not dose related for most exposure conditions (Schultz et al. 1981). Dermal application of Jet A induced an increased incidence (26%) of neoplastic lesions (Clark et al. 1988). An increase in the incidence of confirmed tumors was also noted in animals receiving DMBA as an initiator and hydrodesulfurized kerosene as a promoting agent (API 1989). These data suggest that chronic application of jet fuels can act as a skin carcinogen; however, only one species has been investigated. Further investigation utilizing other species is required to more fully elucidate the mechanism of dermal carcinogenesis and the impact of dermal exposure of jet fuels on humans.

2.6 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).

At present, the use 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 (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 resultof 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 the 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 JP-5 and JP-8 are discussed in Section 2.6.1.

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 and 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. However, such markers are not often substance specific. They also may not be directly adverse, but can still indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by JP-5 and JP-8 are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organis m^3s 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. If biomarkers of susceptibility exist, they are discussed in Section 2.8, Populations That Are Unusually Susceptible,

2.6.1 Biomarkers Used to Identify or Quantify Exposure to JP-5 and JP-8

No biomarkers of exposure were identified specifically for jet fuels; however, there have been suggestions for potential indicators for kerosene exposure. These include the odor of kerosene on the breath, suggesting ingestion (Annobil 1988; Zucker et al. 1986), and the odor of kerosene on clothing, suggesting dermal exposure (Annobil 1988; Tagami and Ogino 1973). The odors of distillate fuels are so similar, however, that use of these markers to identify specific fuels is impractical. Some components of kerosene, other jet fuels, and their metabolites may be detected in the blood and urine, although the route of exposure cannot be determined from this information. For information on biomarkers of exposure for some of the constituents of jet fuels, the ATSDR toxicological profiles on benzene, toluene, xylenes, and polycyclic aromatic hydrocarbons (ATSDR 1989,1990, 1995a, 1995b) can be consulted.

2.6.2 Biomarkers Used to Characterize Effects Caused by JP-5 and JP-8

No specific, quantitative biomarkers of effect for jet fuels were identified.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.7 INTERACTIONS WITH OTHER CHEMICALS

Exposures to two or more substances may cause effects that are additive (the combined effect of the mixture is equal to the sum of the effects of the agents), synergistic (causing an effect that is greater than the sum of the effects of the agents), or antagonistic (one substance interferes with the action of another). No information was located regarding the influence of other chemicals on the toxicity of either JP-5 or JP-8; however, kerosene vapor has been shown to increase the sleeping time of hexobarbital in rats following acute exposure, and to alter the antipyretic action of phenacetin (an antipyretic) following subchronic exposure (Starek and Vojtisek 1986). In comparison to rats treated only with kerosene, intratracheal exposure of rats to chrysotile asbestos (5 mg) and kerosene (0.05 mL) resulted in a decrease in cytochrome P-450 and decreases in the activities of benzo(a)pyrene hydroxylase, epoxide hydrase, and glutathione-S-transferase (Arif et al. 1992). The investigators suggested that asbestos may increase the toxic potential of kerosene.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population is considered to be one that will exhibit a different or enhanced response to JP-5 and JP-8 than will most persons exposed to the same level of JP-5 or JP-8 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 JP-5 and JP-8, or compromised function of target organs affected by JP-5 and JP-8. Populations who are at greater risk due to their unusually high exposure to JP-5 and JP-8 are discussed in Section 5.6, Populations With Potentially High Exposure.

No information was located regarding the toxicity of JP-5 and JP-8 in susceptible populations. Available human data, in general, were based upon case studies that reported ingestion of kerosene by children. Children were not shown to be particularly susceptible to kerosene in the data reviewed; however, children appear to be more likely to be accidentally orally exposed to kerosene than adults. In particular, children who were 5 years old or younger often mistakenly drank kerosene because it was accessible.

Data from a single animal model, however, suggest that children may be more sensitive than adults to at least some of the effects of jet fuels, because younger rats were found to be more susceptible to kerosene than older rats. A single oral dose of 22,400 mg/kg kerosene killed 27% of the adult rats, 66% of the 5-week-old rats, and 100% of the l0-day-old rats (Deichmann et al. 1944). It is not known, however, whether kerosene would also be more toxic in younger humans than in older humans.

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section describes clinical practice and research concerning methods for reducing toxic effects of exposure to JP-5 and JP-8. 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 JP-5 and JP-8. 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 JP-5 and JP-8: Bronstein AC, Currance PL. 1988. Emergency care for hazardous materials exposure. Washington, DC: The C.V. Mosby Company, 175-176. Ellenhom MJ, Barceloux DG. 1988. Medical Toxicology: Diagnosis and treatment of human poisoning. New York, NY. Elsevier Publishing, 944-945. Stutz PR, Janusz SJ. 1988. Hazardous materials injuries: A handbook for pre-hospital care. 2nd ed. Beltsville, MD: Bradford Communications Corporation, 360-36 1.

2.9.1 Reducing Peak Absorption Following Exposure

The mitigation procedures for jet fuels parallel those for hydrocarbon poisoning in general. Inhalation and ingestion appear to be the most serious routes of exposure. In the case of overexposure by inhalation, it is suggested that the patient be moved to an area of fresh air and given basic supportive treatment (CONCAWE 1985; HSDB 1998) including 100% humidified supplemental oxygen as required (HSDB 1998).

For poisoning by ingestion, the treatment protocol is more complex. As with inhalation, it is recommended that the patient receive prompt supportive medical care (Bronstein and Currance 1988; CONCAWE 1985; Goldfrank et al. 1990; Haddad and Winchester 1990; Stutz and Janusz 1988; Zieserl 1979). The primary concern for the person who has ingested hydrocarbons such as kerosene is hydrocarbon aspiration either during ingestion or during gastric evacuation. Aspiration of the hydrocarbon into the lungs can cause hydrocarbon pneumonitis and secondary infections, including pneumonia.

Because of the aspiration risk, a controversy has developed over which (if either) of two gastric evacuation treatments is better: induced vomiting or gastric lavage. In general, the recommendation is that no form of gastric emptying be used if the amount of hydrocarbon ingestion is small (Bronstein and Currance 1988; Ellenhom and Barceloux 1988; Goldfrank et al. 1990; HSDB 1998; Litovitz and Greene 1988; Shirkey 1971; Zieserl 1979). This is usually the case with accidental poisonings. If unknown or large amounts (volumes greater than 100 mL) have been ingested, then the decision as to how and/or whether to evacuate the stomach should be based on the state of the patient, the hydrocarbon's viscosity, and the involvement of other more dangerous chemicals. The viscosity of the fuel is extremely important and may determine the extent of the lung damage following aspiration. For conscious patients with operational gag reflexes and without spontaneous emesis, induced vomiting seems to be the preferred method of gastric emptying (Ellenhom and Barceloux 1988; Goldfrank et al. 1990; Ng et al. 1974; Shirkey 1971; Zieserl l979); otherwise, endotracheal intubation followed by gastric lavage has been suggested (Ellenhom and Barceloux 1988; Haddad and Winchester 1990).

Controversy also exists over whether or not to administer activated charcoal (to bind the hydrocarbon) or cathartics (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; Haddad and Winchester 1990; HSDB 1998; Litovitz and Greene 1988; Shirkey 1971; Stutz and Janusz 1988; Zieserl 1979). Some question the overall effectiveness of activated charcoal and cathartics (Goldfrank et al. 1990; Litovitz and Greene 1988; Zieserl 1979). In addition, activated charcoal may cause vomiting (HSDB 1998), which may or may not be desired. Most agree, however, that if cathartics are administered, they should be saline cathartics, such as magnesium or sodium sulfate or citrate, and not oil-based cathartics such as mineral oil (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; Haddad and Winchester 1990; Stutz and Janusz 1988).

In general, administration of antibiotics andfor corticosteroids does not appear useful in treating hydrocarbon pneumonitis (Brown et al. 1974; Goldfrank et al. 1990; Haddad and Winchester 1990; HSDB 1998; Steele et al. 1972; Wolfsdorf and Kundig 1974; Zieserl 1979). In fact, one study has suggested that steroid administration may increase bacterial colonization in the lungs (Brown et al. 1974). The use of antibiotics is recommended only to treat secondary lung infections (Haddad and Winchester 1990; HSDB 1998; Zieserl 1979).

If the skin is exposed to jet fuels, washing the area of contact with large amounts of soapy water is recommended (CONCAWE 1985; Ellenhom and Barceloux 1988; Goldfrank et al. 1990; HSDB 1998; Stutz and Janusz 1988). If blistering or skin loss occurs, then the use of sterile water alone is suggested

(CONCAWE 1985). For ocular exposure, flushing the eyes liberally with water (CONCAWE 1985; HSDB 1998; Stutz and Janusz 1988) and, if necessary, using proparacaine hydrochloride to assist the irrigation (Bronstein and Currance 1988), are the recommended treatment protocols.

2.9.2 Reducing Body Burden

Little is known about the toxicokinetics of jet fuels, and there are no known methods for the reduction of body burden.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

Although lung response to aerosolized kerosene and the effect of kerosene on heme biosynthesis have been partially investigated, the toxicities of jet fuels as well as their mechanisms are not well defined. As such, no known therapies are available to disrupt the mechanisms of action.

2.10 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of JP-5 and JP-8 is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of JP-5 and JP-8.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs-till be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.10.1 Existing Information on Health Effects of JP-5 and JP-8

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to JP-5 and JP-8 are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of JP-5 and JP-8. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

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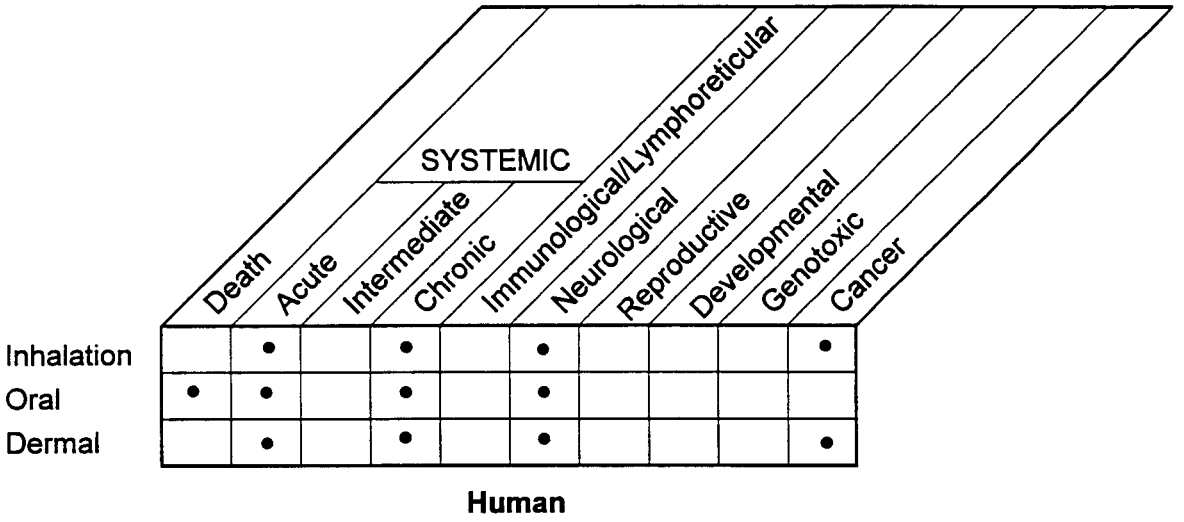
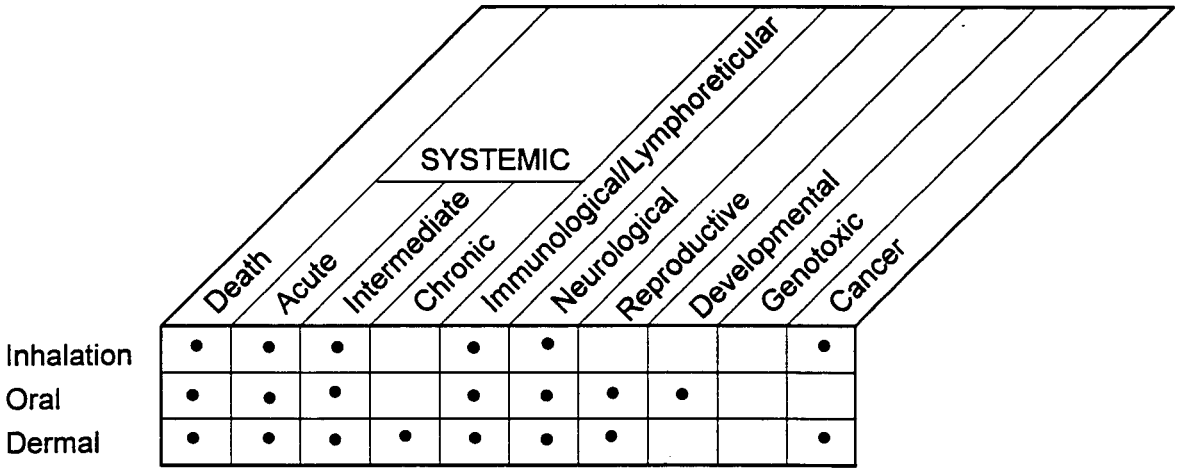
Information is available in humans on acute, intermediate, and chronic systemic effects as well as on neurological and carcinogenic effects following inhalation exposure to JP-5 and JP-8 or some of their compositional analogs; on death, acute systemic, and neurological effects following ingestion; and on intermediate, acute, and chronic systemic and neurological effects following dermal exposure. Information is also available in animals on death and acute and intermediate systemic effects as well as on neurological, developmental, reproductive, genotoxic, and carcinogenic effects following inhalation exposure to jet fuels or some of the compositional analogs; on death and acute systemic effects as well as on neurological and genotoxic effects following ingestion; and on death, acute, intermediate, and chronic systemic effects and immunological, neurological, reproductive, and carcinogenic effects following dermal exposure. Therefore, as Figure 2-4 shows, the majority of the data on health effects of jet fuels concern inhalation or dermal

FIGURE 2-4. Existing Information on Health Effects of JP-5 and JP-8



Human



Animal

• Existing Studies

exposure of animals; however, there are some data for all routes of exposure in both laboratory animals and humans.

2.10.2 Identification of Data Needs

The following are topical sections that identify gaps in the present state of knowledge concerning the toxicology of JP-5 and JP-8. Each of the sections identifies specific areas in which additional data are needed to gain a greater understanding of the toxicity of jet fuels and their constituents as well as of the biochemical mechanisms of their toxicity.

Acute-Duration Exposure. There are many case studies that identify respiratory, neurological, and gastrointestinal effects as the primary effects in humans induced by acute exposures to jet fuels or compositional analogs, particularly by the oral route (Akamaguna and Odita 1983; Aldy et al. 1978; Annobil 1983; Annobil and Ogunbiyi 1991; Mahdi 1988; Santhanakrishnan and Chithra 1978; St. John 1982; Subcommittee on Accidental Poisoning 1962) and, to a lesser extent, by inhalation exposure (Porter 1990). Dermal irritation is also well documented for both humans (Annobill988; Mosconi et al. 1988; Tagami and Ogino 1973) and animals (Kinkead et al. 1992a; NTP/NIH 1986; Upreti et al. 1989) after dermal exposure. Dermal sensitization has also been reported in animals after exposure to JP-5 (Cowan and Jenkins 1981a, 1981 b; Kinkead et al. 1992b) and JP-8 (Kinkead et al. 1992a). Some data indicate that cardiovascular, hematological, and renal effects may occur in humans exposed to the vapor of JP-5 (Porter 1990).

Dose-response data are largely lacking for the effects noted in both humans and laboratory animals. A dose-response relationship was noted in rats following a single exposure to kerosene by oral gavage for the following effects: death, unsteady gait, and drowsiness (Muralidhara et al. 1982). Following gestational exposure by gavage, decreased maternal body weight gain was noted in rats (Cooper and Mattie 1996). However, the majority of animal data have not been verified by more than one study using the same jet fuel, species, and/or route of exposure, and some of the studies only tested one dose (Brown et al. 1974; Casaco et al. 1982; Garcia et al. 1988b; Goodwin et al. 1988; Nouri et al. 1983; Upreti et al. 1989). Additional dose-response data are needed to serve as the basis of both acute oral and acute inhalation MRLs. Acute oral LD_{50} data are available for kerosene in guinea pigs and rabbits (Deichmann et al. 1944). Additional data are needed regarding inhalation and dermal exposures in various species to verify the renal toxicity of jet fuels noted in a few individuals and dermal exposure animal models.

Intermediate-Duration Exposure. Animal data are available for intermediate exposures by the inhalation, oral, and dermal routes. Limited animal data were located for the oral route. Most of these studies found no evidence of toxicity in any of the exposure conditions used (Bruner 1984; Carpenter et al. 1976; NTP/NIH 1986), but toxicity has been observed in rats in an intermediate-duration oral study (Mattie et al. 1995). However, the lack of toxicity in these studies has not been verified by more than one study using the same material, species, andfor route of exposure. Dose-response data are needed to serve as the basis of intermediate oral MRLs. Intermediate-duration studies (inhalation and oral) that compare the toxicity of all jet fuels would be especially useful for MRL derivation. These studies should examine all histopathological end points, as well as perform clinical and biochemical evaluations (including hematology). It would also be useful to administer the jet fuel with a vehicle to possibly prevent the irritation and hyperplasia observed in the gastrointestinal tract in rats in the Mattie et al. (1995) study, which did examine some of these endpoints.

One well-conducted study in mice describes effects (death, hepatic karyomegaly, and dermatitis) from dermal exposures to JP-5 (NTP/NIH 1986). Another study found dose-dependent increases in blood lactate and pyruvate levels and decreases in blood glucose levels in rats after inhalation of kerosene vapor (Starek and Vojtisek 1986). However, neither of these studies can be used for MRL derivation. In the first study the data were obtained following dermal exposures, which cannot be used to derive an MRL. In the other, the biochemical and organ weight effects induced by inhalation of the jet fuels were not supported by pathological changes or the organs affected had not been histopathologically identified as targets in other studies. A third study, in which rats were administered JP-8 orally at doses up to 3,000 mg/kg for 90 days showed decreased lymphocytes, decreased body weights, and gastrointestinal irritation and hyperplasia (Mattie et al. 1995). However, an intermediate-duration oral MRL could not be derived from this study because, as indicated above, treated animals received neat JP-8 by gavage, an administration that is of concern because of the appearance of gastrointestinal irritation.

Chronic-Duration Exposure and Cancer. Epidemiological data regarding respiratory and dermal effects from chronic exposures to jet fuels or petroleum products of similar composition in humans are described elsewhere (see Epidemiological and Human Dosimetry Studies in this section). No other information is available for humans regarding chronic inhalation or oral exposures. A single animal study addressed carcinogenicity in animals via inhalation (Bruner 1984). Animal model data were available for the carcinogenic effects of chronic dermal exposure. It is apparent that chronic dermal application of jet fuels can induce tumorigenesis; however, both the mechanism of induction and the relevance of tumor induction to humans are poorly defined. As such, further elucidation of the biochemical pathway, the relevance of dermal

exposure to humans, and the incidence of tumor induction at sites remote from a dermal exposure site would be of value.

The demonstration of renal toxicity in animal models has been considered significant since case studies have also reported such toxicity. However, data exist that appear to associate the renal toxicity with water loss due to skin lesions induced by chronic dermal application of jet fuels rather than systemic toxicity. Data that clarify this effect would be of interest.

Dose-response data to serve as the basis of chronic inhalation MRLs are also needed.

A thymus tumor was observed in 1 of 10 rats in an intermediate-duration oral study using undiluted JP-8 (Mattie et al. 1995). It is not possible to determine whether this was incidental due to the small number of animals used and the short duration of the study. Long-term oral studies using JP-8 would be useful to determine the carcinogenic potential of JP-8.

Genotoxicity. The data available suggest that these jet fuels are not mutagenic and do not present a genotoxic hazard to humans.

Reproductive Toxicity. No information was found regarding reproductive toxicity in humans from inhalation, oral, or dermal exposures to jet fuels. There were no pathological changes in the reproductive organs of mice following chronic and/or intermediate dermal exposures to JP-5 (NTP/NIH 1986) or in the testes of rats after oral exposure to JP-8 for go-days (Mattie et al. 1995). In the absence of route-specific data, and limited pharmacokinetic data, it is not possible to predict whether JP-5 or JP-8 might affect reproduction across routes of exposures. Additional data are needed to identify the toxic potential of jet fuels on the reproductive system by all routes of exposure.

Developmental Toxicity. No information was found regarding developmental toxicity in humans from inhalation, oral, or dermal exposures to jet fuels. Significant decreases in fetal body weight were found after pregnant rats were treated orally with JP-8 compared to controls from gestational days 6-15 (Cooper and Mattie 1996). These changes in fetal body weight were found in conjunction with significant decreases in maternal body weight gain at 1,000 mgkg and in adjusted maternal body weight at 1,500 mgkg. No other signs of toxicity were found in fetuses or dams in this study. Although pharmacokinetic data may support the potential of JP-8 to cause similar effects by other routes of exposure, it is not possible to predict the levels at

which these effects might occur. Additional data are needed to identify the toxic potential of jet fuels regarding developmental effects by all routes of exposure.

Immunotoxicity. No information was found regarding immunotoxicity in humans from inhalation, oral, or dermal exposures to either JP-5, JP-8, or to petroleum products with similar compositions. Three animal studies were identified that tested immunological effects, one using rats and two using mice. No histopathological changes were observed in the spleen or lymph nodes of male rats treated by gavage with JP-8 (undiluted) for 90-days (Mattie et al. 1995). The mice studies identified cellular effects in the bone marrow, lymph nodes, and/or thymus and decreases in the relative weights of the lymph nodes and thymus from acute dermal exposures to kerosene (Upreti et al. 1989) and from chronic dermal exposures to JP-5 (NTP/NIH 1986). However, the toxicological significance of these effects on the immune system cannot be determined from these data. Additional data are needed to identify the toxic potential of jet fuels on the immune system by all routes of exposure and in various animal systems.

Neurotoxicity. Epidemiological data regarding neurological effects from chronic exposures to jet fuels in humans are described elsewhere (see Epidemiological and Human Dosimetry Studies in this section). Neurological effects from oral exposures are well documented in humans by case studies (Akamaguna and Odita 1983; Aldy et al. 1978; Coruh and Inal 1966; Dudin et al. 1991; Lucas 1994; Mahdi 1988; Majeed et al. 1981; Nouri and Al-Rahim 1970; Saksena 1969; Santhanakrishnan and Chithra 1978; St. John 1982; Subcommittee on Accidental Poisoning 1962). There is limited information in animals regarding neurotoxic effects following oral exposure (Cooper and Mattie 1996; Mattie et al. 1995; Muralidhara et al. 1982) or aspiration (Nouri et al. 1983). Some information is available that identifies neurological effects in humans from inhalation exposures. The available data indicate that coordination and concentration difficulties, headache, intoxication, and/or anorexia may be induced by inhalation of JP-5 vapor (Porter 1990) and that sensory impairment may be induced by deodorized kerosene vapor (Carpenter et al. 1976).
A 90-day oral study in rats found no treatment-related histopathological changes in the brain or sciatic nerve

(Mattie et al. 1995). One animal study found no histopathological changes in the organs of the nervous system in mice following chronic and/or intermediate dermal exposures to JP-5 (NTP/NIH 1986). However, increased response to tactile stimuli and hyperactivity occurred in mice from acute dermal exposures to kerosene (Upreti et al. 1989).

In summary, there is much information regarding the specific neurological effects that may be induced by oral exposures to kerosene in humans, but dose-response data are lacking for both animals and humans. More information is needed to identify the inhalation and dermal effects of jet fuels on the nervous system in both animals and humans.

Epidemiological and Human Dosimetry Studies. There were limited data that indicated that the use of kerosene stoves in the home is not associated with increased respiratory illness (Azizi and Henry 199 1; Tominaga and Itoh 1985), although chronic dermal exposure to kerosene has been related to dermatosis (Jee et al. 1985).

A number of effects have been associated with chronic exposure to jet fuel in factory workers and Air Force employees (Knave et al. 1976, 1978; Smith et al. 1997; Struwe et al. 1983). These effects have included increases in the occurrence of neurasthenia (anxiety and/or mental depression, fatigue, depressed mood, lack of initiative, dizziness, palpitations, thoracic oppression, sleep disturbances), changes in postural balance, or eye irritation. Psychological tests found that attention and sensorimotor speed were impaired in exposed workers, but there were no effects on memory functions or manual dexterity. EEG tests suggested that there may have been instability in the thalamocortical system in the exposed group. Postural balance studies suggested a subtle effect on vestibular/ proprioception functionalities (Smith et al. 1997). However, the type of jet fuels was not noted and there was no control for exposure to other compounds. Inhalation exposure was likely since jet fuel vapor was detected by the study authors; however, dermal and oral (i.e., eating with contaminated hands) exposures may also have been possible.

Limited epidemiological information exists for carcinogenicity in humans following inhalation exposure to kerosene (vapor). No strong association was seen between bronchial cancer and the use of kerosene or gas for cooking (Chan et al. 1979). Of the women with bronchial cancer, mainly adenocarcinomas, 48% were non-smokers. There was no association with their place of residence or occupation, and the cause of the cancer is unknown (Chan et al. 1979). Actual kerosene exposure is unknown since Chan et al. (1979) assumed exposure occurred if a kerosene stove was used. A significant association between incidence of astrocytoma in children and the reported use of kerosene by their mothers during pregnancy, when adjusted for income, was reported by Bunin et al. (1994). However, this data should be interpreted with caution because of maternal exposure to other agents and lack of data on exposure duration and concentrations. A significant association between kidney cancer and jet fuel exposure was observed in a population-based casereferent study, but some of the exposed individuals were also exposed to other substances, such as aviation

gasoline (Siemiatycki et al. 1987). No association between exposure to aircraft fuel and lymphatic or other cancers was detected in a historical prospective study (Selden and Ahlborg 199 1). Animal data have been reported that indicate that chronic dermal application of middle distillate fuels can induce tumorigenesis (Clark et al 1988; Freeman et al. 1993; Schultz et al. 1981; Skisak 1991); however, the mechanism of tumorigenesis remains nebulous. Exposures to jet fuels generally occur in the occupational setting. For this reason, it is difficult to control for confounding factors and to identify levels and durations of exposure. Therefore, if future studies are going to yield useful data concerning the toxicity of jet fuel in humans, rigorous controls must be planned for any confounding factors. Additional cohort studies that control for these factors and use adequate numbers of subjects would be useful to examine possible associations between cancer and fuel exposure. These considerations should also be taken into account when planning studies for the future monitoring of individuals living near hazardous waste sites.

Biomarkers of Exposure and Effect. No specific biomarkers of exposure or effect were identified for either JP-5 or JP-8.

Exposure. Procedures do exist for identifying and quantifying the hydrocarbon components of jet fuels or their analogs, specifically kerosene, in blood, urine, and stomach contents (Hara et al. 1988; Kimura et al. 1988,1991; Yamaguchi et al. 1992). Another potential biomarker of exposure to kerosene is the odor of kerosene on the breath or clothing (Annobil 1988; Tagami and Ogino 1973; Zucker et al. 1986). However, the odors of middle distillates are so similar that the marker would probably lack specificity. Studies delineating the metabolism and excretion of jet fuels are needed to identify potential biomarkers of exposure.

Effect. Although not specific for jet fuels, aminolevulinic acid (ALA) could potentially be used as an adjunct or supplemental biomarker. Kerosene may affect heme metabolism by decreasing the activities of enzymes in the heme biosynthetic pathway (hepatic α-ALA dehydratase and α-ALA synthetase) (Rae and Pandya 1980). Therefore, it may be possible that this effect would generate increased ALA in the urine of exposed individuals. Additional studies of acute, intermediate, and chronic exposure are needed to identify biomarkers of effects for specific target organs following exposure to jet fuels.

Absorption, Distribution, Metabolism, and Excretion. No quantitative data were located regarding the absorption, distribution, metabolism, or excretion of jet fuels following inhalation, oral, or dermal exposure in humans. Very limited data indicate that kerosene is poorly absorbed from the gastrointestinal tract and is distributed to various tissues, although accumulation is low (Mann et al. 1977). Another study in

humans suggests that respiratory toxicity may result from both aspiration from vomiting and gastrointestinal absorption (Subcommittee on Accidental Poisoning 1962). However, aspiration is the primary concern following ingestion. Acute, intermediate, and chronic data are needed to assess the relative rates and extent of absorption, distribution, and excretion of jet fuels with respect to all three routes of exposure as well as with respect to time and dose.

Comparative Toxicokinetics. Limited data are available regarding comparative toxicokinetics. The acute oral LD_{50} values in guinea pigs and rabbits for kerosene have been reported to be 16,320 mg/kg and 22,720 mg/kg, respectively (Deichmann et al. 1944). These data suggest that there may be species differences in the oral toxicity of kerosene (suggesting a species difference for JP-5); however, more data would be needed to thoroughly examine species variation in toxicokinetics. This information would be useful for identifying similar target organs and for adequately assessing which animals can serve as the best models for humans as well as defining mechanisms of action.

Methods for Reducing Toxic Effects. The mitigation procedures for both JP-5 and JP-8 parallel those for hydrocarbon poisoning. Several treatments for hydrocarbon poisoning have been considered controversial: gastric decontamination, induced emesis versus gastric lavage, and administration of activated charcoal, cathartics, antibiotics, and corticosteroids. Most studies indicate that antibiotics and corticosteroids are not effective treatments for hydrocarbon-induced pneumonitis (Brown et al. 1974; Goldfrank et al. 1990; Haddad and Winchester 1990; HSDB 1998; Steele et al. 1972; Wolfsdorf and Kundig 1974; Zieserl 1979). However, more research regarding the usefulness of cathartics and activated charcoal is needed. In addition, elucidating the toxicokinetics of absorption of jet fuels in the gastrointestinal tract would help determine whether gastric decontamination is worth the risk of pulmonary aspiration. Related to gastric decontamination is the question of whether induced emesis is safer than gastric lavage. Since there are presently no known antidotes for hydrocarbon poisoning, research in this area would be beneficial as well.

2.10.3 Ongoing Studies

No on-going studies evaluating the health effects or toxicokinetics of either JP-5 or JP-8 were located.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Information regarding the chemical identities of JP-5 and JP-8 is located in Table 3- 1. Information on the composition of jet fuel no. 1 (kerosene) and JP-5 is presented in Table 3-2. Information on the composition of JP-8 is presented in Table 3-3.

Both JP-5 and JP-8 are distillate fuels consisting of distilled process streams refined from crude petroleum. Characteristics of JP-8 fuel (such as density and distillation temperatures) are very similar to those of JP-5 (DOD 1992). There is no standard formula for jet fuels. Their exact composition depends on the crude oil from which they were refined. Variability in fuel composition occurs because of differences in the original crude oil (Custance et al. 1992; IARC 1989) and in the individual additives. As a result of this variability, little information exists on the exact chemical and physical properties of jet fuels (Custance et al. 1992). However, the differences in these fuels are minor. The primary ingredient of both JP-5 and JP-8 is kerosene, and the composition of these fuels is basically the same as kerosene, with the exceptions that they are made under more stringent conditions and contain various additives not found in kerosene (DOD 1992; IARC 1989). The crude oil from which JP-5 and JP-8 are refined is derived from petroleum, tar sands, oil shale, or mixtures thereof (DOD 1992). Typical additives to JP-5 and JP-8 include antioxidants (including phenolic antioxidants), static inhibitors, corrosion inhibitors, fuel system icing inhibitors, lubrication improvers, biocides, and thermal stability improvers (DOD 1992; IARC 1989; Pearson 1988). These additives are used only in specified amounts, as governed by military specifications (DOD 1992; IARC 1989). Straight-run kerosene, the basic component of the kerosene used for jet fuels, consists of hydrocarbons with carbon numbers mostly in the C_9–C_{16} range. Like all jet fuels, straight-run kerosene consists of a complex mixture of aliphatic and aromatic hydrocarbons (LARC 1989). Aliphatic alkanes (paraffins) and cycloalkanes (naphthenes) are hydrogen saturated, clean burning, and chemically stable and together constitute the major part of kerosene (IARC 1989). Aromatics comprise lo-20% and olefins less than 1% of the jet fuels (JARC 1989). The boiling range of kerosene, JP-5, and JP-8 is well above the boiling point of benzene (a carcinogenic aromatic) and many polycyclic aromatic hydrocarbons (PAHs); consequently, the benzene content of kerosene and these jet fuels is normally below 0.02%, and PAHs are virtually excluded (IARC 1989).

TABLE 3-1. Chemical Identity of JP-5 & JP-8

Characteristic	JP-5	JP-8
Synonym(s)	NATO F-44; AVCAT; MIL-T-5624M; aviation kerosene; kerosene; fuel oil no. 1; jet kerosine; turbo fuel A; straight run kerosene; distillate fuel oils, light[a,b,c,d]	NATO F-34; AVTUR; MIL-T-83133B; aviation kerosene; kerosene; fuel oil no. 1; jet kerosine; turbo fuel A; straight run kerosene; distillate fuel oils, light[a,b,c,d]
Registered trade name(s)	No data	No data
Chemical formula[e]	No data	No data
Chemical structure[e]	No data	No data
Identification numbers:		
CAS registry	8008-20-6[f]/70892-10-3[g]	8008-20-6[b]/70892-10-3[g]
NIOSH RTECS	OA5500000[b] (kerosene)	OA5500000[b] (kerosene)
EPA hazardous waste	No data	No data
OHM/TADS	7217063[g] (kerosene)	7217063[g] (kerosene)
DOT/UN/NA/IMCO shipping	UN 1223; IMO 3.3[b] (kerosene)	UN 1223; IMO 3.3[b] (kerosene)
HSDB	632[b]	632[b] (kerosene)
NCI	No data	No data

[a]RTECS 1998
[b]HSDB 1998
[c]IARC 1989
[d]Army 1988
[e]Fuel oils are mixtures of various hydrocarbons designed to meet specifications set forth by the American Society for Testing and Materials (DOD 1992); therefore, chemical structure and chemical formula cannot be determined.
[f]NTP/NIH 1986
[g]OHM/TADS 1985

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

TABLE 3-2. Analysis of Fuel Oil No. 1 and JP-5

	Volume %	
Hydrocarbon type	Fuel oil no. 1[a]	JP-5[b]
Paraffins (*n*- and iso-)	52.4	30.8
Monocycloparaffins	21.3	No data
Bicycloparaffins	5.1	No data
Tricycloparaffins	0.8	No data
Total cycloparaffins	27.2	52.8
Total saturated hydrocarbons	79.7	No data
Olefins	No data	0.5
Alkylbenzenes	13.5	No data
Indans/tetralins	3.3	No data
Dinaphthenobenzenes/indenes	0.9	No data
Naphthalenes	2.8	No data
Biphenyls/acenaphthenes	0.4	No data
Fluorenes/acenaphthylenes	No data	No data
Phenanthrenes	No data	No data
Total aromatic hydrocarbons	23.6	15.9

[a]Derived from IARC 1989; provided by the American Petroleum Institute
[b]Derived from sample lot used in NTP/NIH 1986 study

TABLE 3-3. Composition of Surrogate JP-8[a]

Hydrocarbon type	Weight %
Isooctane	3.66
Methylcyclohexane	3.51
m-Xylene	3.95
Cyclooctane	4.54
Decane	16.08
Butylbenzene	4.72
1,2,4,5-Tetramethylbenzene	4.28
Tetralin	4.14
Dodecane	22.54
1-Methylnaphthalene	3.49
Tetradecane	16.87
Hexadecane	12.22

[a]Air Force 1991

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of JP-5 and JP-8 is located in Table 3-4.

TABLE 3-4. Physical and Chemical Properties of Jet Fuels[a]

Characteristic	JP-5	JP-8
Molecular weight[b]	No data	No data
Color	Clear and bright[c]	Clear and bright[c]
Physical state	Liquid[d]	Liquid[d]
Melting point	-46°C[c]	-52°C[e] (sample lot)
Boiling point	170°C[f]	170°C[f]
	150–290°C[g]	150–290°C[g]
Density:		
at 15°C	0.788–0.845 kg/L[f]	0.775–0.840 kg/L[f]
Odor	Kerosene-like[e] (kerosene)	Kerosene-like[e] (kerosene)
Odor threshold (ppm)	1[h], 0.082[i] (kerosene)	1[h], 0.082[i] (kerosene)
Solubility		
Water at 20°C	≈5 mg/L[d] (kerosene)	≈5 mg/L[d] (kerosene)
Organic solvent(s)	Miscible with other petroleum solvents[i]	Miscible with other petroleum solvents[i]
Partition coefficients:	3.3–7.06[d] (kerosene)	3.3–7.06[d] (kerosene)
Log K_{ow}	9.6×10^{2} – 5.5×10^{6}[d]	9.6×10^{2} – 5.5×10^{6}[d]
Log K_{oc}	(kerosene)	(kerosene)
Vapor pressure at 21°C	2.12–26.4 mmHg[d] (kerosene)	2.12–26.4 mmHg[d] (kerosene)
Henry's law constant		
At 20°C - atm-m^3/mol	5.9×10^{-5} – 7.4[d] (kerosene)	5.9×10^{-5} – 7.4[d] (kerosene)
Autoignition temperature	229°C[h] (kerosene)	229°C[h] (kerosene)
Flashpoint (minimum)	60°C[c,e]	38°C[c,e]
Flammability limits (% volume in air)	0.7%–5%[h] (kerosene)	0.7%–5%[h] (kerosene)
Conversion factors	No data	No data
Explosive limits	0.7%–5%[j] (kerosene)	0.7%–5%[j] (kerosene)

[a]Values listed are specifications required or general characteristics of each class of jet fuels.
[b]Fuel oils are mixtures of various hydrocarbons designed to meet specifications set forth by the American Society for Testing and Materials (DOD 1992); therefore, molecular weight cannot be determined.
[c]DOD 1992
[d]Air Force 1989b
[e]Air Force 1989a
[f]Army 1988
[g]IARC 1989
[h]Coast Guard 1985
[i]OHM/TADS 1985
[j]HSDB 1998

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Jet fuels are produced from refined crude petroleum to meet specifications for particular uses (Air Force 1989b; IARC 1989). These specifications are designated by the American Society for Testing and Materials (ASTM) (IARC 1989). Light jet fuels such as jet fuel no. 1 (kerosene) are refined from straight distillation of crude oil or distillation of crude oil in the presence of a catalyst. Fuels such as JP-5 and JP-8 are then chemically enhanced with antioxidants, dispersants, or corrosion inhibitors to meet the requirements for a specific application. Jet fuel no. 1 is a product of the straight-run distillation of crude petroleum (HSDB 1998). It consists of a mixture of petroleum hydrocarbons, chiefly of the methane series, which typically have from 10 to 16 carbon atoms per molecule (HSDB 1998; IARC 1989). The typical components of the end product of jet fuel no. 1 include paraffins (*n*-, iso-, monocycle-, bicycle- and tricycle-), olefins, aromatics, and nitrogen and sulfur impurities (Air Force 1989b; IARC 1989).

Although most facilities that refine crude petroleum in the United States produce a jet fuel no. 1 fraction (HSDB 1998), only producers that market jet fuel no. 1 as an end product are listed as commercial manufacturers. These manufacturers are Claibome Gasoline Company (Claibome and Union Parish, Louisiana), Continental Oil Company (Acadia Parish, Louisiana), Sun Production Company (Starr County, Texas), Exxon Corporation (Pledger County, Texas), Atlantic Richfield Company (New York, New York), and Shell Oil Company (Houston, Texas) (HSDB 1998). Because JP-5 and JP-8 are not required to be reported under SARA Section 313, there are no data for JP-5 and JP-8 in the 1992 Toxics Release Inventory (TRI) (TR192 1994).

Production of kerosene has steadily decreased since 1970 (API 1991). The supply of kerosene produced in 1970 was 95,600,000 barrels. By 1975, production volume had dropped to 55,500,000 barrels. As of 1990, only 16,400,000 barrels of kerosene were produced. While the demand for kerosene has gradually declined with time, that for jet fuels has steadily increased. As a result, many refiners have recently chosen to produce Jet A-l (a commercial jet fuel very similar to JP-8) as their basic product and to simply divert a portion of the product for marketing as kerosene (IARC 1989). In the United States, production of jet fuels, including both kerosene-type (JP-5 and JP-8) and wide-cut fuels, increased from 268,452,000O barrels (37,636,000 tons) in 1970 to 406,137,000 barrels (56,939,000 tons) in 1985 (IARC 1989). In the countries of the Organization

for Economic Cooperation and Development (OECD), production increased from 411,282,000 barrels (57,659,000 tons) to 643,967,000 barrels (90,280,000 tons) during the same time (IARC 1989).

4.2 IMPORT/EXPORT

Imports of distillate fuels have varied from year to year since the 1970s. Since 1975, imports of distillate jet fuels such as jet fuel no. 1 into the United States have been low compared to the amount of distillate jet fuels produced in the United States (API 1991). Imports of kerosene fluctuated between 1975 and 1984 and then showed a steady increase from 1985 to 1987, attaining an annual maximum of 6,935,000 barrels in 1987. Between 1988 and 1990, imports of kerosene decreased to a low of 1,825,000 barrels (API 1991).

During the five-year period from 1990 to 1994, kerosene-type jet motor fuel imports into the U.S. have been steady, averaging approximately 27.3 million barrels annually. In 199 1, however, the year of the Persian Gulf War, imports reached a low of 19.7 million barrels. Imports rose to a peak of 29.4 million barrels in 1994 and declined slightly to 28.0 million barrels in 1996 (NTDB 1997). Import data for 1995 is not available.

Exports of jet fuel no. 1 between 1972 and 1975 ranged from 100,000 barrels (14,000 tons) in 1972 to 699,000 barrels (98,000 tons) in 1975 (HSDB 1998). Exports of distillate jet fuels increased almost 1 00-fold between 1975 and 1990 (API 1991). Little kerosene has been exported from the United States since the 1970s. In 1971, approximately 365,000 barrels were exported from the United States. The next 2 years for which export volumes were reported for kerosene were 1983 and 1984, when 365,000 barrels were exported each year. However, export volumes doubled from 730,000 barrels in 1986 to 1,820,000 barrels in 1990 (API 1991). Comprehensive export data for kerosene prior to 1986 are not available. Kerosene exportation between 1987 and 1989 remained relatively constant with a yearly export average of approximately 547,500 barrels. However, by 1990, the annual export of kerosene was 2,190,000 barrels (API 1991), an increase of approximately 400%. U.S. exports of kerosene-type jet motor fuels declined during the 5-year period between 1991 and 1995, from 14.1 to 9.4 million barrels annually NTDB 1997). The largest decrease occurred in 1994 when the quantity dropped 8.9 million barrels from the previous year, from 15.3 in 1993 to 6.4 million barrels in 1994 (NTDB 1997).

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.3 USE

Aviation turbine fuels were not used until the 1930s when the first turbojet engine was developed (IARC 1989). Jet-powered aircraft had only limited use in World War II, but further military and commercial developments allowed jet engines to dominate as power sources for aircraft in the 1960s. JP-1, a mixture of gasoline and kerosene, was the first jet fuel used by the U.S. Army Air Corps in 1944 (Army 1989). A military specification for JP-4, also a mixture of gasoline and kerosene, was first issued in 195 1 (Army 1989). JP-5 was developed by the U.S. Navy in the early 1950s for aircraft use aboard aircraft carriers. Its lower volatility and higher minimum flashpoint (140°F) compared to JP-4 made it safer in the event of a shipboard spill or crash (Army 1989). During the Vietnam War, the Navy's JP-5 proved to be a superior fuel for combat aircraft, as compared to the Air Force's JP-4; the Navy had lower loss rates as a result of fewer gunfire-initiated and post-crash fires and explosions (Air Force 1989a). Statistics showed that the probability of post-crash fires with JP4-fueled aircraft was 83%, but for kerosene (JP5)-fueled aircraft, the probability was only 35% (Air Force 1987). The Navy has also used JP-5 as an alternative fuel on surface ships (Risher 1995). As a result, the Air Force initiated a program to replace JP-4 with a safer, kerosene-based fuel. After extensive tests, Commercial Jet A-1, a low-freezing-point kerosene fuel used by commercial airlines, was determined to be a suitable replacement, and a military specification for JP-8 was prepared and published in 1976 (Air Force 1987). JP-8 is identical to Jet A-l, except for the addition of a fuel system icing inhibitor, a corrosion inhibitor, and a lubricity additive. For continental U.S. flights, U.S. commercial airlines use Jet A, which is basically the same as Jet A-l with a higher freeze point, making it unsuitable for military use (Air Force 1987). Properties of JP-8 were chosen to provide: (1) low volatility, as measured by flashpoint (in order to minimize in-flight and post-crash aircraft fires); (2) low freezing point (needed for high-altitude and worldwide operations); (3) high availability in wartime and low cost in peacetime; and (4) compatibility with existing aircraft (Air Force 1989a). In 1979, the U.S. Air Force switched from JP-4 to JP-8 for its operations in Great Britain (Air Force 1987). NATO has begun the process of switching to JP-8 as the single fuel for land-based air and ground forces. This conversion to one fuel for use by NATO ground and air forces is expected to result in substantial logistics and operations benefits (Army 1989). The U.S. Air Force is currently planning a domestic conversion from naphtha-based JP-4 jet fuel to distillate-based JP-8 jet fuel (Salthouse 1992).

4.4 DISPOSAL

Vapors generated in tank truck loading of jet fuels can be disposed of by the installation of a vapor recovery system (NIOSH 1989). Runoff of jet fuels from loading and unloading aircraft operations can be separated by an on-site oil/water separation system.

Several methods have been investigated for the disposal of jet fuels spilled onto soil from normal aircraft operations or from accidental spills. One method, *in situ* soil venting, involves using vacuum blowers to pull large amounts of air through soil contaminated with jet fuels (Elliot and DePaoli 1990). The vacuum pulls out the soil gas, and the jet fuel contaminants volatilize as a result of disrupted equilibrium. Incineration of free-product extracted from contaminated media is another method of disposal proposed for soils and water contaminated with jet fuels (OHM/TADS 1985). Incineration of soils contaminated with jet fuels has also been investigated (OHM/TADS 1985). Other methods include absorption (straw, polyurethane foam, activated carbon, and peat have been used as absorbents), gelling agents, combustion promoters, dispersants, and mechanical systems (OHM/TADS 1985). Biodegradation has also been suggested as a means of disposal for spills onto soil (OHM/TADS 1985). Hydrocarbon-degrading bacteria have been shown to degrade petroleum products into smaller units and eventually into nonseparable particles (Butt et al. 1988). Soil contaminated with jet fuel no. 1 was found to have a growth response of 10^6 colony-forming units per mL in 7 out of 21 types of bacteria isolated for sample study (Butt et al. 1988). For more information on biodegradation, refer to Chapter 5.

Wastes containing JP-5 and JP-8 are considered hazardous if they meet certain criteria specified by law. Hazardous wastes are subject to the handling, transport, treatment, storage, and disposal regulations as promulgated under the Resource Conservation and Recovery Act (HSDB 1998; IRPTC 1985). Regulations governing the treatment and disposal of wastes containing JP-5 and JP-8 are detailed in Chapter 7.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

JP-5 and JP-8 are complex mixtures of aromatic and aliphatic hydrocarbons whose exposure potentials are based on the mixtures themselves and on the individual components of the mixtures (primarily n-alkanes, branched alkanes, benzene and alkylbenzenes, naphthalenes, and PAHs, particularly in the case of environmental exposures once degradation begins). There are few methods for analyzing the environmental fate of jet fuels *per se*; instead, methods are used to analyze the proportions of the component hydrocarbons of jet fuels.

Jet fuel may be released to the environment by in-flight jettisoning of fuel and from spills or leaks to soil or water during use, storage, or transportation. Jet fuel jettisoned from planes can be transported via airborne dispersion, and some of it can be transformed photochemically to ozone and other components of smog. Jet fuel may form aerosols as a result of reactions with atmospheric chemicals, but the specific composition of the particulate material is not known. Most of the jet fuel released to water evaporates into the air. The more volatile components of jet fuels (low molecular weight alkanes) evaporate from soil and water and enter the atmosphere where they are degraded. Components with higher boiling points persist longer in soil and water. Some components of JP-5 and JP-8 are soluble in water (e.g., the aromatics–benzene, toluene, and xylene). Under turbulent water conditions, the more soluble hydrocarbons remain dissolved longer and may partition to soils and sediments and be biodegraded. The rate and extent of biodegradation are dependent on the ambient temperature, the presence of a sufficient number of microorganisms capable of metabolizing the component hydrocarbons, the amount of aromatic species in the jet fuel, and the concentration of jet fuel. Some components also volatilize or migrate through the soil to groundwater.

The National Occupational Exposure Survey conducted by NIOSH between 1980 and 1983 estimated that 1,076,5 18 employees (including 96,255 females) were exposed to kerosene, a primary component of JP-5 and JP-8, in the workplace. Worker exposure was most likely in industries associated with machinery and special trade contractors. Populations most likely to be exposed to JP-5 and JP-8 include those involved in jet fuel manufacturing or refueling operations, populations near an area where JP-5 or JP-8 have been dumped, and populations working or living on military bases where the fuels are used or stored (and where leaks and spills are likely to occur).

5. POTENTIAL FOR HUMAN EXPOSURE

JP-5 and JP-8 have been found in at least 22 of the 1,445 current or former EPA National Priorities List (NPL) sites (HazDat 1997). However, the number of sites evaluated for JP-5 and JP-8 is not known. The frequency of these sites can be seen in Figure 5-1. Of these sites, all are located in the United States.

5.2 RELEASES TO THE ENVIRONMENT

JP-5 and JP-8 are fuel mixtures used by the U.S. military and NATO as aviation fuels. As a result of normal aircraft operations and fuel storage, JP-5 and JP-8 can be released into the environment. Under some conditions, it is common practice for aircraft to jettison excess fuel into the air, releasing it into the environment (IARC 1989).

Releases of JP-5 and JP-8 are not required to be reported under SARA Section 313; consequently, there are no data for these compounds in the 1992 TRI (TR192 1994).

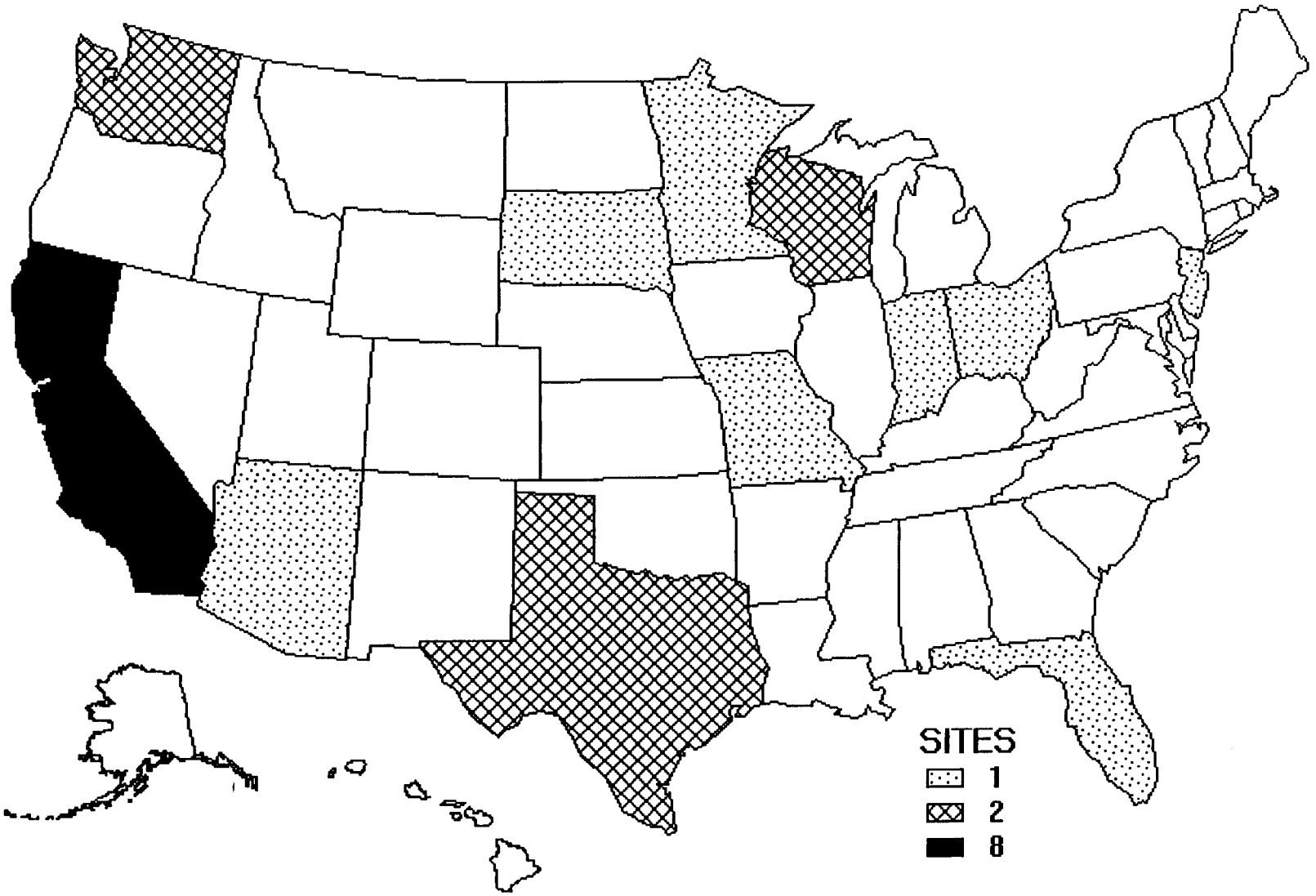
5.2.1 Air

JP-5 and JP-8 may be released into the air as vapors during aircraft loading and unloading operations or as a result of their normal use as a jet fuel for military aircraft (Air Force 1981a; NIOSH 1989). Releases into the air may also occur as a result of volatilization of JP-5 or JP-8 from contaminated soils or spill sites (Air Force 1989b). Atmospheric emissions of jet fuels may be determined primarily by detection of their volatile hydrocarbon components.

5.2.2 Water

Jet fuels may be released into surface water or groundwater as a result of leaking storage tanks and pipelines, surface runoff of unburned fuel residue, airborne jettisoning of fuels, and spills during dispensing operations and aircraft maintenance (Guiney et al. 1987a; Klein and Jenkins 1983). Leakage of jet fuels including JP-5 from storage tanks at the Patuxent Naval Air Test Center (NATC), Patuxent River, Maryland, has resulted in “severe environmental insult” to a Navy fuel farm and adjacent areas (Navy 1988). During the winter of 1976-l 977 a pipeline connecting underground storage tanks ruptured, releasing an undetermined amount of JP-5 and other jet fuels into the subsurface system. The existence and possible extent of groundwater contamination are unknown; however, surface waters near the site are known to be contaminated with jet

Figure 5-1. Frequency of NPL Sites with JP-5 and JP-8 Contamination*



*Derived from HazDat 1997

fuels including JP-5 (Arthur et al. 1992). On October 16, 1982, a crack in a petroleum pipeline near Ebensburg, Pennsylvania, released an estimated 1,3 10 barrels of "aviation kerosene" into a stream (Guiney et al. 1987a).

5.2.3 Soil

JP-5 and JP-8 may be released into soil as a result of accidental spills and leaks in underground or aboveground storage tank systems. From March to June 1971, an accidental spill released more than 14 tons of JP-5 jet fuel mixed with jet fuel no. 2 at a storage facility in Searsport, Maine (Dow et al. 1975). During the winter of 1976-1977, soils at a fuel farm at Patuxent NATC, Patuxent River, Maryland, were contaminated with an unknown quantity of JP-5 when a pipeline connecting underground storage tanks ruptured (Arthur et al. 1992). Since that time, site investigations have revealed that the fuel has moved through several acres of sandy soil to a depth of 20-30 feet (Arthur et al. 1992).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

The transport and dispersion of JP-5 and JP-8 are dependent on the water solubility and volatility of the component hydrocarbon fractions. Lower molecular weight hydrocarbons such as n-alkanes may volatilize relatively quickly from both water and soil, while larger aliphatics (greater than C_9 chain length) may be sorbed to organic particles in water or soil. Aromatic hydrocarbons will be dissolved in the aqueous phase in both soil and water and may undergo some volatilization. Information on the specific physical and chemical properties of several of the component hydrocarbons (e.g., benzene, toluene, xylene, and naphthalene) can be found in the ATSDR toxicological profiles for these chemicals. The many hydrocarbons that compose JP-5 and JP-8 can be divided into a few groups of hydrocarbon classes with similar properties (Air Force 1989b). These include paraffins (also called alkanes, which are saturated straight-chain hydrocarbons), cycloparaffrns (saturated cyclic hydrocarbons), aromatics (fully unsaturated cyclic compounds), and olefins (also called alkenes, which are unsaturated straight-chain and cyclic hydrocarbons). Paraffins and cycloparaffins (alkanes and cycloalkanes) are the major hydrocarbon components of JP-5 and JP-8 and together constitute approximately 80-90% by volume of the fuels (IARC 1989). Aromatics constitute approximately 17% of JP-8 and 18% of JP-5 (Army 1988). It is important to point out that the specific composition of jet fuels varies among manufacturers and probably among batches (Air Force 1989a; DOD 1992). JP-5 and JP-8 may

also contain low levels of nonhydrocarbon contaminants and additives including sulfur compounds, gums, naphthenic acids, antioxidants, static inhibitors, icing inhibitors, and corrosion inhibitors (DOD 1992; IARC 1989).

Transport processes have been shown to be more significant than transformation processes in determining the initial fate of lower molecular weight petroleum hydrocarbons released to soil and groundwater systems (Air Force 1989b). Evaporation from water is the major removal process for low molecular weight, volatile hydrocarbons, such as those found in JP-5 and JP-8 (EPA 1983). Loss of JP-8 from water was determined to be primarily due to evaporation in a quiescent flask test system study (Dean-Ross et al. 1992). Loss of individual hydrocarbon components of JP-8 was related to molecular weight and vapor pressure, with low molecular weight components (toluene and *n*-octane) being removed within 10 days, and high molecular weight components (1-methylnaphthalene and *n*-dodecane) persisting (Dean-Ross et al. 1992). Laboratory experiments have shown that the evaporation rate of jet fuel and its components increases with wind velocity and, to a lesser extent, with temperature and fuel-layer thickness (Air Force 1988). Comparisons of dissolution and evaporation rates under several wind-speed and mixing conditions showed that evaporation was the dominant fate process for jet fuel components in water.

In a study by Coleman et al. (1984), the partitioning of kerosene (the primary constituent of JP-5 and JP-8) into drinking water after 17 hours of incubation resulted in only 0.7% of the kerosene being dissolved in the water. Further analysis of the kerosene indicated that although kerosene contains approximately 50% aliphatic hydrocarbons (by weight percent), the water-soluble fractions (WSFs) contained primarily aromatic constituents (>93%) including benzenes and naphthalenes as shown below (Coleman et al. 1984).

		Water-soluble fraction	
	Whole product*	1/2 hour	17 hours
Kerosene			
Alkanes + cycloalkanes	68.6	4.5	0.5
Benzene + substituted benzenes	13.7	63.5	53.2
Naphthalene + substituted naphthalenes	5.7	29.6	44.8

*Estimated weight percent

JP-8 also evaporates from soil, although evaporation in not as important a fate process in soil as it is in water. When water/sediment slurries were treated with JP-8, rates of removal were much slower than from water

alone. The addition of sediments to water inhibited the evaporative removal of JP-8, apparently by adsorbing the components of JP-8 and thus rendering them unavailable for evaporation (Dean-Ross et al. 1992).

Horizontal and vertical migration of JP-5 has been demonstrated by field observations and laboratory experiments. Model soil core terrestrial ecosystems and outdoor soil cores were treated with JP-5 to mimic a spill and watered to simulate rainfall (Air Force 1982a). The individual hydrocarbon components of JP-5 were found to vertically migrate to varying depths in quantities independent of one another, apparently independent of aqueous leachate movement. Movement of JP-5 in the laboratory occurred to a depth of 50 cm with the majority of hydrocarbons being transported in the first 10 cm. Of the 14 hydrocarbons present, only one component, 1,3,5-trimethylbenzene, was detected below 20 cm. Hydrocarbon components did not persist past the 131st day of the experiment. The outdoor soil core showed movement of JP-5 to a 30-cm depth. The majority of hydrocarbons were seen at 10,20, and 30 cm. Hydrocarbon components were detectable in the core until the 173rd day of the experiment (Air Force 1982a). Horizontal and vertical migration of jet fuels has also been confirmed by detection of JP-5 hydrocarbons in soil several meters from the spill site (Arthur et al. 1992).

The movement of a synthetic kerosene through soil was found to be dependent on the moisture content of the soil. The greater the moisture content (e.g., 4% compared with 0.8%) of the soil, the less the adsorption of the more volatile components of the kerosene and the greater and more rapid the penetration of the liquid component through the soil. Conversely, the upward mobility of both the liquid and vapor phases of kerosene through soil decreased with increased moisture content, and at field capacity, the upward capillary movement of the kerosene was completely inhibited (Acher et al. 1989). Desorption of a simulated kerosene applied to three types of soil, each with a moisture content at 70% of field capacity, was found to be complete after 30 days of exposure to the atmosphere with the slowest desorption from the soil having the greatest organic content (Yaron et al. 1989). Kerosene loss from a dune sand, a loamy sand, and a silty loam soil after 50 days showed that volatilization of all kerosene components was greatest from the dune sand and loamy sand soils. The larger pore size of these types of soil compared with the silty loam soil was thought to be the reason for the increased volatilization (Galin et al. 1990a). Movement of kerosene through three grades of sand was affected mainly by volatilization of the C_9–C_{13} components with a subsequent increase in the viscosity of the remaining kerosene residue and a decrease in the infiltration rate through the inert porous media (Galin et al. 1990b).

The movement of kerosene through various types of soil over a 12-hour period was studied. Upward, downward, and lateral movement was greatest in soil of the mica/kaolinite type (11% clay content)–40, 102, and 45 cm, respectively. Movement through soils that were primarily kaolinite (clay content of 26-52%), regardless of the direction, ranged between 20 and 33 cm (EPA 1986). Application of herbicides such as S-ethyl dibutylthiocarbamate to a field using kerosene as a solvent (up to a volume of 40 gallons per acre) increased the inactivation of the herbicide on soil, whereas acetone, benzene, and xylene did not. The accelerated inactivation possibly resulted from a change in surface tension that facilitated the volatilization of the herbicide from the soil (Danielson and Gentner 1970).

Studies on the permeability of compacted micaceous soil used as a potential liner for landfills found that the permeability of the soil to kerosene varied from three to four orders of magnitude greater compared with water (EPA 1984).

Aquatic organisms are known to bioconcentrate hydrocarbons. Flagfish exposed to concentrations of 1.0-6.8 mg/L JP-8 in surrounding water (from the egg stage to posthatching) have been found to accumulate JP-8 (Klein and Jenkins 1983). The mean concentration of JP-8 in whole-body tissue samples increased with increasing concentration of the WSF of the fuel. The bioconcentration factor (BCF), expressed as the ratio of the concentration in tissue to the concentration of the WSF of JP-8 in the aqueous environment, was found to be 159 (log value = 2.2). Adult flagfish exposed to 2.54 mg/L, for 14 days yielded a BCF of 130 (log value =2.1). Adult flagfish that were placed in uncontaminated water exhibited a depuration rate similar to the accumulation rate. Similar experiments with rainbow trout showed no relationship between JP-8 concentrations in surrounding water and whole-body concentrations in the fish. The relatively low BCF of 63-l 12 (log value = 1.8-2.1) calculated for rainbow trout indicates that the WSF of JP-8 does not concentrate as readily in this species.

5.3.2 Transformation and Degradation

5.3.2.1 Air

No studies on the transformation or degradation of JP-5 or JP-8 in the atmosphere were located. However, volatile components of jet fuels such as benzene, toluene, xylenes, and PAHs may be expected to enter the atmosphere where they are subjected to degradation processes. Further information on the atmospheric degradation of selected volatile hydrocarbons is presented in the ATSDR toxicological profiles for these

chemicals (ATSDR 1989, 1990, 1995a, 1995b). Studies on JP-4, a jet fuel mixture of gasoline and kerosene, indicate that jet fuels react photochemically in air in the presence of nitrogen oxide compounds to form ozone, but the effect of temperature on the nitrous oxide oxidation rate is uncertain (Air Force 1981 b, 1982b). Reactions of JP-4 produce large amounts of aerosol material (Air Force 1981b), and it should be noted that JP-4 has a considerable gasoline component compared to straight kerosene.

5.3.2.2 Water

Biodegradation of jet fuels is dependent on the degradation of the various hydrocarbon fractions present in the oils. The relative order for biodegradation of the hydrocarbon fractions from the most readily degraded to the least is as follows: *n*-alkanes, iso-alkanes, olefins, low molecular weight aromatics (at low, nontoxic concentrations), PAHs, and cycloalkanes (Bartha and Atlas 1977; Edgerton et al. 1987).

Conflicting data exist on the biodegradation of jet fuels and kerosene. Biodegradation of JP-8 in water was studied using quiescent flask test systems (Dean-Ross et al. 1992). Microbial activity in flasks of water incubated at 30°C on a shaker at 200 revolutions per minute for 4 days was inhibited by all concentrations of JP-8 tested (0.0l%, 0.l%, 1%), as indicated by a depression of glucose mineralization in comparison to a control. The study authors suggested that one possible explanation for the lack of biodegradation in water samples is the toxicity of JP-8 to microorganisms, which may severely inhibit microbial activity (Dean-Ross et al. 1992).

Microorganisms readily able to degrade hydrocarbons were found in the Neuse River estuary in North Carolina. Although the estuary was relatively free of hydrocarbon contamination, 63% of the bacteria and 71% of the fungi isolated from surface water samples were able to utilize kerosene as the sole carbon source (Buckley et al. 1976). Weathered kerosene (volatile components were allowed to escape prior to testing) was spiked with four hydrocarbon markers, and the degradation of the markers was monitored. All four markers were degraded by a water-sediment mixture from an “oiled arm” of an Ohio lake; more rapid-degradation was associated with mixtures taken from relatively polluted areas of the lake (Cooney et al. 1985), suggesting that biodegradation is enhanced by the presence of acclimated microorganisms. Marine bacteria capable of using jet fuel no. 1 were isolated from Narragansett Bay, Rhode Island. Most of the bacteria were found to utilize the aliphatic components of the jet fuel, primarily hexadecane, while only a few of the bacteria were able to degrade the aromatic components. The bacteria were able to degrade the hexadecane at 0 °C, but degradation was significantly improved when the incubation temperature was increased to 8 °C and 16 °C; similar but not

such dramatic effects were seen in the degradation of naphthalene with increased temperature (Cundell and Traxler 1976).

Petroleum residues were measured in the northern Arabian Sea to assess the contamination following the oil spills resulting from the Gulf War in 1991. Little change in variables related to oil pollution took place in any compartment of the marine environment-water, plankton, fish, or sediments (Sengupta et al. 1993).

5.3.2.3 Sediment and Soil

Ample evidence exists to indicate that kerosene, JP-5, and JP-8 are biodegraded in soil. Microbial degradation in soils is greatest for the aromatic fractions of jet fuels, while the biodegradation of the aliphatic hydrocarbons decreases with increasing carbon chain length. Evaporation is the primary fate process for these aliphatics (Air Force 1989b).

Application of JP-5 to terrestrial soil core ecosystems and outdoor soil cores resulted in a stressed condition as indicated by an increased rate of carbon dioxide (CO_2) production within 1 day of application (Air Force 1982a). The carbon dioxide production of the cores returned to a rate almost comparable to that of the controls following the increase. A possible reason for this increase was increased activity of microorganisms that utilize the component hydrocarbons of JP-5. The study authors concluded that soil microbes are able to degrade JP-5 in cultures inoculated with soil organisms (Air Force 1989a). In a quiescent flask study, JP-8 was found to be nontoxic to sediment microorganisms (Dean-Ross et al 1992). The study authors found that removal of some components of JP-8 from active soil (soil containing microorganisms) was significantly faster than removal in sterilized soil. Subsurface microorganisms present at a fuel spill at Patuxent NATC were able to utilize JP-5 as their sole carbon source (Navy 1988). The study author concluded that potential exists for promoting *in situ* biodegradation of some of the hydrocarbon components by stimulating the growth of indigenous microflora. Although most soils contain microorganisms capable of degrading hydrocarbons *in situ,* the factors that limit the bioremediation process (e.g., restricted bioavailability of the contaminant, nutrient limitations, potential toxicity of fuel hydrocarbons and associated contaminants, inadequate reduction/oxidation [redox] potential, inadequate or excessive moisture, acidic or basic conditions, and oxygen deficiency) need to be overcome in order to stimulate the degradation of jet fuels in soil and groundwater (Arthur et al. 1992).

5. POTENTIAL FOR HUMAN EXPOSURE

The degradation of kerosene in soil was studied when a pipeline ruptured and showered a wheat field with kerosene. After 6 months, the kerosene concentration began to decrease in the upper 30 cm of soil (with C_{13}-C_{17} n-alkanes disappearing more rapidly compared with C_{l0}-C_{12} *n*-alkanes) and at 21 months was reduced to trace amounts; however, kerosene was still detected at soil depths of 30-45 +cm. The study authors interpreted this as indicating reduced aerobic biodegradation at this depth, especially since the compounds disappeared in the order of their preferential microbial utilization. Seed germination studies using the contaminated soil 1 year after the spill (0.34% kerosene concentrations) showed that kerosene delayed seed germination but that the percent germination was unaffected (Dibble and Bartha 1979). Landfarming techniques (tillage of soil using agricultural implements) developed in The Netherlands to enhance biodegradation of contaminants demonstrated that after one growing season, kerosene (initial concentration of 1,000-10,000 mg/kg dry matter) was significantly degraded (final concentration of 500 mg/kg dry matter) in 40 cm of soil (Soczo and Staps 1988).

The addition of nitrogen (as urea) to soil increases the biodegradation potential of kerosene; however, kerosene was found to inhibit the urease activity of soil microbes by up to 35%, suggesting that sources of nitrogen other than urea should be used (Frankenberger 1988). The bacterial species in the genera *Achromobacter,* Pseudomonas, and *Alcaligenes,* isolated from the soil of an active oil field in Louisiana, were able to aerobically degrade kerosene as determined by oxygen uptake (Cooper and Hedrick 1976). Soil *Pseudomonas* were able to degrade kerosene to a greater extent than were *Enterobucter* with stationary phases occurring after 10 days and 8 days, respectively (Butt et al. 1988). Seven years after the dumping of sludge containing kerosene at two sites, vegetation at each site showed little recovery. Although the bacterial biomass had declined at both sites, microbial activity, as determined by carbon dioxide evolution, was greater at the site that had received more precipitation and had the more aerated soil (Jones 1977).
Oxidation of kerosene by soil microbes, as determined by dehydrogenase activity, increased with increasing loading rates (up to 60% w/w oil/dry soil) for up to seven days of incubation but decreased thereafter. Dehydrogenase activity in soil treated with kerosene was 32 μg formazan/g soil/24 hours (Frankenberger and Johanson 1982).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to JP-5 and JP-8 depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on JP-5

and JP-8 levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring JP-5 and JP-8 in various environmental media are detailed in chapter 6.

5.4.1 Air

JP-5 and JP-8 can enter the atmosphere through evaporation from spills and leaks, vaporization during fueling operations, and burning in engines. In a "third generation closed aircraft shelter," which has approximately three times the interior volume of a "first generation closed aircraft shelter," the concentration of JP-8 in the air was measured as 12 mg/m^3 during refueling operations. In the immediate vicinity of the refueler technician, JP-8 concentrations were determined to be below 22 mg/m^3 (Air Force 198la). In contrast, concentrations of JP-4 (a more volatile jet fuel than either JP-5 or JP-8) ranged from 75 to 267 mg/m^3 in a similar structure during fueling operations. Concentrations of JP-4 in a first-generation shelter ranged from 533 to 1,160 mg/m^3 (Air Force 1981a).

A study by Puhala et al. (1997) examined jet fuel vapor exposures at three U.S. Air Force bases in the United States. At the time of sampling, JP-8 was only used at one base, JP-5 and JP-8 at another, and a third used only JP-4. Breathing zone samples were collected for workers in aircraft maintenance, fuel handling, and flight-line positions.

Mean exposure concentrations for all samples collected were 0.01 ppm benzene (SD=0.0l) and 1.33 ppm naphthas (SD=l.95) for aircraft maintenance positions; 0.01 ppm benzene (SD=0.0l) and 0.61 ppm naphthas (SD=0.90) for fuel handling positions, and 0.004 ppm benzene (SD=0.005) and 0.33 ppm naphthas (SD=0.40) for flight-line positions.

5.4.2 Water

No data were located that discussed specific levels of JP-5 or JP-8 in water. During October of 1983, a leaking pipeline south of Ebensburg, Pennsylvania, released approximately 1,310 barrels of "aviation kerosene" into a trout stream (Guiney et al. 1987a, 1987b). Total organic carbon (TOC) content in the stream water was approximately 30-60 ppm during the initial few months following the spill, which is approximately 1.5-2 times greater than background (Guiney et al. 1987b). During the winter of 1976-1977,

a leak of unknown quantity in a pipeline at Patuxent NATC in Maryland resulted in surface water contamination and possible groundwater contamination by JP-5 (Arthur et al. 1992).

5.4.3 Sediment and Soil

No data were located that discussed specific levels of JP-5 or JP-8 in sediments and soil. An unknown quantity of JP-5 leaked from a pipeline during the winter of 1976-1977 at Patuxent NATC in Maryland, resulting in several acres of soil contamination to a depth of 20-30 feet (Arthur et al. 1992).

5.4.4 Other Environmental Media

No data were located that discussed specific levels of JP-5 or JP-8 in other environmental media such as foodor terrestrial or aquatic plants and animals. Concentrations of kerosene-range hydrocarbons in fish collected during the year following an “aviation kerosene” leak into a trout stream ranged from 2.60 to 14.37 ppm by weight (Guiney et al. 1987b). Shellfish taken from unpolluted waters have been found to contain between 1 and 12 μg/g wet weight of total hydrocarbons, while fish have been found to contain between 4 and 14 μg/g total hydrocarbons (steam distillable) (Connell and Miller 1980).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The National Occupational Exposure Survey, conducted by NIOSH between 1980 and 1983, estimated that 1,076,518 employees were exposed to kerosene in the workplace (NOES 1992).

Exposure of the general population to JP-5 and JP-8 is most likely to be limited to populations living on or near a military installation where JP-5 or JP-8 are utilized. Unintentional exposure to JP-5 and JP-8 may occur as a result of groundwater contamination from spilled jet fuels or contact with soils that have been contaminated with jet fuels. Occupational exposure will occur in individuals involved in the production of kerosene and JP-5 and JP-8, fueling and defueling aircraft, and cleaning up spills and leaks of jet fuel.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Military workers involved in fueling and defueling operations may be exposed to higher levels of JP-5 and JP-8 than members of the general population (Air Force 1981a). Maintenance workers who monitor jet fuel

storage tanks may be exposed to JP-5 and JP-8 via inhalation of jet fuel vapors. Maintenance workers may also be dermally exposed to jet fuels while sampling, gauging, and draining water (condensation) from fuel storage tanks (NIOSH 1989). Workers in the petroleum industry may receive intermittent inhalation, oral, and dermal exposure to kerosene and jet fuels during the refining process. Exposure is most likely to occur during the distillation of crude oil, when monitoring and servicing of equipment are carried out, or when sampling must be done (Runion 1988). Use of a respirator, protective clothing, and increased ventilation can all reduce worker exposure to jet fuel vapor. The use of JP-8 rather than JP-4 reduces occupational exposure to jet fuel vapors for maintenance workers and pilots because the vapor pressure of JP-8 is an order of magnitude less than JP-4 at 38°C. This results in less vapor being vented from JP-8-fueled aircraft than JP-4-fueled aircraft (Air Force 1981a). The similarly low volatility of JP-5 suggests that reduced exposure to JP-5 vapors will also occur in aircraft fueled with JP-5.

5.7 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of JP-5 and JP-8 is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of JP-5 and JP-8.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of JP-5 and JP-8 (kerosene) and their primary component chemicals are well defined and can be used to estimate the fate of these jet fuels following release to the environment (Air Force 1989b; IARC 1989). However, because jet fuels are complex mixtures of hydrocarbons, their environmental fate is determined by both the characteristics of the

mixture and the individual components, making modeling based on physical and chemical properties difficult. Data needs associated with specific compounds that are components of JP-5 and JP-8 (e.g., benzene, toluene, xylene, and PAHs) are presented in the ATSDR toxicological profiles for these chemicals (ATSDR 1989, 1990,1995a, 1995b).

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986,42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1994, became available in May of 1996. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

JP-5 and JP-8 are used primarily as military aviation fuels (Air Force 1989b; IARC 1989). Most releases of jet fuels are the result of in-flight jettisoning of fuel and spills either on land or water (Arthur et al. 1992; IARC 1989). Few data are available on current production and import/export volumes for JP-5 and JP-8. Further information on the production volumes for each jet fuel, environmental releases, and disposal of jet fuels would aid in assessing the potential for human exposure as a result of accidental or intentional release.

Environmental Fate. The environmental fate of JP-5 and JP-8 is based on the environmental partitioning of the major hydrocarbon fractions. For aliphatic hydrocarbons, volatilization of lower molecular weight alkanes and sorption to organic matter for larger aliphatics, followed by biodegradation, are the primary degradation processes (Air Force 1982a; Cooney et al. 1985; Dean-Ross et al. 1992). Aromatic components are most susceptible to biodegradation in warm water or soil, although some volatilization may occur in colder waters (Walker et al. 1976). Jet fuel contaminants that migrate through soil may contaminate groundwater. The deposition of aliphatics from the water column may persist for over a year (Oviatt et al. 1982). Jet fuel that spills or leaks into soil can migrate both vertically and horizontally (Air Force 1982a). JP-5 and JP-8 jettisoned into the atmosphere probably contribute photochemically to the formation of ozone and particulates (Air Force 1981b, 1982b), and some of the fuel components and reactant products are probably transported via wind dispersion. Environmental fate data needs associated with specific compounds that are components of JP-5 and JP-8 (e.g., benzene, toluene, xylene, and PAHs) are presented in the ATSDR toxicological profiles for these chemicals (ATSDR 1989, 1990, 1995a, 1995b). Information on light- and chemical-mediated reactions of jet fuel components would aid in determining the fate of JP-5 and JP-8 in soil and water. More information on the fate of individual components of JP-5 and JP-8 under varying environmental conditions, including the interaction of JP-5 and JP-8 with different soil types, would be

helpful in determining any horizontal and vertical migration patterns of jet fuels in contaminated groundwater systems.

Bioavailability from Environmental Media. The extent of absorption of JP-5 and JP-8 by inhalation, oral, and/or dermal routes is unknown. However, toxicity data are available for humans exposed to jet fuels and kerosene by each of these routes (Porter 1990; Subcommittee on Accidental Poisoning 1962). These data indicate that absorption does occur. The extent of absorption by these routes depends on the volatility, solubility, lipophilicity, and other properties of the specific jet fuel components. Several of these component compounds have been discussed in their individual ATSDR toxicological profiles (e.g., benzene, toluene, xylene, and PAHs), which should be consulted for further information (ATSDR 1989, 1990,1995a, 1995b). More data linking exposure levels of jet fuels with biological levels of component chemicals would be useful in determining which chemicals in the mixture are most likely to be absorbed and by which routes. This information would aid in determining daily human exposure levels and more accurately assessing the risks associated with exposure to jet fuels.

Food Chain Bioaccumulation. Data on the bioaccumulation of JP-8 in flagfish, rainbow trout, and golden shiners suggest that bioaccumulation and biomagnification are low (Klein and Jenkins 1983). Aquatic organisms are able to bioaccumulate some hydrocarbon fractions; however, depuration occurs if the source of the contamination is removed (Klein and Jenkins 1983). JP-5 and JP-8 are expected to separate into their individual hydrocarbon components in the environment, and the bioaccumulation potentials of these components are believed to be independent of each other. Further studies are needed to determine the biomagnification potentials of these components up the food chain within aquatic and terrestrial ecosystems. Specific research needs are presented in the individual ATSDR toxicological profiles on specific hydrocarbon components such as benzene, toluene, xylenes, and PAHs (ATSDR 1989,1990a, 1995a, 1995b). Research on the biomagnification of jet fuels as actual mixtures would not be useful because they are not available to the food chain as mixtures.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of JP-5 and JP-8 in contaminated media at hazardous waste sites are needed so that the information obtained on levels of JP-5 and JP-8 in the environment can be used in combination with the known body burden of JP-5 and JP-8 to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. There is limited information available on the levels of jet fuels found in air, soil, or water where jet fuels are used or stored. Some information exists on the levels of JP-8 in the air in closed buildings during refueling

operations (Air Force 198 1 a). Very little information is available for JP-5 or JP-8 concentrations in soil, water, and other environmental media (Arthur et al. 1992; Guiney et al. 1987a, 1987b; Navy 1988). More data on levels of jet fuels or their components in the environmental media around facilities where jet fuels are produced, stored, and used would be useful to assess the potential risk from these likely sources of exposure.

Reliable monitoring data for the levels of JP-5 and JP-8 in contaminated media at hazardous waste sites are needed so that the information obtained on levels of JP-5 and JP-8 in the environment can be used in combination with the known body burdens of JP-5 and JP-8 to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Populations known to have an increased risk of exposure to JP-5 and JP-8 and their component hydrocarbons include: workers who manufacture or use the fuels; workers involved with monitoring and servicing jet fuel storage tanks; people living or working on military installations where jet fuels are used or stored; and populations living or working near a spill, leak, or dump site (Air Force 1981a; NIOSH 1989; Runion 1988). Further information is needed to assess the approximate levels of exposure for these populations. This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries. No exposure registries for JP-5 and JP-8 were located. These substances are not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

5.7.2 Ongoing Studies

An investigation into the development of JP-8 with improved thermal oxidative stability isbeing conducted by the U.S. Air Force (FEDRIP 1994). The U.S. Navy is conducting an investigation into developing a membrane extraction process for shipboard recovery of the JP-5 icing inhibitor additive from water separated from JP-5 aviation turbine fuel. This technology will enable reblending of the additive (FEDRIP 1994).

5. POTENTIAL FOR HUMAN EXPOSURE

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, will be analyzing human blood samples for JP-5 and JP-8 and other volatile organic compounds. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring JP-5 and JP-8, its metabolites, and other biomarkers of exposure and effect to JP-5 and JP-8. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL SAMPLES

No analytical methods were located for detecting either JP-5 or JP-8 in biological materials. JP-5 and JP-8, however, are both primarily composed of kerosene (Air Force 1989a; Army 1988; DOD 1992), for which analytical methods for detection in biological samples do exist. See Table 6-l for a summary of the analytical methods most commonly used to measure kerosene in biological samples. For more analytical methods information, see the previous profiles on some of the individual hydrocarbon components of JP-5 and JP-8 (e.g., benzene, toluene, xylenes, and PAHs) (ATSDR 1989, 1990, 1995a, 1995b).

The primary method for detecting kerosene in biological materials such as blood is gas chromatography (GC). GC may be combined with mass spectroscopy (MS) for peak identification with the gas chromatograph in the electron impact mode (Kimura et al. 1988,199l). Quantification methods include the use of mass fragmentography (Kimura et al. 1988). Hydrocarbon components of kerosene are determined based on analysis of headspace gas above the sample (Kimura et al. 1991). This method is useful to distinguish between kerosene intoxication and gasoline intoxication since kerosene gives a high toluene peak and has a pseudocumene-to-toluene ratio only half that of gasoline. Capillary columns were used, with either Porapak, ChromosorbB, or ChemipakB, giving acceptable results (Kimura et al. 1988). The percent recoveries of these methods were not provided. Wide-bore capillary columns have also been used (Hara et al. 1988) for GC/MS analysis combined with flame ionization detectors (FTD). This method determined levels of *m*-and

TABLE 6-1. Analytical Methods for Determining Kerosene in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Add internal standard; extract with *n*-pentane; centrifuge; freeze; decant solvent; concentrate; inject to gas chromatograph	GC/MS	50 pg	NR	Kimura et al. 1988
Blood	Mix sample with internal standard; add salt solution; equilibrate; aspirate headspace vapor and inject to gas chromatograph	GC/MS	50 pg (toluene)	NR	Kimura et al. 1991
Stomach contents, blood, urine	Extract sample with ethyl acetate; condense; inject to gas chromatograph	GC/FID/MS	0.2 µg/mL	93–100	Hara et al. 1988

FID = flame ionization detector; GC = gas chromatography; MS = mass spectrometry; NR = not reported

o-xylene (components of kerosene) in the blood, urine, and stomach contents. The sensitivity and precision of this method was generally good (93-100% recovery).

No analytical methods studies were located for detecting kerosene in biological samples other than blood, urine, or stomach contents.

6.2 ENVIRONMENTAL SAMPLES

Because JP-5 and JP-8 are composed of a complex mixture of hydrocarbons, there are few methods for the environmental analysis of the actual mixtures (IARC 1989). However, methods are reported for the analysis of the component hydrocarbons of kerosene. The methods most commonly used to detect the major hydrocarbon components of kerosene in environmental samples are GCEID and GC/MS. See Table 6-2 for a summary of the analytical methods used to determine hydrocarbon components in environmental samples. Several of the components of kerosene and jet fuels have been discussed in detail in their individual toxicological profiles (e.g., benzene, toluene, xylenes, and PAHs), which should be consulted for more information on analytical methods (ATSDR 1989,1990,1995a, 1995b).

GC is the most commonly used method to selectively detect, identify, and quantify the volatile hydrocarbon components of kerosene in air (Andrasko 1983; Baldwin 1977; NIOSH 1994a). Air samples may be collected on adsorbent tubes such as charcoal, Plorisil®, Tenax®, Porapak®, or Chromosorb®. Active carbon wires have also been used (Andrasko 1983). The hydrocarbons are extracted from the tubes by thermal desorption or with a liquid solvent such as carbon disulfide and analyzed on the gas chromatograph. Precision is good (relative standard deviation = 0.052) using the charcoal tubes (NIOSH 1994a); recovery data were not reported for the other types of adsorption tubes, although desorption from the active carbon wires ranged between 90 and 99% recovery, with a detection limit in the ppb range. A Tenax-TA®. Sorbent trap has been used with subsequent thermal desorption (Andrasko 1983). Combining sample concentration with the headspace method allows for sampling of smaller air volumes and for other environmental samples, such as kerosene combustion debris, that have undergone significant evaporation. The headspace method requires concentrating the sample prior to analysis (Andrasko 1983; Baldwin 1977).

GC/FID and GC/MS have been used to measure the water-soluble components of kerosene in industrial effluents and estuarine water (Bianchi et al. 1991), sea water (Boylan and Tripp 1971), drinking water

TABLE 6-2. Analytical Methods for Determining Kerosene and Hydrocarbons in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Adsorb to solid sorbent tube (e.g., charcoal); desorb in CS_2; equilibrate; inject aliquot to gas chromatograph	GC/FID	0.1 mg/ 5–10 mL sample	96–106	NIOSH 1994a
Air	Adsorb to Florisil filter; elute with CS_2; evaporate under vacuum	GC	NR	NR	Baldwin 1977
Water	Strip sample in sparger with helium; adsorb effluent gas to adsorption tube; thermally desorb to gas chromatograph	GC/FID/MS	10 µg/L	89.7–95.7	Bianchi et al. 1991
Water	Acidify sample; extract with hexane; dry solvent phase; inject to gas chromatograph	GC/FID	0.25 mcl/L	NR	Dell'Acqua and Bush 1973
Water (purgeable aromatics)	Purge sample with inert gas; adsorb vapor in trap; heat trap; backflush to gas chromatograph	GC/PID	0.2 µg/L	92–96	EPA 1991b

TABLE 6-2 (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Purge sample with helium; collect vapor on adsorption tube; thermally desorb; concentrate; backflush to gas chromatograph	GC/FID	10 µg/L	91–112	Belkin and Esposito 1986
Water	Purge sample with ambient air, adsorb to charcoal filter; extract filter with CS_2; inject to gas chromatograph	GC/MS	5 ng/L	0.4–89 (75% average)	Coleman et al. 1981
Water	Extract aqueous sample with pentane; equilibrate; inject to gas chromatograph	GC/MS	NR	NR	Coleman et al. 1984
Water (base/neutral and acids)	Adjust sample pH to >11; extract sample with CH_2Cl_2 solvent; adjust pH to <2; reextract; dry; concentrate; inject to gas chromatograph	GC/MS	1.5–7.8 µg/L (varies with actual compound)	NR	EPA 1991b

TABLE 6-2 (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Seawater	Extract aqueous phase of sample with pentane; evaporate; inject to gas chromatograph	GC/MS	NR	NR	Boylan and Tripp 1971
Soil (other solid materials)	Extract sample with CCl_4; inject extract	GLC	NR	NR	Midkiff and Washington 1972
Soil	Extract sample with CCl_4; centrifuge; remove water and humic materials with Na_2SO_4 and Al_2O_3; inject extract	GC/FID	NR	NR	Galin et al. 1990a
Soil	Purge at elevated temperatures; heat trap to desorb material into gas chromatography column	GC	NR	NR	Chang et al. 1992
Soil	Sample extracted using water and cyclohexane	Synchronous scanning fluorescence spectroscopy	NR	NR	Pharr et al. 1992
Sediment	Sample dried, ground, and extracted with *n*-pentane	GC/FID	NR	NR	Guiney et al. 1987b

TABLE 6-2 (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Fish tissue	Extract with KOH in methanol; partition into *n*-pentane; concentrate; analyze using gas chromatograph	GC/FID	NR	95	Guiney et al. 1987b

Al_2O_3 = aluminum oxide; CCl_4 = carbon tetrachloride; CH_2Cl_2 = dichloromethane (methylene chloride); CS_2 = carbon disulfide; FID = flame ionization detector; GC = gas chromatography; GLC = gas liquid chromatography; KOH = potassium hydroxide; MS = mass spectrometry; Na_2SO_4 = sodium sulfate; NR = not reported; PID = photoionization detector

(Coleman et al. 1984; Dell'Acqua and Bush 1973), and groundwater (Thomas and Delfino 1991). Purgeand-trap sample preparation methods have been used to determine purgeable (volatile) aromatic compounds in stream water contaminated by an "aviation kerosene" spill (Guiney et al. 1987b). This method requires a trap with a Tenax®/ChromosorbB absorbent and the use of a gas chromatograph with a photoionization detector (PID) (EPA 1991b), an ion trap detector (ITD), or FID (Guiney et al 1987b; Thomas and Delfino 1991). A modification of the purge-and-trap method uses ambient temperatures, has the advantage of being applicable to a variety of waters, requires virtually no sample preparation (no solvents are required), and has an analysis time of approximately 30 minutes (Bianchi et al. 1991). While this method may be used for determining the presence of petroleum contaminants in water, it cannot distinguish between various sources of this contamination.

Distinctions between WSFs of mixed hydrocarbons may be made by using solvent extraction of the watersoluble base/neutral and acid fractions with methylene chloride (EPA 1991b; Thomas and Delfino 1991). This separation of base/neutral and acid fractions till permit GC resolution of the type of water-soluble hydrocarbons present in the aqueous phase. Hexane has also been used as a solvent (Dell'Acqua and Bush 1973), as has pentane (Coleman et al. 1984).

A dynamic thermal stripper has also been used to detect low levels (ppb range) of kerosene present in water samples (Belkin and Esposito 1986). This method traps the fuels on an adsorption tube using helium gas for purging. The fuel is then thermally desorbed and backflushed to a gas chromatograph with FID. This method also does not require any solvent and needs only a 15mL sample. Recovery for this method is good (91-114%) with precision ranging from 6.4 to 14.3% relative standard deviation. A modified Grob closed-loop-stripping method, which uses a wall-coated open tubular glass capillary column combined with GC/MS, has been used to extract and quantify low levels (ppt) of hydrocarbons in water samples. The method continually recirculates an ambient air stream through the 3.8-L water sample for approximately two hours and collects the vapor on an activated carbon filter, followed by extraction with carbon disulfide and analysis (Coleman et al. 1981).

GC/FID (Galin et al. 1990a), gas liquid chromatography (GLC) with FID (Midkiff and Washington 1972), and elevated temperature purge and trap with GC (Chang et al. 1992) have been used to measure jet fuels in soils. Sediments of a trout stream contaminated with "aviation kerosene" were analyzed for hydrocarbon residues using GC/FID (Guiney et al. 198713). Carbon tetrachloride is the recommended solvent because causes less interference with the chromatographic peaks of the jet fuels (Galin et al. 1990a; Midkiff and

Washington 1972). Synchronous scanning fluorescence spectroscopy can be used to identify kerosene and other aromatic-containing products in groundwater and soil samples. This analytical method is more efficient than chromatographic methods, and its spectra are easier to interpret for identification purposes (Pharr et al. 1992).

High-performance liquid chromatography (HPLC), followed by GC/MS, has been used to fractionate and then quantitate the aliphatic and aromatic hydrocarbons present in liquid fuel precursors in order to determine the fuel potential of the compounds. Kerosene has the advantage of not requiring any sample preparation. An alternative method for fractionating and purifying petroleum hydrocarbons prior to GC or HPLC separation has been developed (Theobald 1988). The method uses small, prepacked, silica or C_{18} columns that offer these advantages: rapid separation (approximately 15 minutes for a run); good recovery of hydrocarbons (85% for the C_{18} column and 92% for the silica column); reusability of the columns; and for the silica column in particular, good separation of hydrocarbon from nonhydrocarbon matrices as may occur with environmental samples.

Tissue of fish from a trout stream contaminated with "aviation kerosene" were analyzed for kerosene-range hydrocarbon residues using standard GC/FID techniques (Guiney et al. 1987b). GC analyses of the fish samples revealed greater than 95% recovery.

6.3 ADEQUACY OF THE DATABASE

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The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. No biomarkers of exposure were identified for JP-5 or JP-8. While standard procedures exist for identifying or quantifying exposure to volatile compounds based on hydrocarbon components in blood, urine, and stomach contents (Hat-a et al. 1988; Kimura et al. 1988, 1991), none of these are applicable solely to jet fuels. These methods are sensitive enough to measure the levels at which health effects occur and may be adequate for determining background levels in the population. However, they cannot distinguish between exposure to JP-5 and JP-8 and to other types of hydrocarbon mixtures. Biomonitoring studies are needed to assess exposure to JP-5 and JP-8 adequately.

Effect. No biomarkers of effects were identified for JP-5 or JP-8 because the effects associated with exposure to jet fuels are not unique for them, i.e., the effects may be caused by other chemicals or hydrocarbon mixtures. General neurologic effects such as loss of coordination, headache, fatigue, intoxication, dizziness, difficulty concentrating, moodiness, and sleep disturbances were observed in people exposed to general "jet fuel" and JP-5 vapors (Knave et al. 1978; Porter 1990). These effects are not used as biomarkers of effect because they are nonspecific and could also indicate exposure to other chemicals or hydrocarbons. No standard procedures exist for identifying and quantifying biomarkers of effect for JP-5 or JP-8.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods exist to detect major hydrocarbon components of JP-5 and JP-8 in air (Andrasko 1983; Baldwin 1977; NIOSH 1994a), water (Bianchi et al. 1991; Boylan and Tripp 1971; Dell'Acqua and Bush 1973; EPA 1991b; Guiney et al. 1987b), sediment (Guiney et al. 1987b), soil (Galin et al. 1990a; Midkiff and Washington 1972), and biological media (Guiney et al. 1987b). The most commonly used methods are GC/FlD and GC/MS. These methods are relatively sensitive, selective, and reliable and can be used to detect the levels of the various components of jet fuels found in the environment and the levels at which health effects occur.

6.3.2 Ongoing Studies

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, is developing methods for the analysis of JP-5 and JP-8 and other volatile organic compounds in blood. These methods use purge and trap methodology, high resolution gas chromatography, and magnetic sector mass spectrometry which gives detection limits in the low parts pertrillion (ppt) range.

No other on-going studies were located for JP-5 or JP-8.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding JP-5 and JP-8 in air, water, and other media are summarized in Table 7- 1. There are only a few regulations specific to JP-5 and JP-8; however, a number of regulations exist for kerosene and other components of jet fuels.

An intermediate inhalation MRL of 3 mg/m^3 was derived for JP-5 and JP-8 from the study by Gaworski et al. (1984) in which hepatocellular fatty changes and vacuolization were observed in mice exposed to JP-5 at 150 mg/m^3 continuously for 90 days. Similar effects on the liver were also observed at 750 mg/m^3.

EPA has not verified a reference dose (RfD) or reference concentration (RfC) for JP-5 or JP-8 (IRIS 1998).

Under the Hazardous Materials Transportation Act, aviation fuel is designated as a hazardous substance subject to special requirements for packaging, labeling, and transportation (DOT 1989a, 1989b). EPA has established guidelines to control air pollution from aircraft and aircraft engines (EPA 1982).

TABLE 7-1. Regulations and Guidelines Applicable to Jet Fuels[a]

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification of jet fuels	Group 3[b]	IARC 1998
NATIONAL			
Regulations:			
a. Air:			
AFOSH	PEL TWA		
	Petroleum distillates (naphtha)	400 ppm	Air Force 1989b
	STEL (15 minutes)		
	Petroleum distillates (naphtha)	500 ppm	
EPA	NAAQS	None listed	EPA 1995
NIOSH	TWA		
	Petroleum distillates (naphtha)	(85 ppm) 350 mg/m^3	NIOSH 1997
	Kerosene	100 mg/m^3	
	Ceiling REL (15 minutes)		
	Petroleum distillates (naphtha)	438 ppm (1,800 mg/m^3)	
	Kerosene	None listed	
OSHA	PEL TWA		OSHA 1997 (29 CFR 1910.1000)
	Petroleum distillates (naphtha)	500 ppm (2,000 µg/m^3)	
	Kerosene	None listed	
b. Other:			
DOT	Hazardous Material Transportation Act: Aviation fuel is designated as a hazardous material subject to requirements for packaging, shipping, and transporting	Yes	DOT 1989a (49 CFR 172.101 Appendix A); DOT 1989b
EPA	Toxic Substances Control Act: Manufacturers and processors of the C_9 aromatic hydrocarbon fraction must test this fraction for the following: Neurotoxicity, mutagenicity, developmental toxicity, reproductive effects, and oncogenicity	Yes	EPA 1991a (40 CFR 799.2175); EPA 1987
Guidelines:			
a. Air:			
EPA	Control of air pollution from aircraft and aircraft engines	Yes	EPA 1982 (40 CFR 87)
ACGIH	Threshold Limit Values (TWA)	None listed	ACGIH 1997
b. Other:			
EPA	Domestic water supply must be virtually free from oil and grease, particularly from the tastes and odors that emanate from petroleum products	Yes	EPA 1986
	For aquatic life, levels must be ≤ 0.01 of the lowest continuous flow 96-hour LC_{50}	Yes	EPA 1986

TABLE 7-1 (*continued*)

Agency	Description	Information	References
NATIONAL (*Cont'd*)			
	Clean Water Act: Oil and grease are designated as conventional pollutants. Effluent limitations for oil and grease (polynuclear aromatic hydrocarbons) exist for almost all point sources under the general pretreatment standards for new and existing sources	Yes	EPA 1988a (40 CFR 403.2); EPA 1988b
EPA	Drinking water regulations and health advisories		EPA 1996
	MCLG	None listed	EPA 1996
	MCL	None listed	
EPA	Title 40 protection of environment	None listed	EPA 1996
EPA	CERCLA Reportable Quantity	None listed	EPA 1996
EPA	Toxic chemical release reporting: Community right-to-know	None listed	EPA 1997
STATE			
Regulations and Guidelines:			
a. Air:			
	Acceptable ambient air concentrations (Navy Fuels JP-5)		NATICH 1991
Connecticut	(8 hours)	2.00×10^{3} µg/m^3	
Maryland		0.00	
Oklahoma	(24 hours)	1.00×10^{4} µg/m^3	
Texas	(30 minutes)	1.00×10^{3} µg/m^3	
Texas	(annual)	1.00×10^{2} µg/m^3	
	Regulations on hydrocarbon emissions (including kerosene)		CELDS 1991
Connecticut		Yes	
Kansas		Yes	
Wisconsin		Yes	
	Regulations on VOCs		CELDS 1991
Alabama		Yes	
Arizona		Yes	
Florida		Yes	
Maine		Yes	
Maryland		Yes	
Michigan		Yes	
New Jersey		Yes	
South Carolina		Yes	
Virginia		Yes	
Texas		Yes	
Washington, DC		Yes	
Maine	Regulations on the open burning of fuel oils (kerosene)	Yes	CELDS 1991

TABLE 7-1 (*continued*)

Agency	Description	Information	References
STATE (*Cont'd*)			
b. Water:			
Alaska	Aquatic life criterion for total hydrocarbons in marine and surface waters	15 µg/L	State of Alaska 1989
	Aquatic life criterion for aromatic hydrocarbons in marine and surface waters	10 µg/L	State of Alaska 1989
New York	Maximum contaminant level of kerosone in drinking water	50 µg/mL	State of New York 1989
South Dakota	Water quality standard for all petroleum products in surface waters	10 mg/L	State of South Dakota 1989
Virginia	Water quality standard for petroleum hydrocarbons in groundwater	1 mg/L	Commonwealth of Virginia 1988
Wyoming	Water quality standard for all surface waters classes	10 mg/L	State of Wyoming 1990
c. Other:			
	Regulations on the transport of flammable/hazardous liquids (petroleum distillates or VOCs)	Yes	CELDS 1991
California	Regulations on leaking underground fuel tanks	Yes	CELDS 1991

[a]International, national, and state regulations and guidelines regarding JP-5, JP-8, and kerosene in air, water, and other media
[b]Group 3 = Not classifiable as to its carcinogenicity to humans

AFOSH = Air Force Office of Health and Safety; DOT = Department of Transportation; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; IDLH = Immediately Dangerous to Life or Health; LC_{50} = lethal concentration (50% kill); NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = Permissible Exposure Limit; REL = Recommended Exposure Limit; STEL = Short-Term Exposure Limit; TWA = Time-Weighted Average; VOC = Volatile Organic Compound

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9. GLOSSARY

Acute Exposure-Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{OC})-The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)-The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL)-The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen-A chemical capable of inducing cancer.

Ceiling Value-A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure--Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity-The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity-Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory-An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)-The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure-Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

9. GLOSSARY

Immunologic Toxicity-The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro-Isolated from the living organism and artificially maintained, as in a test tube.

In Viva-Occurring within the living organism.

Lethal Concentration $_{(LO)}$ (LC_{LO})-The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})-A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO})-The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})-The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time(50) (LT_{50})-A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)-The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations-Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level-An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen-A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity-The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL)-The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})-The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL)-An allowable exposure level in workplace air averaged over an 8-hour shift.

9. GLOSSARY

q_1*-The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The ql* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually ug/L for water, mg/kg/day for food, and ug/m3 for air).

Reference Dose (RfD)-An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)-The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 3 11 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity-The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL)--The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 mm between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity-This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen-A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)-A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Tie-Weighted Average (TWA)-An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50})-A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF)-A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

ATSDR MINIMAL RISK LEVEL

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-4991, requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (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 for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1-14 days), intermediate (15-364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

APPENDIX A

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MT& Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

Chemical Name: JP-5 and JP-8
CAS Number: 8008-20-6 (kerosene)/70892-10-3
Date: April 1998
Profile Status: Draft 3 Postpublic Comment
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 3
Species: Mouse

Minimal Risk Level: 3 [ ] mg/kg/day [x] mg/m^3

Reference: Gaworski et al. 1984

Experimental design:

Groups of 37–50 female C57BL/6 mice were exposed by inhalation to JP-5 at 0, 150, or 750 mg/m^3 continuously for 90 days. End points evaluated included: clinical signs, hematology, blood chemistry, body weight, and histopathological examination of major tissues (adrenals, anus, bladder, brain, colon, duodenum, esophagus, gall bladder, heart, ileum, kidneys, larynx, liver, lungs and bronchi, mammary gland, mandibular lymph node, nasal cavity, ovaries, pancreas, parathyroids, pituitary, prostate, salivary gland, sciatic nerve, seminal vesicles, skin, spleen, bone-sternebrae, vertebrae or femur plus marrow, stomach, testes, thigh muscle, thymus, thyroid, trachea, and uterus).

Effects noted in study and corresponding doses:

No effect on body weight gain was noted. The only remarkable finding in mice was hepatocellular fatty changes and vacuolization at 150 and 750 mg/m^3. The effect was not concentration-related over the range of concentrations studied.

Dose and endpoint used for MRL derivation:

[ ] NOAEL [x] LOAEL

150 mg/m^3; hepatocellular fatty changes and vacuolization. The LOAEL of 150 mg/m^3 was used to calculate a human equivalent concentration (HEC) of 854 mg/m^3. To derive the MRL, the HEC was divided by the uncertainty factors described below.
854 mg/m^3 ÷ 300 = 3 mg/m^3.

Uncertainty Factors used in MRL derivation:

[x] 10 for use of a LOAEL
[x] 3 for extrapolation from animals to humans
[x] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No
If so, explain:

If an inhalation study in animals, list the conversion factors used in determining human equivalent concentration:

A human equivalent concentration (HEC) of 854 mg/m^3 was calculated by multiplying the mouse LOAEL by the ratio of the alveolar ventilation rate divided by the body weight of mice to the same parameters for humans.

$$150 \text{ mg/m}^3 \text{ ([0.04 m}^3\text{/day/0.0246 kg]} \div \text{[20 m}^3\text{/day/70 kg])} = 854 \text{ mg/m}^3$$

Other additional studies or pertinent information which lend support to this MRL:

No significant adverse effects were observed in rats or dogs exposed to $\leq$ 100 mg/m^3 deodorized kerosene 6 hours/day, 5 days/week for 13 weeks (Carpenter et al. 1976).

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2- 1,2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).
The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

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2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2- 1).

5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAFLs from different studies. In this case (key number 1 S), rats were exposed to 1 ,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

10) Reference The complete reference citation is given in chapter 8 of the profile.

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11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The ame health effects appear in the LSE table.

15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m3 or ppm and oral exposure is reported in mg/kg!day.

16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

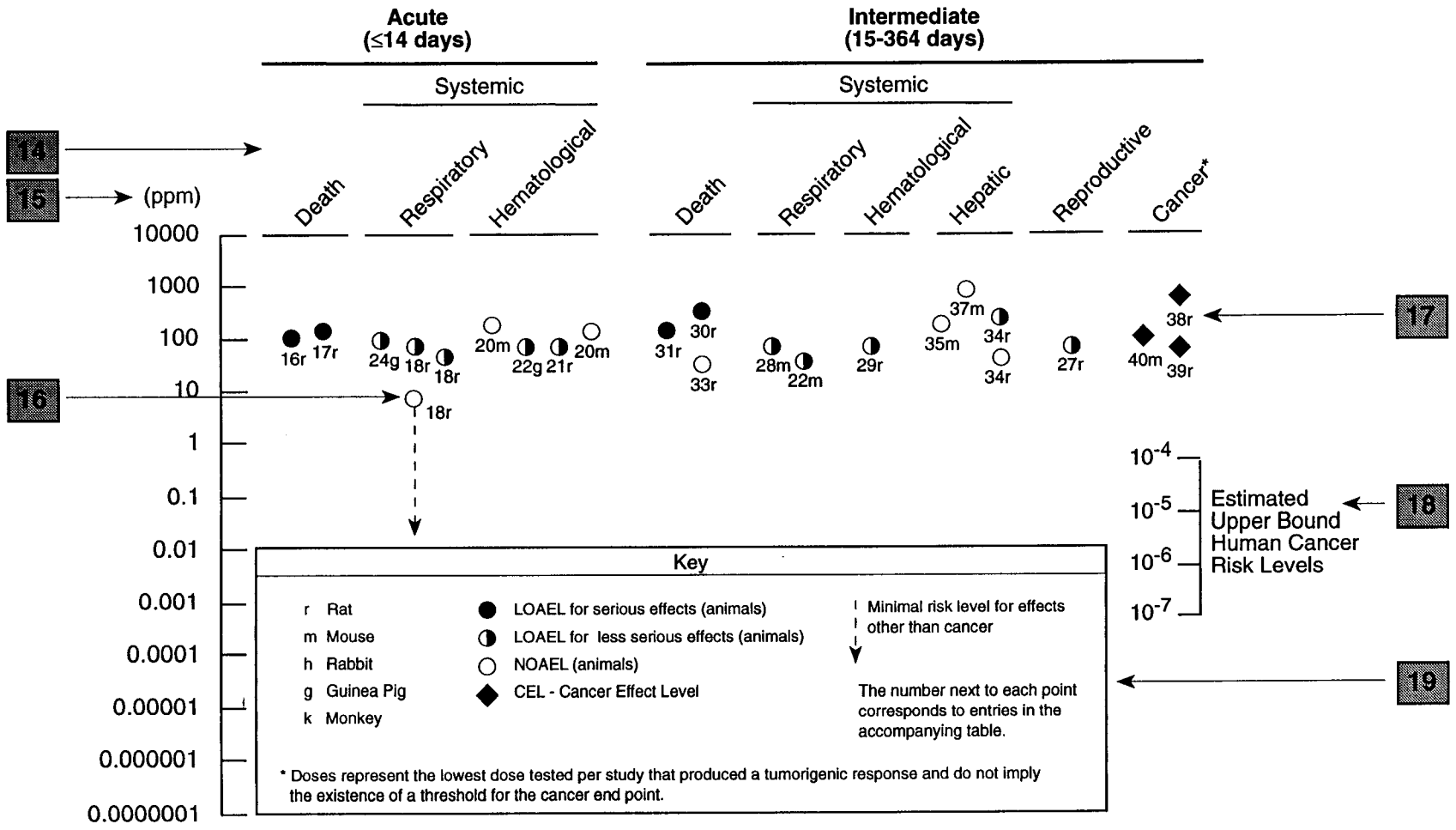
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE						
	5	6	7	8	9	10
3 → Systemic	↓	↓	↓	↓	↓	↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3 [b]	10 (hyperplasia)	Nitschke et al. 1981
CHRONIC EXPOSURE						
					11	
					↓	
Cancer						
38	Rat	18 mo 5d/wk 7hr/d			20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



APPENDIX B

Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1 . What effects are known to occur in humans?

2 . What effects observed in animals are likely to be of concern to humans?

3 . What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. h4RLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.7, “Interactions with Other Substances,” and 2.8, “Populations that are Unusually Susceptible” provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

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To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient

L	liter
LC	liquid chromatography
LC_{LO}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{LO}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio

STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micrometer
μg	microgram