TOXICOLOGICAL PROFILE FOR JP-5, JP-8, AND JET A FUELS

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

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DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

UPDATE STATEMENT

A Toxicological Profile for JP-5, JP-8, and Jet A Fuels, Draft for Public Comment was released in February 2016. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

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Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch
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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 these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a 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.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic 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. Staffs 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 under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Chapter 1	**How Can (Chemical X) Affect Children?**
Chapter 1	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional material is available online at www.atsdr.cdc.gov:

Case Studies in Environmental Medicine—Case Studies are self-instructional publications designed to increase primary care provider's knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials

incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: (202) 245-0625 or 1-800-CDC-INFO (800-232-4636).

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Publically Available Information

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. 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.

2. 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.

3. Data Needs Review. The Environmental Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

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

1. Errol Zeiger, Ph.D., J.D., A.T.S., Errol Zeiger Consulting, Chapel Hill, North Carolina;

2. Luis Haro Garcia, M.D., MSc, Ph.D., Departamento de Salud Pública, Facultad de Medicina, Universidad Nacional Autónoma de México, México DF, México; and

3. Wayne G. Landis, Ph.D., Western Washington University, Huxley College of Environmental Studies, Bellingham, Washington.

These experts collectively have knowledge of JP-5, JP-8, and Jet A fuel'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(I)(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.

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 FOR JP-5, JP-8, and JET A FUELS

This Public Health Statement summarizes the Agency for Toxic Substances and Disease Registry's findings on JP-5, JP-8, and Jet A fuels, tells you about them, the effects of exposure, and describes what you can do to limit that exposure.

The U.S. Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are sites targeted for long-term federal clean-up activities. U.S. EPA has not found JP-5, JP-8, and Jet A fuels in at least 1,832 current or former NPL sites. The total number of NPL sites evaluated for JP-5, JP-8, or Jet A fuels is unknown. But the possibility remains that as more sites are evaluated, the sites at which JP-5, JP-8, or Jet A fuels are found may increase. This information is important because these future sites may be sources of exposure, and exposure to JP-5, JP-8, and Jet A fuels may be harmful.

If you are exposed to JP-5, JP-8, or Jet A fuels, many factors determine whether you'll be harmed. These include how much you are exposed to (dose), how long you are exposed to it (duration), and how you are exposed (route of exposure). You must also consider the other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

WHAT ARE JP-5, JP-8, AND JET A FUELS?

JP-5 and JP-8 stand for jet propellant-5 and jet propellant-8. Propellants are substances that move other objects or give thrust. JP-5 and JP-8 are used as military aircraft fuels. They can also be used for fueling land vehicles and as a fuel source for heaters and lights. Jet A is the type of fuel used in civilian aircraft; however, the U.S. Air Force has recently started using Jet A (plus certain additives) for flying in the continental United States. JP-5, JP-8, and Jet A fuels are colorless liquids that are flammable and smell like kerosene. The fuels are made from chemical compounds called hydrocarbons, which are found naturally in the earth as crude oil. Hydrocarbons are compounds that contain only carbon and hydrogen. The crude oil is refined into a number of different types of fuel. Jet A, JP-5, and JP-8 fuels may also contain various additives such as antioxidants and additives to prevent icing in the fuel lines. More information on the chemical and physical properties of these fuels is found in Chapter 4. More information on the production and use of these fuels is found in Chapter 5.

WHAT HAPPENS TO JP-5, JP-8, AND JET A FUELS WHEN THEY ENTER THE ENVIRONMENT?

JP-5, JP-8, and Jet A fuels are made up of hundreds of hydrocarbon compounds; many of these hydrocarbons are also present in gasoline. These hydrocarbons can be grouped into several classes of chemicals which have similar chemical properties. The different chemical classes can behave differently when they enter the environment. For example, some of these can easily evaporate into the air during aircraft loading and unloading operations or as a result of their normal use as a jet fuel for civilian or military aircraft. Some may also evaporate when jet fuels are spilled accidentally onto soils or surface waters. Other chemical classes are more likely to dissolve in water following spills to surface waters or leaks from underground storage tanks. Some chemical classes found in jet fuels may slowly move down through the soil to the groundwater, while others may 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 or other chemicals in the air. The chemicals that dissolve in water may also be broken down into other substances by microorganisms found in water and sediment. However, this may take many years to occur, depending on the environmental conditions. Some chemicals that attach to soil or other matter (for example, marsh sediment) may remain in the environment for more than a decade. Some of the chemicals in jet fuels may be detected in fish and aquatic organisms after an accidental release into a lake, river, or stream. These hydrocarbons are not expected to persist in aquatic organisms. For more information on what happens to JP-5, JP-8, and Jet A fuels when they enter the environment, see Chapter 6.

HOW MIGHT I BE EXPOSED TO JP-5, JP-8, AND JET A FUELS?

It is unlikely that you will be exposed to JP-5, JP-8, or Jet A fuels unless you work with jet fuels or live very close to where they are used or were spilled. Exposure to jet fuels 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, JP-8, or Jet A fuels if you swim in waters where jet fuels have been spilled. If jet fuels have leaked from underground storage tanks and entered groundwater, you may be exposed from contaminated well water. 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.

Workers involved in making or transporting jet fuels, aircraft or fuel tank maintenance, or in refueling aircraft that use JP-5, JP-8, or Jet A fuels may be exposed to some of the chemicals that have evaporated from the fuel. Workers in the vicinity of an aircraft during cold engine startup may also be exposed to airborne jet fuels. Some workers may be exposed to JP-5, JP-8, or Jet A fuels 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, JP-8, or Jet A fuels, see Chapter 6.

HOW CAN JP-5, JP-8, AND JET A FUELS ENTER AND LEAVE MY BODY?

The chemicals in JP-5, JP-8, and Jet A fuels can enter your body through your lungs, digestive tract, or skin. We do not have information on how much of the chemicals in JP-5, JP-8, or Jet A fuels can pass into the bloodstream, but we do know that large amounts of some of the chemicals in jet fuels can easily do so. Studies examining the absorption of jet fuels through the skin have shown that damage to the skin and the longer jet fuels stays on your skin will increase the amount of chemicals that will enter your body. Once jet fuels enter your body, the chemicals in the fuel will be distributed throughout your body. A number of the chemicals in jet fuels were found in the blood, fat, brain, lungs, and liver following exposure to JP-8 in air. Some of the chemicals in JP-5, JP-8, or Jet A fuels will be broken down in the body to form other chemicals. The chemicals in JP-5, JP-8, or Jet A fuels will be eliminated from the body in the urine, feces, or breath.

HOW JP-5, JP-8, AND JET A FUELS CAN AFFECT MY HEALTH?

The health effects of JP-5, JP-8, and Jet A fuels depend on how much of these fuels you are exposed to and for how long. We know very little about the human health effects caused by JP-5, JP-8, or Jet A fuels. A few studies of military personnel have provided suggestive evidence that JP-8 can affect the nervous system. Some of the effects that have been observed in humans include changes in reaction time and other tests of neurological function. Humans who accidentally ingested kerosene, a fuel oil similar in composition to JP-5, JP-8, and Jet A fuels, were reported as suffering harmful effects on the respiratory tract, gastrointestinal tract, and nervous system. The observed effects included cough and difficulty breathing, abdominal pain and vomiting, drowsiness, restlessness, and convulsions.

Studies in laboratory animals have examined the toxicity of JP-5, JP-8, and Jet A fuels following inhalation, ingestion, or dermal contact. In most cases, the levels tested in laboratory animals are higher than levels the public might encounter through dermal contact with contaminated water or soil or by drinking contaminated water. Health effects of JP-5, JP-8, or Jet A fuels observed in these studies include

damage to the liver, decreased immune response, impaired performance on neurological function tests, and impaired hearing. Dermatitis and damage to the skin have also been observed in laboratory animals following dermal contact.

There are no reliable studies of cancer in humans exposed to JP-5, JP-8, or Jet A fuels. A few studies that examined the possible association between exposure to various types of jet fuels or to kerosene and various types of cancer did not provide conclusive results. Because the studies involved exposure to several fuel types and there was no information on exposure concentrations, these studies were not considered adequate to assess the carcinogenicity of JP-5, JP-8, or Jet A fuels.

No inhalation or oral studies evaluated the carcinogenicity of JP-5, JP-8, or Jet A. No increases in tumor incidences were observed in rats administered kerosene by a feeding tube for 2 years. JP-5 applied to the skin for 2 years was not carcinogenic in mice. Increases in skin tumors were observed in mice dermally exposed to Jet A for 52–62 weeks; however, tumors were only observed at concentrations resulting in damage to the skin. Similarly, increased numbers of skin tumors were observed in mice that received applications of undiluted kerosene on the skin for 2 years, but this occurred only in the presence of skin damage.

The U.S. Department of Health and Human Services (DHHS) and the EPA have not classified JP-5, JP-8, or Jet A fuels as to their carcinogenicity. The International Agency for Research on Cancer (IARC) has classified JP-5, JP-8, and Jet A as Group 3 carcinogens (not classifiable as to their carcinogenicity to humans).

See Chapters 2 and 3 for more information on health effects of JP-5, JP-8, and Jet A fuels.

HOW CAN JP-5, JP-8, AND JET A FUELS AFFECT CHILDREN?

Exposure JP-5, JP-8, or Jet A fuels mainly occurs in occupational settings where children are unlikely to be exposed. No studies examining the health effects of JP-5, JP-8, or Jet A fuels in children were found. There are a number of reports of accidental kerosene ingestion in children in developing countries where kerosene may typically be stored in containers and places easily accessible to children. Some of the more commonly reported effects include coughing, pneumonia, shortness of breath, vomiting, fever, unconsciousness, drowsiness, and irritability. These effects are similar to the effects seen in adults who ingest kerosene.

Studies in laboratory animals exposed to JP-8 during pregnancy did not find birth defects in the newborn animals. However, some effects on muscle coordination and immune function were found in the offspring.

HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO JP-5, JP-8, AND JET A FUELS?

If your doctor finds that you have been exposed to significant amounts of JP-5, JP-8, or Jet A fuels, ask whether your children or unborn baby might be at risk. Your doctor might need to ask your state health department to investigate. It is unlikely that you or your family will be exposed to JP-5, JP-8, or Jet A fuels. Jet fuels are not likely to be common contaminants in foods or drinking water. If you get JP-5, JP-8, or Jet A fuels on your work clothes, you should change your clothes before leaving your job and returning home.

ARE THERE MEDICAL TESTS TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO JP-5, JP-8, AND JET A FUELS?

Many of the individual chemicals found in JP-5, JP-8, and Jet A fuels and their breakdown products (metabolites) can be measured in blood and urine. Finding these chemicals does not mean that you were exposed to jet fuels because these chemicals may have come from a different source including exposure to gasoline fumes when pumping gas. The levels of these chemicals in your body cannot predict the kind of health effects that might occur or whether you will have any effects. JP-5, JP-8, and Jet A fuels and their metabolites leave the body fairly rapidly and tests to detect these chemicals need to be conducted within days of exposure.

For more information on the different substances formed by the breakdown of JP-5, JP-8, and Jet A fuels breakdown and on tests to detect these substances in the body, see Chapters 3 and 7.

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

The federal government develops regulations and recommendations to protect public health. Regulations can 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 as "not-to-exceed" levels; that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value usually based on levels that affect animals; levels are then adjusted to help protect humans. Sometimes these not-to-exceed levels differ among federal organizations. Different organizations use different exposure times (i.e., an 8-hour workday or a 24-hour day), different animal studies, or emphasize some factors over others, depending on their mission.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that issued the regulation or recommendation.

OSHA has not set a legal limit for jet fuels in workroom air. NIOSH has set a recommended limit of 100 mg/m^3 for kerosene in air averaged over a 10-hour work day. The EPA does not have recommended drinking water guidelines for jet fuels.

WHERE CAN I GET MORE INFORMATION?

If you have any questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below. ATSDR can also provide publically available information regarding medical specialists with expertise and experience recognizing, evaluating, treating, and managing patients exposed to hazardous substances.

- Call the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636) or

- Write to:

  Agency for Toxic Substances and Disease Registry
  Division of Toxicology and Human Health Sciences
  1600 Clifton Road NE
  Mailstop F-57
  Atlanta, GA 30329-4027

Toxicological profiles and other information are available on ATSDR's web site: http://www.atsdr.cdc.gov.

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO JP-5, JP-8, AND JET A FUELS IN THE UNITED STATES

JP-5, JP-8, and Jet A are kerosene-based jet fuels. 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; Jet A serves as the base fuel for JP-8. The performance-enhancing additives found in JP-5, JP-8, and Jet A 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. Jet fuels are composed of more than 200 aliphatic and aromatic hydrocarbons (C_6-C_{17+}); 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.

Many of the constituents of JP-5, JP-8, and Jet A fuels are volatile and will evaporate into the air when jet fuels are spilled accidentally onto soils or surface waters. Other components of these jet fuels 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. The chemicals that evaporate will undergo photodegradation by atmospheric oxidants such as hydroxyl radicals. The photooxidation half-life range for a group of representative chemicals of kerosene, JP-5, JP-8, and Jet A was reported as 0.2–1.1 days. In soil and water, the constituents of JP-5, JP-8, and Jet A fuels are biodegraded at varying rates. Exposure to JP-5, JP-8, and Jet A fuels by the general population is expected to be low and could occur through atmospheric, soil, or groundwater contamination. Military or civilian personnel who are employed in jet fuel storage or re-fueling activities are generally at higher exposure dose risk via inhalation and dermal routes to these substances than the general population. Occupational exposure could involve exposure to raw fuel, vapor phase, aerosol phase, a mixture of vapors and aerosols, or fuel combustion exhaust. General population exposure is most likely to occur in populations living near military installations using JP-5 or JP-8 or commercial airports using Jet A. Airborne exposure to jet fuel vapors and/or aerosols can result from fuel spillage, engine cold starts, and high-altitude fuel jettisoning. Jet fuel spills can also result in exposure via contaminated groundwater or soil.

Because JP-5, JP-8, and Jet A fuels are complex mixtures of both aliphatic and aromatic hydrocarbons, exposure is typically measured by monitoring the total hydrocarbon concentration (THC) and the levels of certain aromatic substances, such as benzene, toluene, ethylbenzene, xylene, and naphthalene, that are present in jet fuels. Since there are multiple sources of these components in the environment, exposure studies usually include a control population that has had little or no exposure to jet fuels in order to establish a baseline level of these substances that would exist in the absence of jet fuel exposure. In a study of Air Force personnel exposed to JP-8 during regular work shifts, the geometric mean concentration of THC in the breathing zone of a high exposure group was 4.4 mg/m^3, while that of a low exposure group was 0.9 mg/m^3. The geometric mean concentrations of naphthalene were reported as 4.8 and 0.7 $\mu g/m^3$ for the high and low exposure groups, respectively. See Chapter 6 for more information on levels of exposure and environmental fate of JP-5 and JP-8.

2.2 SUMMARY OF HEALTH EFFECTS

Although JP-5 and Jet A fuels have been used for over 60 years and JP-8 was identified by the Department of Defense as its single military fuel over 30 years ago, there are very little data on the toxicity of kerosene-based jet fuels in humans. Most of the studies focused on the potential neurotoxicity of JP-8 fuel. Single studies in humans exposed to JP-8 fuel reported increases in white blood cell neutrophil and monocyte levels with no change in lymphocyte subpopulations and an inverse association between aliphatic hydrocarbons in exhaled breath and serum levels of luteinizing hormone (LH). However, exposure to JP-8 was not associated with higher odds of menstrual disorders. Limited information is available on the carcinogenic potential of jet fuels in humans. Studies in laboratory animals have examined the toxicity of JP-5, JP-8, and Jet A fuels following inhalation, oral, or dermal exposure and have reported a number of targets of toxicity, including the lungs, liver, skin, immunological system, nervous system, and developing organism. Although renal effects have also been observed in male rats exposed to JP-5 or JP-8, the lesions are considered to be characteristic of $alpha_{2u}$-globulin nephropathy, which is only observed in male rats and is not considered to be toxicologically relevant to humans. JP-5 was not carcinogenic in mice in a 2-year dermal bioassay. Increases in skin tumors were observed in mice dermally exposed to Jet A for 52–62 weeks; however, tumors were only observed at concentrations resulting in significant skin damage (inflammation and necrosis). Similarly, increased numbers of skin tumors were observed in mice that received applications of undiluted kerosene on the skin for 2 years, but this occurred only in the presence of moderate-to-marked skin damage. No inhalation or oral studies evaluated the carcinogenicity of JP-5, JP-8, or Jet A in laboratory animals; no increases in tumor incidences were observed in rats administered kerosene by gavage for 2 years.

Neurological Effects. Studies in subjects occupationally exposed to JP-8 have reported alterations in balance associated with cumulative exposure to benzene, a component of JP-8, and alterations in neuropsychological test results in workers with daily exposures to <10 mg/m^3 JP-8. Another study of workers did not find an association between daily exposures to JP-8 and balance. A study of veterans found alterations in reaction time on divided attention tests following 3 weekly 7-minute exposures to 0.00057 ppm JP-8 vapor. Kerosene induces neurological effects in humans, as evidenced in many reports of acute accidental ingestion of this fuel. Neurological effects noted most frequently in these reported cases included unconsciousness or semiconsciousness, drowsiness, restlessness, and irritability. 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. In laboratory animals, JP-5 and JP-8 caused alterations in performance in a battery of tests in rats exposed to 1,200 mg/m^3 JP-5 vapor or 1,000 mg/m^3 JP-8 vapor in intermediate-duration inhalation studies. Exposure to 1,000 mg/m^3 JP-8 vapor also resulted in impaired performance on higher cognitive tests, but not on simple memory tests. Another study found hyperlocomotive activity and increased arousal levels in rats exposed to aerosolized JP-8 for 4 weeks. In contrast, lethargy was observed in mice administered Jet A gavage doses of 100 mg/kg/day and was observed once in most rats exposed to 500 mg/kg/day. In addition to the central nervous system effects, exposure to JP-8 can result in auditory effects. Acute- and intermediate-duration exposure to JP-8 followed by exposure to noise resulted in alterations in the peripheral auditory system and the central auditory processing area.

Respiratory Effects. No human studies have examined the potential of JP-5, JP-8, or Jet A to induce respiratory effects. Respiratory effects are a common finding in humans ingesting kerosene; the observed effects include bronchopneumonia, bronchitis, pneumonitis, lung infiltrates and effusions, cough, dyspnea, and tachypnea. However, these effects are likely attributable to aspiration of the kerosene. The results of studies in laboratory animals suggest that the respiratory tract is a target for airborne JP-8. Most of this information comes from a series of studies conducted at the University of Arizona in which rats and mice were exposed to aerosolized JP-8 1 hour/day for 1 or 7 days. There are several limitations to these studies: the primary limitation being that only the aerosol component of the test atmosphere was measured, resulting in a large underestimation of the JP-8 exposure (the studies' limitations are discussed in greater detail in Section 3.2.1). These studies reported an increase in respiratory permeability, increased lung resistance, and terminal bronchiole lesions. These effects were usually accompanied by increased biomarkers of inflammation in bronchoalveolar lavage fluid (BALF). In contrast, an acute-duration study in which rats were exposed to Jet A aerosols and vapors and most intermediate-duration

inhalation studies involving exposure to JP-5 or JP-8 vapor did not report respiratory effects. The exception is the finding of enlarged alveolar capillaries in rats exposed to 500 mg/m^3 JP-8 vapor 6 hours/day for 90 days; the no-observed-adverse-effect level (NOAEL) was 250 mg/m^3. No histological alterations were observed in the respiratory tracts of rats exposed to ≤1,980 mg/m^3 Jet A aerosols and vapors 4 hours/day, 5 days/week for 14 days, in rats continuously exposed to ≤1,000 mg/m^3 JP-8 vapor for 90 days, or in rats, mice, and dogs continuously exposed to ≤750 mg/m^3 JP-5 vapor for 90 days. One possible explanation for the conflicting results between studies is the differences in the composition of the test atmosphere. For example, a vapor test atmosphere could contain a higher percentage of low molecular weight, more volatile compounds than the raw fuel, and aerosolizing the jet fuel could generate liquid droplets enriched in higher molecular weight n-alkanes.

Hepatic Effects. Several studies in laboratory animals provide evidence that the liver is a sensitive target of jet fuel toxicity; however, the findings are not consistent across studies, which may be due to species or strain differences or differences in the physical properties of the fuel (e.g., aerosols versus vapor). Continuous exposure to ≥150 mg/m^3 JP-5 vapor resulted in hepatocellular fatty changes and vacuolization in mice. In similarly exposed rats and dogs, exposure to 750 mg/m^3 JP-5 vapor resulted in no effects in rats and mild diffuse hepatocellular swelling in dogs. Dilated sinusoids and fatty hepatocytes were observed in rats exposed to ≥500 mg/m^3 JP-8 vapor for 91 days; another 90-day study found no histological alterations in rats exposed to 1,000 mg/m^3 JP-8 vapor. A 14-day exposure to 1,980 mg/m^3 Jet A vapor and aerosol also did not result in histological alterations or changes in alanine aminotransferase (ALT) levels. In acute-duration gavage studies, increases in ALT and aspartate aminotransferase (AST) levels were observed in rats administered a single gavage dose of 19 mg/kg JP-5 or single or repeated gavage doses of >18,000 mg/kg JP-5. Intermediate-duration gavage administration of ≥750 mg/kg/day JP-8 for 90 days in rats resulted in non-dose-related increases in ALT and AST; this study also found an increase in total bilirubin levels at ≥750 mg/kg/day, but no histological alterations. A 90-day gavage exposure to 500 mg/kg/day Jet A also did not result in histological alterations in the livers of rats or mice; the exposure did result in an increase liver weight and enlarged livers in rats. Chronic dermal exposure to 500 mg/kg/day JP-5 resulted in liver amyloidosis in mice.

Dermal Effects. Studies in rats, mice, rabbits, and pigs demonstrate the dermal toxicity of topically applied JP-5, JP-8, and Jet A. Similar effects have been observed for all three fuel types, although the results of one study suggests that Jet A may be slightly more irritating than JP-8 in pigs exposed for 5 hours. Single 1-hour exposures to low concentrations did not result in visible damage to the skin; however, evidence of inflammation (increased granulocyte infiltration and increased levels of

inflammatory biomarkers) was observed. Additionally, ultrastructural changes suggest that jet fuel exposure alters the epidermal-dermal barrier, which could result in increased absorption. Overt signs of dermal toxicity have been observed following repeated exposures; effects ranged from erythema and edema to dermatitis to ulceration. The severity of the lesions increased with duration and concentration. Other factors that can affect the dermal toxicity include the test vehicle and whether the application site is occluded. At a given dose, undiluted jet fuel resulted in more severe erythema and desquamation, as compared to jet fuel diluted in mineral oil or acetone:olive oil. Occluding the application site resulted in moderate-to-severe erythema and moderate edema as compared to slight erythema when the application site was not occluded.

Immunological Effects. Inhalation, oral, and dermal studies in animals have shown that exposure to JP-8 and Jet A can affect immune parameters; immunotoxicity has not be adequately evaluated in JP-5 studies. A number of alterations in immune parameters were reported in a series of acute-duration studies in which mice were exposed to JP-8 vapors and aerosols 1 hour/day. However, most of the studies only measured the aerosol component of the test atmosphere, which underestimated the JP-8 exposure, and the animals were likely exposed to plasticizers (see Section 3.2.1 for discussion of the limitations of this series of studies conducted by the University of Arizona). Effects included decreased viable immune cells in the thymus, lymph nodes, and peripheral blood; impaired response to stimulation with the T cell mitogen concanavalin A; increased severity in the response to influenza virus infection; and suppressed immune response to injected tumor cells. A later study by this group in which the vapor and aerosol components of the test atmosphere were measured found decreased thymus weight and the proliferative response to stimulation with antigens at ≥1,000 mg/m^3 JP-8 vapor and aerosol (1 hour/day for 7 days); at higher concentrations, decreases in viable immune cells were observed in the thymus, spleen, peripheral blood, and bone marrow. Decreases in spleen and thymus weights and an impaired response to concanavalin A were observed in mice exposed to aerosolized Jet A in another University of Arizona study. A study of Jet A by another investigator did not find alterations in spleen weights or splenocyte phenotypes in rats exposed to Jet A aerosols and vapors for 14 days. The results of the two Jet A studies cannot be directly compared because the first study did not measure the vapor component of the test atmosphere. In acute-duration (14-day) oral studies that assessed multiple immune parameters in mice, JP-8 suppressed humoral immunity, as evidenced by an altered response to sheep red blood cells (SRBCs) at the lowest dose tested, 500 mg/kg/day. Dermal exposure to ≥50 µL JP-8 inhibited contact and delayed hypersensitivity in mice and ≥25 µL suppressed immune memory in mice previously exposed to *Candida albican*s. Dermal exposure to Jet A also resulted in suppression of delayed type hypersensitivity in mice. Production of prostaglandin E_2 by mast cells and of suppressive cytokines, presumably by epidermal

cells, were proposed as possible mechanisms involved in the immunotoxicity of dermally applied JP-8. JP-8 was also shown to be a weak skin sensitizer; however, neither JP-8+100 nor Jet A were skin sensitizers. Intermediate-duration dermal exposure to Jet A did not result in alterations in spleen or thymus weights, spleen lymphocyte phenotypes, or response to SRBCs.

The issue of which component or components in JP-8 are responsible for the immune effects of this fuel has been explored in a few studies. Acute inhalation exposure of mice to a synthetic fuel (S8) with no polycyclic aromatic hydrocarbons (PAHs) induced immune effects similar to JP-8, suggesting that the PAHs in JP-8 are not responsible for the immune effects. Exposure of mice to vapors of jet fuel kerosene (Jet A free of performance additives) and in the same range of concentrations as in the studies mentioned above did not suppress innate, humoral, or cell-mediated immunity, suggesting that the additives, at least in part, are responsible for the effects of JP-8 on immune parameters. In yet a third study, dermal exposure of mice to S8 did not induce immune suppression, as measured by the delayed-type hypersensitivity reaction (DTH). However, when a cocktail of seven of the most prevalent aromatic hydrocarbons in JP-8 were added to S8, exposure to the latter resulted in suppression of DTH.

Developmental Toxicity. Assessment of standard developmental end points showed that JP-8 was not embryotoxic or teratogenic in rats exposed orally during gestation, although fetal weight was decreased with doses (≥1,000 mg/kg/day; administered via gavage) that significantly reduced (≥31%) maternal body weight gain during gestation and pup body weights were decreased on postnatal days (PNDs) 4 and 11 at maternal gavage dose of 1,500 mg/kg/day. Inhalation (University of Arizona study, which only measured the aerosol component) or oral (1,000 mg/kg/day) exposure of pregnant mice to JP-8 resulted in suppressed immune function in the offspring when assessed before 8 weeks of age. JP-8 also induced a transient delay in motor coordination in offspring from rats exposed to ≥325 mg/kg/day before and during gestation and during lactation. The developmental toxicity of JP-5 and Jet A has not been evaluated.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for JP-5, JP-8, and Jet A fuels. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based

on noncancerous health effects only and do not consider carcinogenic effects. MRLs may 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.

Inhalation MRLs

Acute-Duration Inhalation MRL

JP-5. Information on the acute toxicity of airborne JP-5 is limited to a study in mice that estimated a concentration resulting in a 50% reduction in respiratory rate (RD_{50}) following a 30-minute exposure to JP-5 vapor and aerosol (Whitman and Hinz 2001); the RD_{50} was 3,338 mg/m^3. This study is not considered a suitable basis for an acute-duration inhalation MRL because a limited number of end points were examined and because of the short exposure duration.

JP-8. Although a number of studies have examined the acute toxicity of airborne JP-8, the studies focused on a small number of potential targets of toxicity. The studies reported signs of respiratory and ocular irritation, immunotoxicity, and altered auditory function. Signs of upper respiratory irritation and ocular irritation have been observed in rats following a 4-hour exposure to 3,430 mg/m^3 JP-8 vapor or 3,570 mg/m^3 JP-8+100 vapor (Wolfe et al. 1996). However, no signs of respiratory or ocular irritation were observed in rats following a 4-hour exposure to 4,440 mg/m^3 JP-8 vapor and aerosol or 4,540 mg/m^3 JP-8+100 vapor and aerosol (Wolfe et al. 1996). RD_{50} values of 2,876 and 1,629 mg/m^3 were calculated for a 30-minute exposure to JP-8 or JP-8+100 vapor, respectively (Whitman and Hinz 2001). Wong et al. (2008) reported significant increases in inspiratory and expiratory lung resistance in mice exposed to 53 mg/m^3 JP-8 vapor and aerosol 1 hour/day for 7 days (Wong et al. 2008). However, Herrin et al. (2006) did not find significant alterations in lung function in mice exposed to 45 or 267 mg/m^3 JP-8 vapor and aerosol 1 hour/day for 7 days, but did find a decrease in inspiratory dynamic lung compliance at

406 mg/m^3. It is unclear why the studies had conflicting results for lung function. Both studies found ultrastructural changes in the morphology of alveolar type II cells, particularly increases in lamellar body volume density at all tested concentrations. Suppression of the immune response to mitogens was observed in mice exposed to 1,000 mg/m^3 JP-8 vapor and aerosol 1 hour/day for 7 days (Hilgaertner et al. 2011). At higher concentrations, decreases in the number of viable immune cells were observed in the thymus (2,000 mg/m^3), spleen and peripheral blood (4,000 mg/m^3), and bone marrow (8,000 mg/m^3). Exposure of rats to 1,000 mg/m^3 JP-8 mostly vapors for 4 hours/day for 1 or 5 days did not result in auditory impairment or damage to cochlear hair cells (Fechter et al. 2007); however, a loss of cochlear hair cell function was observed in rats exposed to 2,000 mg/m^3 JP-8 vapor 4 hours/day for 5 days (Fechter et al. 2010). Exposure to 1,000 mg/m^3 for 1 or 5 days followed by a 1- or 4-hour exposure to noise with an intensity of 97–105 dB resulted in impaired hair cell function, as compared to rats exposed only to noise or only to JP-8 (Fechter et al. 2007, 2010); no alterations were observed in rats exposed to 500 mg/m^3 JP-8 followed by 4 hours of noise with 97–99 dB intensity (Fechter et al. 2010).

In addition to these acute-duration inhalation studies, investigators at the University of Arizona conducted a number of respiratory toxicity and immunotoxicity studies. However, the interpretation of these studies is limited by an inaccurate measurement of the concentration of JP-8 in the test atmosphere and the possible exposure to plasticizers (see Section 3.2.1 for a more complete discussion of these studies). The studies involved nose-only exposure for 1 hour/day for 1 or 7 days, and only reported exposure levels for the aerosol component of the test atmosphere. These studies found lung tissue damage and impaired lung function (Hays et al. 1995; Pfaff et al. 1995, 1996; Robledo and Witten 1998; Robledo et al. 2000; Wong et al. 2004) and immunosuppression (Harris et al. 1997a, 1997b, 1997c; 2007b, 2007c, 2008). The observed effects in rats and mice included increases in inspiratory resistance and inspiratory dynamic pulmonary compliance (Pfaff et al. 1995), an increase in lung permeability (Hays et al. 1995; Pfaff et al. 1995; Robledo and Witten 1998), congestion with hemorrhaging in the distal lung (Hays et al. 1995; Pfaff et al. 1996; Robledo and Witten 1998), and ectasia of respiratory bronchioles and alveoli (Wong et al. 2004). Electron microscopic examination also revealed breaks in the alveolar capillary membrane, congestion of small blood vessels and capillaries, and changes in type II cells, which included swollen mitochondria, fused lamellar bodies, and short irregular microvilli (Hays et al. 1995). The immunological effects included decreases in the number of viable immune cells in the thymus and spleen (Harris et al. 1997a, 1997b), alterations in the number of viable immune cells in the lymph nodes, peripheral blood, and bone marrow (Harris et al. 1997a, 1997b), an impaired immune response to concanavalin A (Harris et al. 1997a, 1997c), an increased severity of influenza virus infection (Harris et al. 2008), and suppression of the immune response to injected tumor cells (Harris et al. 2007c). This group also found a decrease in the

number of viable immune cells in the thymus and spleen, as well as suppressed immune function in the at 6–8-week-old offspring of rats exposed to JP-8 on gestation days (GDs) 7–21 or 15–21 (Harris et al. 2007b).

Although the available database on the acute toxicity of JP-8 consists of a number of studies providing evidence that the lungs and immune system are targets of toxicity, there is some uncertainty as to whether these are the most sensitive targets of toxicity for JP-8. No acute studies were identified that examined all regions of the respiratory tract, other systemic targets such as the liver, or neurological end points (outside of the potential auditory effects); findings from longer-term JP-8 inhalation or oral studies suggest that these may be potential targets of toxicity. Additionally, the Herrin et al. (2006), Hilgaertner et al. (2011), and Wong et al. (2008) studies, which identified the lowest adverse effect levels, all involved a 1 hour/day exposure to JP-8 for 7 days. There is considerable uncertainty in extrapolating from a 1-hour exposure to a continuous exposure as the resulting MRL might be overly conservative. Thus, the database was considered inadequate for derivation of an acute-duration inhalation MRL for JP-8.

Jet A. Information on the acute toxicity of Jet A is limited to two studies conducted by Sweeney et al. (2013) in which rats were exposed to Jet A aerosol and vapor 4 hours/day, 5 days/week for 14 days. Although these studies found some subclinical alterations, such as alterations in bronchoalveolar lavage fluid parameters that could be indicative of lung inflammation, the findings were not consistent across studies or concentration-related. The study did not find any histological alterations at exposure levels as high as 1,980 mg/m^3. Additionally, no alterations in spleen organ weights or immune cell population were found. The Sweeney et al. (2013) studies are well-designed studies that examined a number of potential targets of Jet A toxicity. However, they are not suitable as the basis of an acute-duration inhalation MRL because the highest tested concentration is a NOAEL and it is ATSDR's practice to not derive MRLs based on free-standing NOAEL values.

Intermediate-Duration Inhalation MRL

JP-5

- An MRL of 2 mg/m^3 has been derived for intermediate-duration inhalation exposure (15–365 days) to JP-5 vapor.

Information on the toxicity of JP-5 following intermediate-duration inhalation exposure comes from a study in which rats, mice, and dogs were continuously exposed to JP-5 vapors for 90 days (Gaworski et al. 1984). In mice and dogs, the liver was the most sensitive target of toxicity. Hepatocellular fatty

changes and vacuolization were observed in female mice exposed to ≥150 mg/m^3 JP-5 vapor (Gaworski et al. 1984) and diffuse hepatocellular swelling was observed in male and female dogs exposed to 750 mg/m^3 JP-5 vapor (Gaworski et al. 1984). Gaworski et al. (1984) also reported a significant increase in the occurrence of hyaline droplets in the proximal renal tubules of male rats exposed to ≥150 mg/m^3 JP-5 vapor; no renal lesions were observed in female rats, female mice, or male and female dogs (Gaworski et al. 1984). The renal effects observed in the male rats is likely due to an accumulation of alpha$_{2u}$-globulin in hyaline droplets, which can lead to cell necrosis, regeneration of tubule cells, and tubular hyperplasia (EPA 1991a; Hard et al. 1993). The production of alpha$_{2u}$-globulin appears to be unique to male rats and the accumulation of alpha$_{2u}$-globulin in hyaline droplets and subsequent renal damage is not considered to be relevant to humans (EPA 1991a; Flamm and Lehman-McKeeman 1991; Hard et al. 1993; Swenberg 1993). A neurobehavioral study found an increase in forelimb grip strength in rats exposed to 1,200 mg/m^3 JP-5 vapor 6 hours/day, 5 days/week for 6 weeks (Rossi et al. 2001); no other alterations in performance on the neurobehavioral battery tests were observed.

The available data on the intermediate-duration toxicity of JP-5 vapors have identified two targets: the liver in mice and dogs and the nervous system in rats. These end points are consistent with the results of intermediate-duration vapor exposure studies with JP-8 (Hanas et al. 2010; Ritchie et al. 2001; Rossi et al. 2001). Immunotoxicity has also been identified as a sensitive end point following acute inhalation exposure to JP-8 and is likely a target for JP-5 toxicity. The lowest reliable LOAEL for immunotoxicity following inhalation exposure to JP-8 was 1,000 mg/m^3 in rats exposed 1 hour/day for 7 days (Hilgaertner et al. 2011). This LOAEL is much higher than the LOAEL for liver effects, suggesting that an MRL based on liver effects would be protective for potential immune effects.

The 150 mg/m^3 concentration that resulted in hepatocellular fatty changes and vacuolization in mice continuously exposed to JP-5 vapor for 90 days (Gaworski et al. 1984) was selected as the point of departure for the MRL; the effects were considered minimally adverse and the concentration was identified as a minimal LOAEL. A human equivalent concentration of the LOAEL (LOAEL$_{HEC}$) was calculated by multiplying the LOAEL by the ratio of the human to mouse blood:gas partition coefficient ratio. Because human and mouse blood:gas partition coefficients are not measurable for a complex mixture such as JP-5, a default value of 1 was used for the human-animal blood:gas partition coefficient ratio; thus, the LOAEL$_{HEC}$ was 150 mg/m^3. The minimal LOAEL$_{HEC}$ of 150 mg/m^3 was divided by an uncertainty factor of 90 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustment, and 10 for human variability), resulting in an intermediate-duration inhalation MRL of 2 mg/m^3 for vapor exposure.

JP-8

- An MRL of 3 mg/m^3 has been derived for intermediate-duration inhalation exposure (15–365 days) to JP-8 vapor.

In a well-designed intermediate-duration inhalation study, no systemic effects were observed in rats continuously exposed to concentrations of JP-8 vapor as high as 1,000 mg/m^3 for 90 days (Mattie et al. 1991). However, another study involving a 91-day intermittent exposure to JP-8 vapors (6 hours/day, 7 days/week) reported a number of systemic effects in two of the three rats exposed to 500 mg/m^3 including enlarged alveolar capillaries, myocardial scarring, 50% reduction in fat cells in the bone marrow, and dilated hepatic sinusoids with fatty hepatocytes (Hanas et al. 2010). It is unclear why these studies had conflicting results. Both studies also reported kidney effects in the male rats. Mattie et al. (1991) reported hyaline nephropathy in males exposed to ≥500 mg/m^3 JP-8 vapor and Hanas et al. (2010) reported proximal tubule damage in males exposed to ≥250 mg/m^3 JP-8 vapor; no renal lesions were observed in the female rats in the Mattie et al. (1991) study. As noted in the discussion of the intermediate-duration JP-5 data, the renal effects were likely due to an accumulation of alpha$_{2u}$-globulin in hyaline droplets and the effect is not considered relevant to humans. A number of studies have reported neurobehavioral alterations and auditory effects in rats following exposure to JP-8 vapor. Impaired learning of moderately difficult tasks was observed in rats exposed to1,000 mg/m^3 JP-8 vapor 6 hours/day, 5 days/week for 6 weeks (Ritchie et al. 2001); this effect was not observed at 500 mg/m^3. A similar exposure to 1,000 mg/m^3 JP-8 vapor also resulted in an alteration in a novel appetitive stimulus test, which was hypothesized to quantify dopamine system sensitization in rats (Rossi et al. 2001); no other alterations in performance on the neurobehavioral battery tests were found. Intermediate-duration exposure to JP-8 vapor also results in damage to the auditory system. Exposure to 1,000 mg/m^3 JP-8 vapor also resulted in central auditory processing dysfunction, but no damage to cochlear hair cells, in rats exposed 6 hours/day, 5 days/week for 4 weeks (Guthrie et al. 2014, 2015). Another study found significant alterations in auditory function in rats exposed to 1,500 mg/m^3 JP-8 vapor 6 hours/day, 5 days/week for 4 weeks (Fechter et al. 2012). However, simultaneous exposure to JP-8 and non-damaging noise (85 dB) resulted in impaired auditory function, as compared to the control group; exposure to 85 dB noise alone did not significantly impair auditory function. In addition to these studies, three University of Arizona studies have reported edema and inflammation of the terminal bronchioles in rats exposed 1 hour/day for 28 or 56 days to JP-8 aerosols and vapors (Hays et al. 1995; Pfaff et al. 1995, 1996). Hays et al. (1995) also found increased lung epithelial permeability and alveolar permeability.

The Hanas et al. (2010) study identified the lowest LOAEL (500 mg/m^3) for JP-8 vapors; however, the alveolar capillary, cardiac, and bone marrow effects have not been observed in other JP-8 studies or in studies with JP-5 or Jet A. The liver effects are similar to those observed in mice exposed to JP-5 vapors (Gaworksi et al. 1984); however, no liver effects have been observed in rats exposed to JP-8 vapor (Mattie et al. 1991), JP-5 vapor (Gaworski et al. 1984), or administered JP-8 via gavage (Mattie et al. 1995). Given the small number of animals tested (3/group) and the conflicting results with more robust studies, the Hanas et al. (2010) study was not selected as the basis of an MRL. Rather, the NOAEL of 500 mg/m^3 for neurotoxicity identified in the Ritchie et al. (2001) study was selected as the point of departure. The NOAEL was adjusted for intermittent exposure (6 hours/day, 5 days/week) resulting in a $NOAEL_{ADJ}$ of 89 mg/m^3. The $NOAEL_{HEC}$ of 89 mg/m^3 was calculated by multiplying the $NOAEL_{ADJ}$ by the default human to rat blood:gas partition coefficient ratio of 1 (blood:gas partition coefficients are not measurable for a complex mixture such as JP-8). Dividing the $NOAEL_{HEC}$ by an uncertainty factor of 30 (3 for animal to human extrapolation with dosimetric adjustment and 10 for human variability) results in a JP-8 intermediate-duration inhalation MRL of 3 mg/m^3 for vapor exposure.

Jet A. No intermediate-duration studies evaluated the inhalation toxicity of Jet A precluding derivation of an MRL.

Chronic-Duration Inhalation MRL

Chronic-duration inhalation MRLs for JP-5, JP-8, and Jet A fuels were not derived due to the lack of reliable chronic-duration studies.

Oral MRLs

Acute-Duration Oral MRL

JP-5. Data on the acute oral toxicity of JP-5 are limited to two single exposure studies in rats. A single gavage dose of 18,912 mg/kg/day JP-5 resulted in an increase in white blood cell levels, hepatocyte vacuolization, and weight loss (Parker et al. 1981). Another study by Parker et al. (1981) reported hepatocellular vacuolization and hyaline droplet in renal tubular epithelial cells in male rats administered via gavage 47,280 mg/kg/day. An acute-duration oral MRL was not derived for JP-5 due to the lack of repeated exposure studies.

JP-8

- An MRL of 3 mg/kg/day has been derived for acute-duration oral exposure (≤14 days days) to JP-8.

Acute-duration studies evaluating the oral toxicity of JP-8 (administered via gavage) have primarily focused on immunological and developmental toxicity. Suppressed humoral immunity, specifically an impaired response to SRBCs, has been observed in mice administered 1,000 mg/kg/day JP-8 for 7 days (Dudley et al. 2001) or 500 mg/kg/day JP-8 for 14 days (Keil et al. 2004; Peden-Adams et al. 2001); the NOAEL identified in the 14-day study was 250 mg/kg/day. At 2,000 mg/kg/day, decreases in thymus weight and cellularity were observed (Dudley et al. 2001); no other immune effects were found. The three immunotoxicity studies also reported significant increases in liver weight at 1,000 mg/kg/day (Dudley et al. 2001; Keil et al. 2004; Peden-Adams et al. 2001); the studies did not include a histological examination of the liver. A developmental study also conducted by this group found decreases in the plaque-forming response to SRBCs in the offspring of mice administered 1,000 mg/kg/day on GDs 6–15 (Keil et al. 2003). A small decrease (4–6%) in fetal weights was observed in a study in which rat dams were administered 1,000 mg/kg/day JP-8 on GDs 6–15 (Cooper and Mattie 1996); decreases in maternal weight gain and maternal deaths were also observed at this dose level.

The lowest-adverse-effect level identified in the acute-duration JP-8 oral database is 500 mg/kg/day for altered immune function in mice (Keil et al. 2004). The immunotoxicity NOAEL of 250 mg/kg/day was selected as the point of departure for the MRL. Although the systemic toxicity of JP-8 has not been adequately addressed in the available acute-duration oral studies, intermediate-duration oral studies (Mattie et al. 1995, 2000) suggest that liver or other systemic effects are not likely to occur at doses lower than the lowest LOAEL for immunotoxicity (500 mg/kg/day). An additional end point that has not been adequately addressed in the acute oral studies is the potential for neurodevelopmental effects; this was the most sensitive end point following intermediate oral exposure. However, the LOAEL (350 mg/kg/day) from the intermediate study (Mattie et al. 2001) is similar to the lowest acute-duration LOAEL (500 mg/kg/day) and it is likely that the MRL using 250 mg/kg/day point of departure would be protective of neurodevelopmental effects.

The acute-duration oral MRL for JP-8 of 3 mg/kg/day was derived by dividing the NOAEL for immunological effects (Keil et al. 2004) by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Jet A. No acute-duration oral studies were identified for Jet A precluding derivation of an MRL.

Intermediate-Duration Oral MRL

JP-5. No studies examined the toxicity of JP-5 following intermediate oral exposure precluding derivation of an MRL.

JP-8

- An MRL of 0.3 mg/kg/day has been derived for intermediate-duration oral exposure (15–365 days) to JP-8.

Three studies have examined the toxicity of JP-8 following intermediate-duration oral exposure (administered via gavage). Administration of 750 mg/kg/day JP-8 to male rats for 90 days resulted in stomach hyperplasia, increases in serum ALT and AST activities, perianal dermatitis, hypoglycemia, and hyaline droplet formation in the kidneys (Mattie et al. 1995). In a 90-day study in female rats, stomach hyperplasia was observed at 750 mg/kg/day and perianal dermatitis was observed at 1,500 mg/kg/day; no alterations in blood glucose levels were observed (Mattie et al. 2000). The Mattie et al. (2000) study also found no effects on male or female fertility. Maternal exposure to JP-8 for 90 days prior to mating and during gestation resulted in an 11% decrease in pup body weight on postnatal day (PND) 4 (Mattie et al. 2000) and a dose-related decrease in coordinated motor movements on a swimming test at ≥325 mg/kg/day (Mattie et al. 2001). This effect was only observed at ≥325 mg/kg/day on PND 8 and at ≥750 mg/kg/day on PND 14; no alterations were observed on PND 10, 12, 16, or 18. The investigators suggested that the effect was due to a delay in motor coordination related to delayed neurodevelopment of the cerebellum and noted that PND 8 corresponds with maturation of the basket cells in the cerebellum and PND 14 corresponds with eye opening time and the final days of cellular organization and development of functional integrity in the cerebellum (Mattie et al. 2001). No other alterations in performance on neurobehavioral tests were observed in the offspring.

The intermediate-duration toxicity of ingested JP-8 has been investigated in systemic toxicity, reproductive toxicity, and developmental toxicity studies. The most sensitive effect appears to neurodevelopmental. The intermediate-duration database is lacking immunotoxicity studies; however, a comparison of the NOAEL (250 mg/kg/day) and LOAEL (500 mg/kg/day) values from an acute-duration oral study (Keil et al. 2004) with the LOAEL (325 mg/kg/day) from the Mattie et al. (2001) neurodevelopmental study suggests that an MRL based on this LOAEL should be protective for immunological effects. An intermediate-duration oral MRL of JP-8 was calculated by dividing the LOAEL of 325mg/kg/day by an uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for

extrapolation from animals to humans, and 10 for human variability) resulting in an MRL of 0.3 mg/kg/day.

Jet A. Information on the intermediate-duration oral toxicity of Jet A comes from a 90-day gavage study in rats and mice. Significant increases in absolute and relative liver weights and enlarged liver were observed in female rats administered 500 mg/kg/day Jet A for 90 days (Smith et al. 1999); no histological alterations were observed. Increases in salivation and a shoveling behavior were also observed in rats exposed to 100 or 500 mg/kg/day; the investigators suggested that these effects were likely due to mouth irritation. No other biologically-relevant effects were observed in rats. No systemic effects were observed in similarly exposed male mice; the highest tested concentration was 500 mg/kg/day (Smith et al. 1999). However, lethargy and hunched posture were observed in mice administered 100 or 500 mg/kg/day; lethargy was also observed in mice administered 20 mg/kg/day, but was only observed once in 5 of the 15 exposed mice. Similarly, lethargy was observed in rats administered 500 mg/kg/day, but in most rats it was only observed once in the 90-day exposure period (Smith et al. 1999).

There are limited data evaluating the toxicity of Jet A following intermediate-duration oral exposure. The most sensitive effects were signs of mouth irritation in rats and lethargy and hunched posture in mice administered ≥100 mg/kg/day Jet A (Smith et al. 1999). These clinical observations have not been observed in Jet A inhalation studies (Sweeney et al. 2013) and it is not known whether the effects were seen because the animals received the Jet A as a bolus dose and would not occur if the Jet A fuel was administered in drinking water or food, which are relevant routes of human exposure. In the absence of additional information on the mechanisms involved in the induction of lethargy or mouth irritation, the database was not considered adequate for derivation of a Jet A intermediate-duration oral MRL.

Chronic-Duration Oral MRL

Chronic-duration oral MRLs for JP-5, JP-8, and Jet A were not derived due to the lack of reliable chronic-duration studies.

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3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of JP-5, JP-8, and Jet A fuels. 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.

JP-5, JP-8, and Jet A fuels are kerosene-based jet fuels (NRC 2003; Ritchie et al. 2003). The components of jet fuels are primarily aliphatic and aromatic hydrocarbons of length C_8–C_{17+} (NRC 2003). There is no single formula for JP-5, JP-8, or Jet A fuels and the exact composition of the jet fuel varies depending on the crude oil from which it is refined. The fuels are refined by a straight distillation of crude or shale oil, or by a distillation of crude oil in the presence of a catalyst. Although the jet fuels are kerosene based, they are refined under more stringent conditions than kerosene and contain various additives not found in kerosene; Jet A is the base fuel for the production of JP-8 (NRC 2003). 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 discussion of health effects is focused on exposure to JP-5, JP-8, and Jet A fuel rather than exposure to individual components of the fuel mixture. For information concerning the possible toxicity associated with exposure to some of the individual components of jet fuels, the reader is referred to the ATSDR toxicological profiles on these compounds, for example benzene (ATSDR 2007a), toluene (ATSDR 2015b), total xylenes (ATSDR 2007b), ethylbenzene (ATSDR 2010), and naphthalene, 1-methyl-naphthalene, and 2-methylnaphthalene (ATSDR 2005). In addition, the health effects associated with exposure to jet fuel exhaust or combustion products will not be discussed because these products contain other substances that are not constituents of JP-5, JP-8, and Jet A fuel itself. However, when needed to fill in data gaps, information on the toxicity of kerosene is presented because JP-5, JP-8, and Jet A are kerosene-based fuels and it is likely that jet fuels and kerosene will have similar toxicological effects.

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

3.2 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-adverse-effect 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 (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

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.

3.2.1 Inhalation Exposure

The human and laboratory animal studies discussed in this section involve exposure to jet fuel vapors or a mixed exposure to vapors and aerosols. The method used to generate the test atmosphere can result in very different chemical compositions (NRC 2003). Heating the fuel can result in complete volatilization and generation of a test atmosphere with a similar composition to that of the raw fuel. Other methods of vapor generation could produce a test atmosphere that is enriched with low molecular weight, more volatile compounds, as compared to the raw fuel. Aerosolization of the jet fuels could lead to inhalation of vapors enriched with low molecular weight compounds and respiratory tract surface deposition of liquid droplets enriched in higher molecular weight n-alkanes. The differences in test atmosphere generation methods and differences of the chemical composition of the raw fuels complicate comparisons of the results across studies.

The toxicity of JP-8 aerosols has been examined in a number of studies conducted by the University of Arizona (Baldwin et al. 2001, 2007; Harris et al. 1997a, 1997b, 1997c, 2000a, 2000b, 2000c, 2002, 2007a, 2007c, 2008; Hays et al. 1995; Herrin et al. 2006; Hilgaertner et al. 2011; McGuire et al. 2000; Pfaff et al. 1995, 1996; Robledo and Witten 1998, 1999; Robledo et al. 2000; Wang et al. 2001; Wong et al. 2004, 2008). However, the interpretation of most of these studies and comparison of the results to other studies are limited by several methodological issues that may have led to underestimating of exposure levels and possible exposure to plasticizing chemicals. With the exception of the Herrin et al. (2006), Hilgaertner et al. (2011), and Wong et al. (2008) studies, JP-8 was aerosolized via a DeVilbiss Ultra-Neb nebulizer and aerosol concentrations were measured after each exposure using a seven-stage cascade impactor. However, this system was only capable of measuring aerosol concentrations; the JP-8 vapor concentrations were not quantified. Hilgaertner et al. (2011) compared this generation/ measurement methodology to one in which a Lovelace jet nebulizer was used to aerosolize the jet fuel, and vapor and aerosol concentrations were measured using an in-line, real-time total hydrocarbon analysis system. The study found that a total exposure to 1,000 mg/m^3 JP-8 represents an exposure to 125 mg/m^3 aerosolized JP-8 and 875 mg/m^3 JP-8 vapor; the vapor/aerosol distribution is likely to vary with the JP-8 concentration. Thus, reporting only the aerosol levels underestimated the actual exposure to JP-8. As noted in a memorandum from the Air Force Research Laboratory to ATSDR (Mattie 2013), a site visit to the University of Arizona laboratory revealed that the generation of the test atmosphere using the

DeVilbiss nebulizer involved using plastic cups as reservoirs for the liquid JP-8. The plastic cups began to disintegrate during generation of the test atmosphere and needed to be replaced every 15 minutes; replacing the cup required a shutdown of the test generation and re-equilibration of the exposure chamber; thus compromising the exposure concentration and duration of exposure. Additionally, it is noted that the test atmosphere may have contained particles of plastic or plastic components dissolved by JP-8 test atmosphere (Mattie 2013). While pertinent to the understanding of the toxicity of JP-8, most of the studies are not considered key studies due to significant dose quantification limitations and the potential co-exposure to plasticizing chemicals. The studies are considered supporting data and are discussed throughout the document. Exposure levels are not reported for the studies that only reported the concentration of the aerosol component of the test atmosphere and these studies are not included in Table 3-1 and Figure 3-1.

3.2.1.1 Death

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

No deaths occurred in rats exposed to 5,000 mg/m^3 kerosene (physical form not specified) for 4 hours (Vernot et al. 1990a). 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 520 mg/m^3 (aerosol component only) for 1 hour/day for 7 days or 495 mg/m^3 for 1 hour/day for 28 days (Pfaff et al. 1995). No deaths occurred in male or female F-344 rats exposed whole-body to 4,440 mg/m^3 JP-8 combination of vapors and aerosol or to 3,430 mg/m^3 vapors for 4 hours (Wolfe et al. 1996).

There were no deaths among rats, mice, or dogs exposed continuously whole-body to up to 750 mg/m^3 JP-5 vapors for 90 days (Gaworski et al. 1984).

3.2.1.2 Systemic Effects

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 3-1 and plotted in Figure 3-1.

Respiratory Effects. No studies were located regarding respiratory effects in humans during or following inhalation exposure to JP-5, JP-8, or Jet A fuels. There was no throat irritation in six volunteers following a 15-minute 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

Table 3-1 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m^3)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m^3)	Serious (mg/m^3)		
ACUTE EXPOSURE								
Systemic								
1	Rat (Sprague-Dawley)	4 hr/d 5 d/wk 14 d	Resp	1662 F			Sweeney et al. 2013 Jet A	Vapor and aerosol exposure
			Cardio	1662 F				
			Gastro	1662 F				
			Hemato	1662 F				
			Hepatic	1662 F				
			Renal	1662 F				
			Bd Wt	1662 F				
2	Rat (Sprague-Dawley)	4 hr/d 5 d/wk 14 d	Resp	1980 F			Sweeney et al. 2013 Jet A	Vapor and aerosol exposure
			Cardio	1980 F				
			Gastro	1980 F				
			Hemato	1980 F				
			Hepatic	1980 F				
			Renal	1980 F				
			Bd Wt	1980 F				

Table 3-1 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m^3)	LOAEL Less Serious (mg/m^3)	LOAEL Serious (mg/m^3)	Reference Chemical Form	Comments
3	Rat (F344)	4 hr/d 5 d/wk 14 d	Resp	1980 F			Sweeney et al. 2013 Jet A	Vapor and aerosol exposure
			Cardio	1980 F				
			Gastro	1980 F				
			Hemato	1980 F				
			Hepatic	1980 F				
			Renal	1980 F				
			Bd Wt	1980 F				
4	Rat (Fischer- 344)	4 hr	Resp		3430	(signs of upper respiratory irritation)	Wolfe et al. 1996 JP-8	Vapor exposure
			Ocular		3430	(signs of eye irritation)		
5	Rat (Fischer- 344)	4 hr	Resp	4440			Wolfe et al. 1996 JP-8	Aerosol/vapor exposure NOAELs for eye and respiratory irritation
			Ocular	4440				
6	Rat (Fischer- 344)	4 hr	Resp		3570	(signs of respiratory irritation)	Wolfe et al. 1996 JP-8+100	Vapor exposure
			Ocular		3570	(signs of eye irritation)		

Table 3-1 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m^3)	LOAEL Less Serious (mg/m^3)	LOAEL Serious (mg/m^3)	Reference Chemical Form	Comments
7	Rat (Fischer- 344)	4 hr	Resp	4540			Wolfe et al. 1996 JP-8+100	Aerosol/vapor exposure NOAELs for eye and respiratory irritation
			Ocular	4540				
8	Mouse (C57BL/6N)	7 d 1 hr/d	Resp	45 M			Herrin et al. 2006 JP-8	Aerosol/vapor exposure
9	Mouse (Swiss-Webster)	30 min	Resp		2876 M (RD50)		Whitman and Hinz 2001 JP-8	Mostly vapor exposure
10	Mouse (Swiss-Webster)	30 min	Resp		1629 M (RD50)		Whitman and Hinz 2001 JP-8+100	Mostly vapor exposure
11	Mouse (Swiss-Webster)	30 min	Resp		3338 M (RD50)		Whitman and Hinz 2004 JP-5	Aerosol/vapor exposure; except 804 mg/m3 concentration which was vapor exposure
12	Mouse (C57BL/6N)	7 d 1 x/d	Resp		53 M (increased lung resistance)		Wong et al. 2008 JP-8	Aerosol/vapor exposure
Immuno/ Lymphoret								
13	Rat (Sprague-Dawley)	4 hr/d 5 d/wk 14 d		1662 F			Sweeney et al. 2013 Jet A	Vapor and aerosol exposure

Table 3-1 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
14	Rat (Sprague-Dawley)	4 hr/d 5 d/wk 14 d		1980 F			Sweeney et al. 2013 Jet A	Vapor and aerosol exposure
15	Rat (F344)	4 hr/d 5 d/wk 14 d		1980 F			Sweeney et al. 2013 Jet A	Vapor and aerosol exposure
16	Mouse (C57BL/6N)	7 d 1 hr/d			1000 (decreased splenic immune function and immune organ weight)		Hilgaertner et al. 2011 JP-8	Aerosol/vapor exposure
Neurological								
17	Rat (Long- Evans)	1-5 d 4 hr/d		1000 M			Fechter et al. 2007 JP-8	Mostly vapor exposure NOAELfor auditory impairment.
18	Rat (Long- Evans)	4 hr/d 5 d		1000 M	2000 M (transient decrease in auditory function)		Fechter et al. 2010 JP-8	Vapor exposure

Table 3-1 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE								
Systemic								
19	Rat (Fischer- 344)	90 d 24 hr/d	Resp	750			Gaworski et al. 1984, 1985 JP-5	Vapor exposure; observed renal effects in male rats are not relevant to humans
			Cardio	750				
			Gastro	750				
			Hemato	750				
			Musc/skel	750				
			Hepatic	750				
			Renal	750 F	150 M (hyaline droplets in tubular epithelium)			
			Endocr	750				
			Dermal	750				
			Bd Wt	750 F	150 M (15-19% reduced final body weight)			
			Metab	750				
			Other	750				

Table 3-1 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
20	Rat (Sprague-Dawley)	91 d 6 hr/d	Resp	250 M	500 M (enlarged alveolar capillaries)		Hanas et al. 2010 JP-8	Vapor exposure
			Cardio	250 M	500 M (myocardial scarring in 2/3 rats)			
			Hemato	250 M	500 M (50% reduction in fat cells/globules in bone marrow)			
			Hepatic	250 M	500 M (dilated sinusoids, fatty hepatocytes in 2/3 rats)			
			Renal		250 M (proximal tubule damage in 2/3 rats)			
21	Rat (Fischer- 344)	90 d 24 hr/d	Resp	1000			Mattie et al. 1991 JP-8	Vapor exposure; observed renal effects in male rats are not relevant to humans
			Hemato	1000				
			Hepatic	1000				
			Renal	1000 F	500 M (hyaline nephropathy)			
			Bd Wt	1000				
22	Rat (Sprague-Dawley)	6 wk 5 d/wk 6 hr/d	Bd Wt	1000 M			Witzmann et al. 2000 JP-8	Vapor exposure

Table 3-1 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
23	Mouse (C57BL/6N)	90 d 24 hr/d	Resp	750 F			Gaworski et al. 1984, 1985 JP-5	Vapor exposure
			Cardio	750 F				
			Gastro	750 F				
			Musc/skel	750 F				
			Hepatic		150 F[b] (hepatocyte fatty change and vacuolization)			
			Renal	750 F				
			Endocr	750 F				
			Dermal	750 F				
			Bd Wt	750 F				
			Other	750 F				

Table 3-1 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
24	Dog (Beagle)	90 d 24 hr/d	Resp	750			Gaworski et al. 1984, 1985 JP-5	Vapor exposure
			Cardio	750				
			Gastro	750				
			Hemato	750				
			Musc/skel	750				
			Hepatic	150	750 (diffuse hepatocellular swelling)			
			Renal	750				
			Endocr	750				
			Dermal	750				
			Bd Wt	750				
			Metab	750				
			Other	750				
Immuno/ Lymphoret								
25	Rat (Fischer- 344)	90 d 24 hr/d		750			Gaworski et al. 1984, 1985 JP-5	Vapor exposure Histology of lymphoreticular organs.
26	Mouse (C57BL/6N)	90 d 24 hr/d		750 F			Gaworski et al. 1984, 1985 JP-5	Vapor exposure Histology of lymphoreticular organs

Table 3-1 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
27	Dog (Beagle)	90 d 24 hr/d		750			Gaworski et al. 1984, 1985 FO1JP5	Vapor exposure Histopathology of lymphoreticular organs.
Neurological								
28	Rat (Fischer- 344)	4 wk 5 d/wk 6 hr/d		1500			Fechter et al. 2012 JP-8	Mostly vapor exposure NOAEL for auditory function
29	Rat (Fischer- 344)	90 d 24 hr/d		750			Gaworski et al. 1984, 1985 JP-5	Vapor exposure Histology of the brain and sciatic nerve.
30	Rat (Long- Evans)	6 hr/d 5 d/wk 4 wk			1000 (central auditory processing dysfunction)		Guthrie et al. 2014 JP-8	mostly vapor exposure
31	Rat (Fischer- 344)	4 wk 5 d/wk 6 hr/d			1000 M (central auditory dysfunction)		Guthrie et al. 2015 JP-8	
32	Rat (Sprague-Dawley)	6 wk 5 d/wk 6 hr/d		500[c] M	1000 M (impaired learning in moderately difficult tasks)		Ritchie et al. 2001 JP-8	Vapor exposure
33	Rat (Sprague-Dawley)	6 wk 5 d/wk 6 hr/d			1000 M (altered appetite reinforcement approach sensitization)		Rossi et al. 2001 JP-8	Vapor exposure

Table 3-1 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
34	Rat (Sprague-Dawley)	6 wk 5 d/wk 6 hr/d			1200 M (increased forelimb grip strength)		Rossi et al. 2001 JP-5	Vapor exposure
35	Mouse (C57BL/6N)	90 d 24 hr/d		750 F			Gaworski et al. 1984, 1985 JP-5	Vapor exposure Histology of the brain and sciatic nerve.
36	Dog (Beagle)	90 d 24 hr/d		750			Gaworski et al. 1984, 1985 JP-5	Vapor exposure Histopathology of the brain and sciatic nerve.
Reproductive								
37	Rat (Fischer- 344)	90 d 24 hr/d		750			Gaworski et al. 1984, 1985 JP-5	Vapor exposure Histology of reproductive organs.
38	Mouse (C57BL/6N)	90 d 24 hr/d		750 F			Gaworski et al. 1984, 1985 JP-5	Vapor exposure Histology of the reproductive organs.

Table 3-1 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
39	Dog (Beagle)	90 d 24 hr/d		750			Gaworski et al. 1984, 1985 JP-5	Vapor exposure Histopathology of the reproductive organs.

a The number corresponds to entries in Figure 3-1.

b Used to derive an intermediate-duration Minimal Risk Level (MRL) of 2 mg/m3 for JP-5 vapor. The LOAEL was multiplied by the ratio of the animal-to-human blood:gas partition coefficients to calculate a human equivalent concentration (HEC). The LOAELHEC was divided by an uncertainty factor of 90 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

c Used to derive an intermediate-duration MRL of 3 mg/m3 for JP-8 vapor. The NOAEL was adjusted for intermittent exposure and multiplied by the ratio of the animal-to-human blood:gas partition coefficients to calculate a human equivalent concentration (HEC). The NOAELHEC was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); Metab = metabolism; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; RD50 = exposure concentration producing a 50% decrease in respiratory rate; Resp = respiratory; x = time(s); wk = week(s)

Figure 3-1 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Inhalation

Acute (≤14 days)

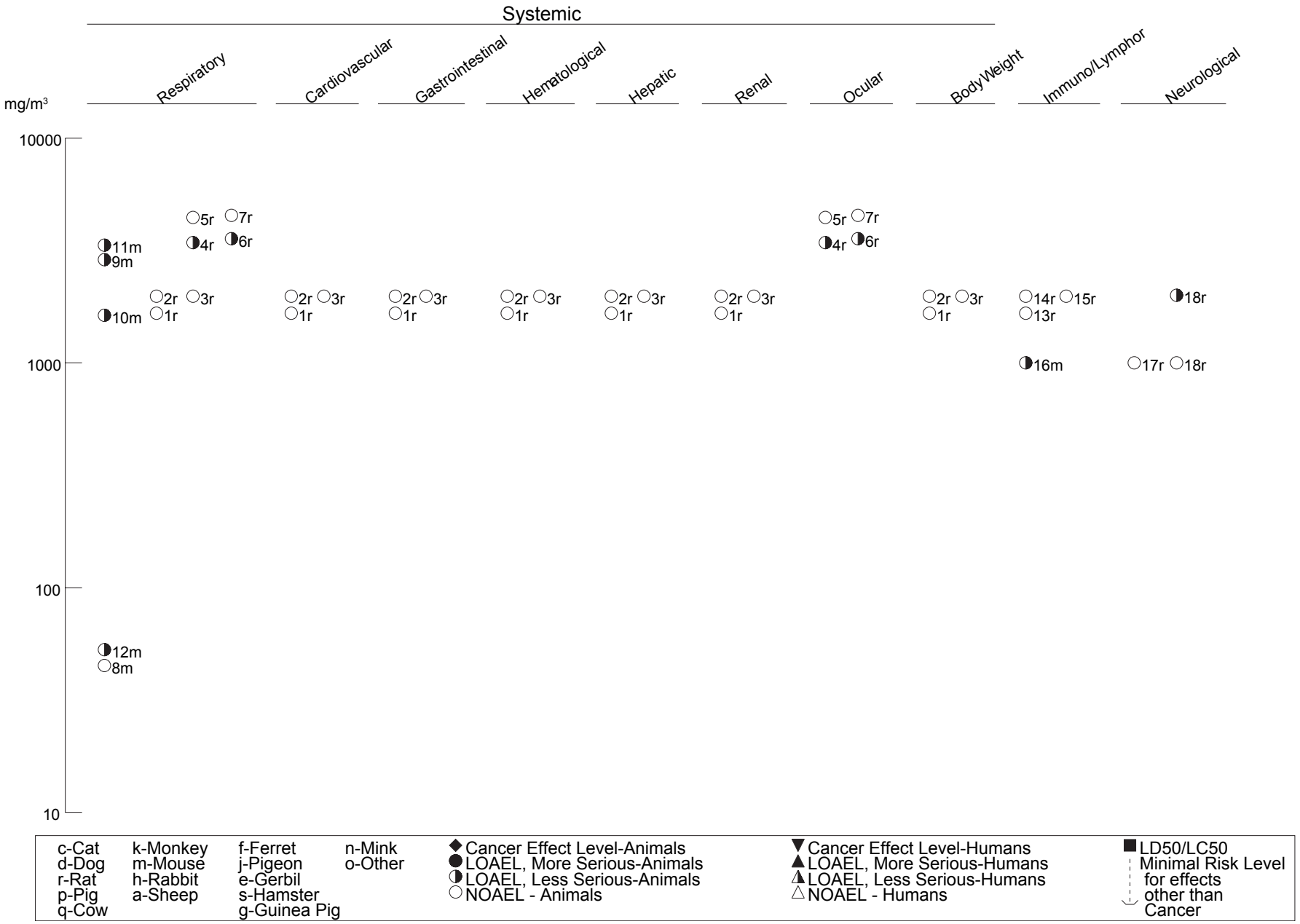


Figure 3-1 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Inhalation *(Continued)*

Intermediate (15-364 days)

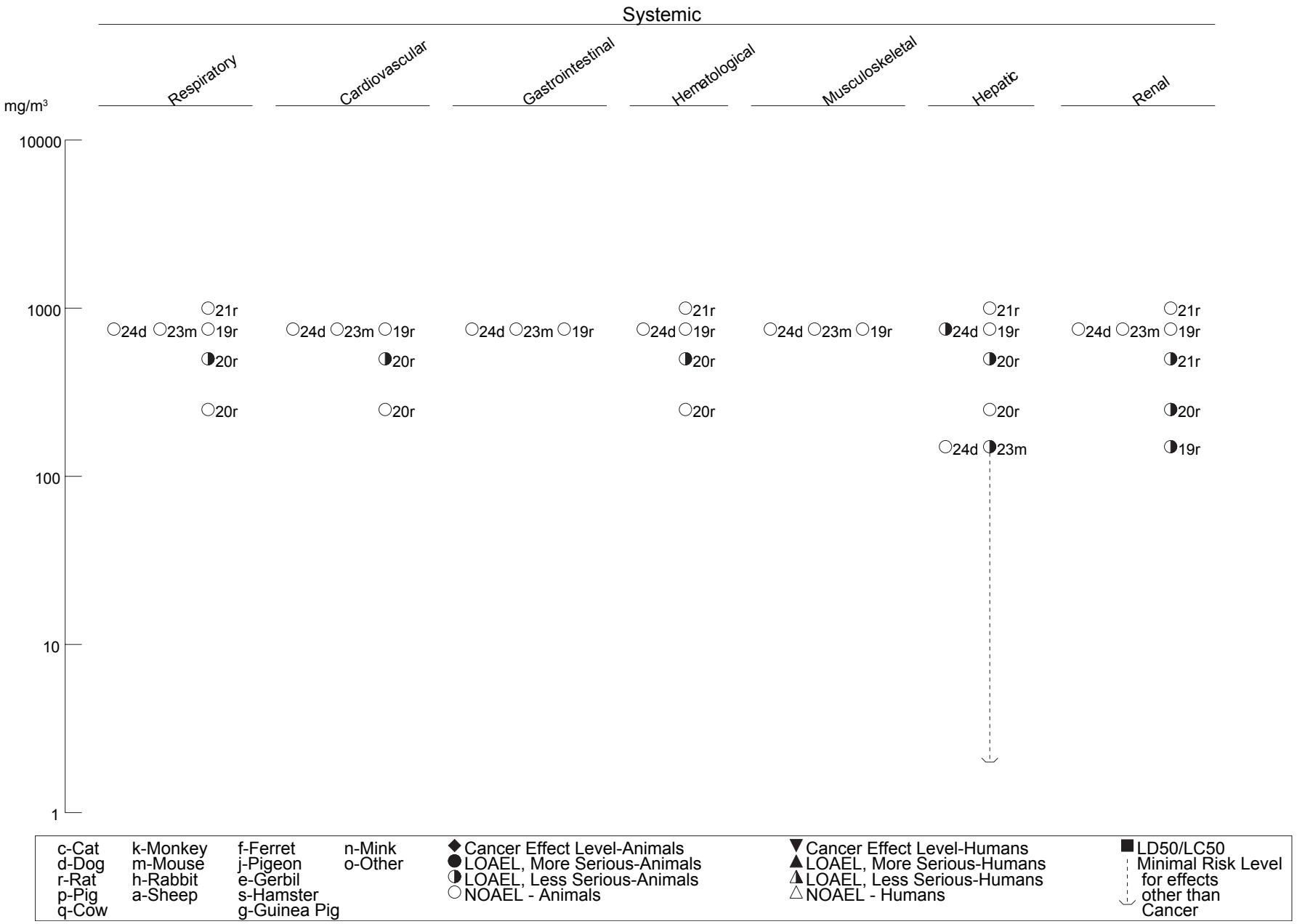


Figure 3-1 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Inhalation *(Continued)*

Intermediate (15-364 days)

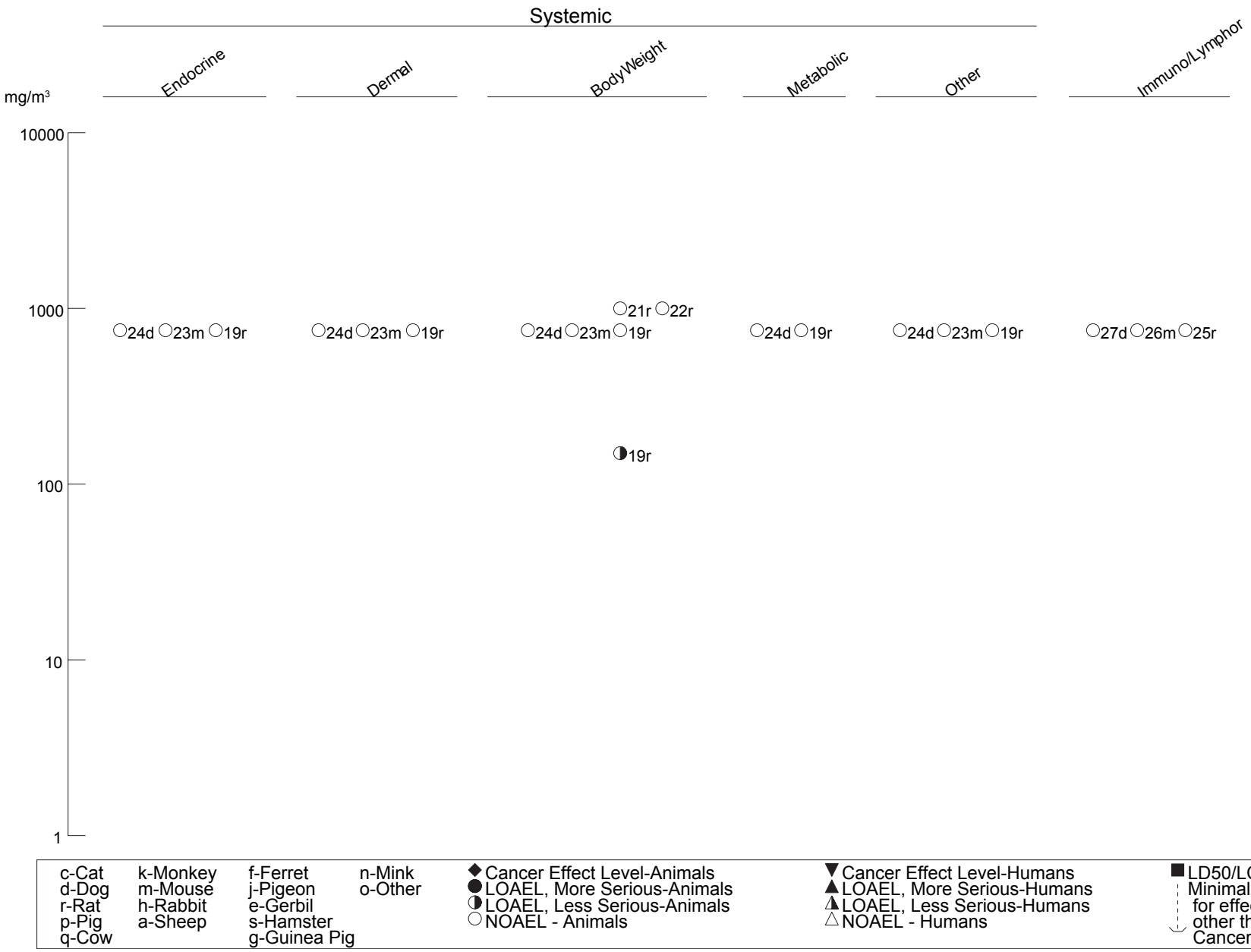
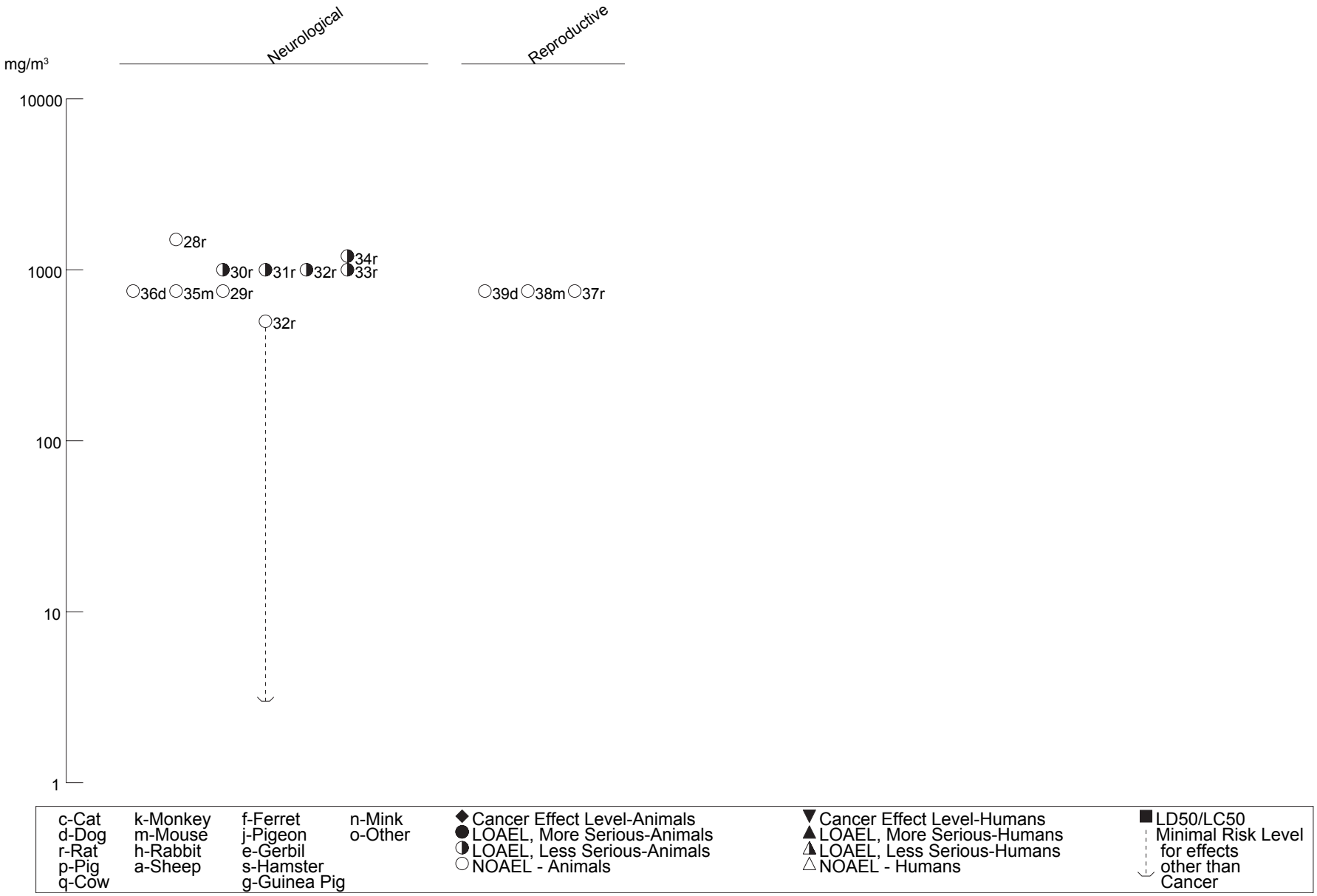


Figure 3-1 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Inhalation *(Continued)*

Intermediate (15-364 days)



material and reported that the concentration was probably the "highest attainable concentration at which vapor analysis is representative of liquid analysis." At a concentration of deodorized kerosene vapor of approximately 100 mg/m^3 (25°C), air is substantially saturated with kerosene vapor, although this is dependent upon the constituents of the mixture (Carpenter et al. 1976).

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 1991). 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.

Studies in rats and mice provide suggestive evidence that JP-8, at high concentrations, is a respiratory irritant. In a study conducted by Whitman and Hinz (2001), RD_{50} (concentration resulting in a 50% decrease in respiratory rate) values of 2,876 mg/m^3 (95% confidence interval of 2,107–3,925 mg/m^3) and 1,629 mg/m^3 (95% confidence interval of 1,418–1,871 mg/m^3) were calculated for aerosolized JP-8 and JP-8+100 (mostly vapors) (JP-8+100 is JP-8 fuel with additives to increase the thermal stability by 100°F), respectively, following a 30-minute head-only exposure in male Swiss-Webster mice. The investigators noted that there were no signs of narcosis or pulmonary irritation for either substance. In a similar study, an RD_{50} of 3,338 mg/m^3 (95% confidence interval of 1,759–6,332 mg/m^3) was calculated for aerosolized JP-5 (concentrations are for aerosol and vapor components) (Whitman and Hinz 2001). Signs of upper respiratory irritation were observed in rats exposed to 3,430 mg/m^3 JP-8 vapor or 3,570 mg/m^3 JP-8+100 vapor (Wolfe et al. 1996). However, exposure to 4,440 mg/m^3 JP-8 or 4,540 mg/m^3 JP-8+100 as a vapor/aerosol mixture did not result in signs of respiratory irritation (Wolfe et al. 1996).

Several studies have examined the possible toxicity of JP-8 and Jet A to the respiratory tract following acute exposure. Herrin et al. (2006) and Wong et al. (2008) found that nose-only exposure of mice to 45 or 53 mg/m^3 aerosolized JP-8 (vapor and aerosol components) 1 hour/day for 7 days resulted in ultrastructural changes in the alveolar type II cells, particularly an increase in volume density of lamellar

bodies; this change was not considered an adverse effect. Wong et al. (2008) found increases in inspiratory and expiratory lung resistance, but no effect on total lung compliance at 53 mg/m^3. Respiratory permeability was increased by 31.2% by JP-8 exposure, but this was not significantly different compared to controls. However, Herrin et al. (2006) found a significant decrease in inspiratory dynamic lung compliance at 406 mg/m^3 (aerosol and vapor components) and no change in lung resistance or respiratory permeability at concentrations as high as 406 mg/m^3 (aerosol and vapor components). It is unclear why the results of the Herrin et al. (2006) and Wong et al. (2008) differ.

Two studies conducted by Sweeney et al. (2013) found no histological alterations in the respiratory tract following a 4-hour/day, 5-day/week exposure to Jet A vapors and aerosols for 14 days. The highest tested concentrations were 1,662 mg/m^3 in the first study with Sprague-Dawley rats and 1,980 mg/m^3 in the second study with Sprague-Dawley rats and F344 rats. Some alterations in lung lavage fluid parameters, which may be indicative of inflammation were observed in the second study. The alterations included increases in monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein 2 (MIP-2) in F344 rats exposed to 869 or 1,980 mg/m^3 Jet A and increases in MCP-1 in Sprague-Dawley rats exposed to 1,980 mg/m^3. The biological relevance of these alterations in the absence of morphological alterations is not known.

Several studies in rats, mice, and dogs have examined the respiratory tract following intermediate-duration exposure JP-5 or JP-8 vapor. No histological alterations were observed in the respiratory tract of rats, mice, or dogs exposed continuously to up to 750 mg/m^3 JP-5 vapor (the highest concentration tested) for 90 days (Gaworski et al. 1984). Similarly, no respiratory tract lesions were observed in rats continuously exposed to up to 1,000 mg/m^3 JP-8 vapor for 90 days (Mattie et al. 1991). Alveolar capillary distention was observed in male Sprague-Dawley rats exposed to 500 or 1,000 mg/m^3 JP-8 vapor 6 hours/day for 91 days (Hanas et al. 2010); no effects were observed at 250 mg/m^3. It should be noted that this study only examined three rats per group.

A series of studies were conducted at the University of Arizona to evaluate the potential respiratory toxicity of JP-8 (Hays et al. 1995; Pfaff et al. 1995, 1996; Robledo and Witten 1998, 1999; Robledo et al. 2000; Wang et al. 2001; Wong et al. 2004). As noted in the discussion in Section 3.2.1, these studies only measured the aerosol component of the test atmosphere; thus, the concentrations reported by the investigators underestimate the actual JP-8 exposure (vapor and aerosol phases). These studies provide information on the toxicity of JP-8, but do not provide reliable concentration-response data. The studies used similar experimental designs in which small groups of rats or mice were nose-only exposed to

several concentrations of JP-8 for 1 hour or for 1 hour/day for 7 days; studies in rats also involved exposures for 1 hour/day for 28 or 56 days. A 7-day exposure resulted in pulmonary congestion with hemorrhaging in the distal lung with breaks in the alveolar capillary membranes (Hays et al. 1995; Pfaff et al. 1996). Electron microscopy showed degeneration of alveolar type II cells (Pfaff et al. 1995). Interstitial perivascular edema and thickening of the bronchiolar epithelium were observed after a 56-day exposure (Hays et al. 1995). Other respiratory effects observed in rats at similar concentrations include an increase in respiratory permeability following ≥7 days of exposure (Hayes et al. 1995; Pfaff et al. 1995), increases in inspiratory resistance and inspiratory dynamic compliance (Pfaff et al. 1995), and a decrease in substance P and corresponding increase in neutral endopeptidase (NEP) concentration in the bronchoalveolar lavage fluid (BALF) samples (Pfaff et al. 1995, 1996). NEP is the primary tachykinin degradative enzyme in the lung and its origin is primarily epithelial; substance P is thought to play a role in airway reactivity and pulmonary epithelial integrity. Similar effects have been observed in mouse studies conducted at the University of Arizona; however, comparing the results of the rat studies to the mouse studies suggests that mice may be more sensitive than rats since effects are observed at lower concentrations. The morphological effects observed in mice include peribronchiolar edema and deterioration of the alveolar-capillary barrier (Robledo and Witten 1998; Robledo et al. 2000) and ectasia of respiratory bronchioles and alveoli at higher concentrations (Wong et al. 2004). BALF analysis showed increased total protein levels, total cell counts, neutrophil levels, decreased macrophage levels, increased lactate dehydrogenase, and/or N-acetyl-β-D-glucosaminidase activities (Robledo and Witten 1998; Robledo et al. 2000; Wang et al. 2001). In addition to these morphological alterations, increases in dynamic compliance (Wang et al. 2001) and increases in respiratory permeability (Robledo and Witten 1998; Robledo et al. 2000; Wang et al. 2001) were observed. A study investigating the molecular mechanism of the lung effects found alterations in the levels of proteins suggestive of impaired protein synthetic/processing machinery, ultrastructural damage, toxic/metabolic stress and detoxification systems, and functional responses to carbon dioxide handling, acid-base homeostasis, and fluid secretion (Witzmann et al. 1999). A subsequent study by this group found decreases in α1-anti-trypsin levels in JP-8 exposed mice (Drake et al. 2003); α-1-anti-trypsin deficiency has been show to play a role in the development of pulmonary emphysema. The Wang et al. (2001) study examined possible age-related differences in the respiratory toxicity of JP-8 in 3.5- and 12-month-old mice. Alterations in lung function and respiratory permeability appeared to be similar in the two groups, but some differences in BALF analysis were detected. The levels of tumor necrosis factor-α (TNF-α) in the BALF were significantly increased in the adult-exposed group and significantly decreased in the young-exposed groups, as compared to their respective controls. Macrophage inflammatory protein-2 levels in the BALF were significantly increased in the adult and young mice; the levels in the adult-exposed group were

significantly higher than the young-exposed group, but no differences were found between the two control groups. Prostaglandin E2 (PGE2) release was significantly lower in both exposed groups, as compared to the respective control groups; the levels in the adults were higher than the young-exposed groups, but the adult controls also had higher levels than the young controls. The investigators concluded that the young and adult mice had similar toxicities to JP-8, although the inflammatory mechanisms may be different.

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 and it is not known if JP-5 was the causative agent (Porter 1990). No relevant data were located for JP-8 and Jet A.

Multifocal damage, consisting of myocardial scarring and inflammatory cell infiltration, was observed in male Sprague-Dawley rats exposed to 500 or 1,000 mg/m^3 JP-8 vapor 6 hours/day for 91 days (Hanas et al. 2010). The extent of the damage increased with the exposure concentration, and no effects were observed at 250 mg/m^3. Continuous exposure of rats, mice, or dogs to up to 750 mg/m^3 JP-5 vapor for 90 days did not induce gross or microscopic alterations in the heart (Gaworski et al. 1984). Inhalation of kerosene aerosol by guinea pigs for 15 minutes/day for 21 days induced aortic plaques that resembled those seen in atherosclerosis in that species (Noa and Illnait 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.

A significant decrease in absolute heart weight was observed in Sprague-Dawley rats exposed to 1,622 mg/m^3 Jet A vapors and aerosols 4 hours/day, 5 days/week for 14 days; however, no histological alterations were observed in the heart (Sweeney et al. 2013). No significant or treatment-related 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/day, 5 days/week for 13 weeks (Carpenter et al. 1976).

Gastrointestinal Effects. One of two individuals who 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 or not the nausea was related to the JP-5 exposure could not be determined. No relevant data were located for JP-8 or Jet A.

Continuous exposure of rats, mice, or dogs to up to 750 mg/m^3 JP-5 vapors for 90 days did not induce gross or microscopic alterations in the gastrointestinal tract (Gaworski et al. 1984). A significant decrease in absolute gastrointestinal weight was observed in rats exposed to 1,622 mg/m^3 Jet A vapors and aerosols 4 hours/day, 5 days/week for 14 days (Sweeney et al. 2013); this alteration was observed 14 days post-exposure, but was not observed 24 hours or 7 days after exposure termination. No histological alterations were observed in the gastrointestinal tract, and alterations in gastrointestinal weight were not observed in a subsequent study in which rats were exposed to 1,980 mg/m^3 4 hours/day, 5 days/week for 14 days (Sweeney et al. 2013). 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/day, 5 days/week for 13 weeks (Carpenter et al. 1976).

Hematological Effects. Complete blood counts performed on two individuals exposed to unknown concentrations of JP-5 vapor for approximately 1 hour while flying a small airplane were normal (Porter 1990). A study of active duty military personnel performing fuel system maintenance found significant increases in white blood cell counts, neutrophil levels, and monocyte levels among 45 workers with high exposure to JP-8 fuel, as compared to 78 workers with low or no exposure to jet fuels; no significant alterations in lymphocyte subpopulations were observed (Rhodes et al. 2003). Exposure was monitored by measuring levels of naphthalene in environmental air and in breath. The mean concentration of naphthalene in air was 583 µg/m^3 for the high-exposure group and 2.47 µg/m^3 for the low-exposure group. The respective post-exposure breath concentrations of naphthalene were 3.80 and 0.80 µg/m^3. There were no differences in pre-exposure breath concentrations of naphthalene between the two groups, (0.71 vs. 0.75 µg/m^3).

Exposure to JP-8 vapor 6 hours/day for 91 days resulted in a reduction in fat cells/globules and cell proliferation in bone marrow from male Sprague-Dawley rats; the extent of the fat cell reduction was concentration-related (Hanas et al. 2010). There was a 10% reduction in fat cells at 250 mg/m^3, a 50% reduction at 500 mg/m^3, and a scarce number remained at 1,000 mg/m^3. Continuous exposure of rats to 150 or 750 mg/m^3 JP-5 vapors for 90 days induced significant changes in hematology including decreased red blood cells in mid- and high-exposure males, decreased hemoglobin in high-exposure males, increased red blood cells in mid- and high-exposure females, and increased white blood cells in mid- and high-exposure females (Gaworski et al. 1984). However, all of these parameters were within normal limits. In similarly exposed dogs, hematology parameters were within normal limits, although there were slight decreases in red blood cell counts, hematocrit, and hemoglobin in high-exposure dogs (Gaworski et al. 1984). No hematological alterations were observed 24 hours after termination of a 14-day exposure to

Jet A vapors and aerosols (4 hours/day, 5 days/week) (Sweeney et al. 2013). Seven days post-exposure, a decrease in the percentage of lymphocytes and a decrease in the total number of lymphocytes were observed in Sprague-Dawley rats exposed to 1,021 and 1,662 mg/m^3; no alterations were observed 14 days post-exposure. The biological significance of this effect is not known. 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/day, 5 days/week for 13 weeks (Carpenter et al. 1976).

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

Continuous exposure of rats, mice, or dogs to up to 750 mg/m^3 JP-5 vapors for 90 days did not induce gross or microscopic alterations in bone or skeletal muscle (Gaworski et al. 1984).

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

Several histological alterations were observed in the livers of male Sprague-Dawley rats exposed to 500 or 1,000 mg/m^3 JP-8 vapor 6 hours/day for 91 days (Hanas et al. 2010); no liver effects were observed at 250 mg/m^3. The hepatic effects included dilated sinusoids, cytoplasmic clumping, and fatty hepatocytes. No histological alterations were noted in the livers of rats continuously exposed to JP-8 vapor concentrations as high as 1,000 mg/m^3 for 90 days (Mattie et al. 1991). Rats exposed to JP-5 vapor, 6 hours/day, 5 days/week for approximately 30 days, did not exhibit any significant changes in hepatic tissue morphology or serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels; the concentration was reported at 1,100 mg/m^3 as decane (Bogo et al. 1983). Continuous exposure of rats to up to 750 mg/m^3 JP-5 vapor for 90 days did not induce gross or microscopic alterations in the liver (Gaworski et al. 1984). However, mice similarly exposed to 150 or 750 mg/m^3 JP-5 vapor showed significantly increased incidences of hepatocellular fatty change and vacuolization (Gaworski et al. 1984). The incidences were 8/37 (22%), 29/33 (88%), and 23/34 (68%) in the control, mid- and high-exposure groups, respectively. In the same study, dogs exposed to 750 mg/m^{3}JP-5, but not 150 mg/m^3, showed mild, diffuse hepatocellular swelling. Electron microscopy revealed this to be excessive glycogen accumulation. No alterations in serum alanine aminotransferase levels or histological alterations were observed in Sprague-Dawley rats or F344 rats exposed to 1,980 mg/m^3 Jet A vapors and aerosols 4 hours/day, 5 days/week for 14 days (Sweeney et al. 2013). Following exposure to up to 100 mg/m^3 deodorized kerosene vapor for 6 hours/day, 5 days/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).

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). No relevant information was located for JP-8 or Jet A fuels.

Several studies have identified a nephropathy in male rats that is associated with exposure to some organic chemicals, including some jet fuels (Gaworski et al. 1984; Hanas et al. 2010; Mattie et al. 1991). Male rats exposed continuously to ≥150 mg/m^3 JP-5 vapor (Gaworski et al. 1984) or ≥500 mg/m^3 JP-8 vapor for 90 days (Mattie et al. 1991) showed hyaline droplets in the tubular epithelium; proximal tubule damage was also observed in rats exposed to 250 mg/m^3 JP-8 vapors, 6 hours/day for 91 days (Hanas et al. 2010). This hydrocarbon-induced nephropathy has only been demonstrated in adult male rats and has been linked to a specific protein, alpha$_{2u}$-globulin, which is produced under hormonal control by the liver (Alden 1986; Swenberg 1993); concentration-related increases in alpha$_{2u}$-globulin levels were measured in rats exposed to 250–1,000 mg/m^3 JP-8 vapors (Hanas et al. 2010). Alpha$_{2u}$-globulin accumulates in hyaline droplets and the buildup of alpha$_{2u}$-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. However, alpha$_{2u}$-globulin is unique to male rats and is not present in human kidneys; hence the renal effects observed in male rats exposed to JP-8 are not relevant to humans (EPA 1991a; Flamm and Lehman-McKeeman 1991; Hard et al. 1993; Swenberg 1993).

Female rats exposed to up to 1,980 mg/m^3 Jet A vapors and aerosols 4 hours/day, 5 days/week for 14 days (Sweeney et al. 2013) or continuously to up to 1,000 mg/m^3 JP-8 vapors for 90 days (Mattie et al. 1991) did not show histological alterations in the kidneys. Similarly, no renal lesions have been observed in female mice continuously exposed to 750 mg/m^3 JP-5 vapors (Gaworski et al. 1984), male and female dogs continuously exposed to 750 mg/m^3 JP-8 vapor (Gaworski et al. 1984), or male dogs exposed to 100 mg/m^3 deodorized kerosene vapor 6 hours/day, 5 days/week for 13 weeks (Carpenter et al. 1976). Male rats exposed to JP-5 vapor (concentration reported as 1100 mg/m^3 decane), 6 hours/day, 5 days/week for approximately 30 days did not exhibit any significant changes in renal tissue morphology, but did report increased water consumption which may be indicative of renal damage (Bogo et al. 1983).

Endocrine Effects. No histopathological changes were noted in the adrenal or thyroid glands of rats or dogs exposed to up to 100 mg/m^3 deodorized kerosene vapor 6 hours/day, 5 days/week for 13 weeks (Carpenter et al. 1976) or rats, mice, or dogs continuously exposed to 750 mg/m^3 JP-5 vapors for 90 days (Gaworski et al. 1984).

Ocular Effects. One case study describes eye irritation in two individuals exposed to unknown concentrations of JP-5 vapor for approximately 1 hour while flying a small airplane (Porter 1990); it is not known if JP-5 was the causative agent. No relevant data were located for JP-8 or Jet A. 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 was also reported for one of the individuals; this effect subsided after 4 days. All effects appear to have been local in nature. No eye irritation was reported in six volunteers exposed to 140 mg/m^3 deodorized kerosene vapor for 15 minutes (Carpenter et al. 1976).

Nose-only exposure of male Swiss Webster mice to 1,000 or 2,500 mg/m^3 (aerosol component only) aerosolized JP-8+100 1 hour/day for 7 days did not result in gliosis or histopathological alterations in the retina (McGuire et al. 2000). However, increased immunoreactivity of anti-GSTM antibodies in the retinal Müller cells, which may be indicative of oxidative stress, was found at both concentrations.

Signs of eye irritation were reported in F-344 rats exposed whole-body to 3,430 mg/m^3 JP-8 vapor or 3,570 mg/m^3 JP-8+100 vapor for 4 hours, but no such effects were reported during exposures to 4,440 mg/m^3 that included a combination of vapor and aerosolized JP-8 fuel or 4,540 mg/m^3 JP-8+100 vapor/aerosol (Wolfe et al. 1996).

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

No biologically relevant alterations in body weight gain were observed in Sprague-Dawley and F344 rats exposed to up to 1,980 mg/m^3 Jet A vapor and aerosol 4 hours/day, 5 days/week for 14 days (Sweeney et al. 2013). There was no significant change in body weight gain in mice, dogs, or female rats following 90-day continuous inhalation exposure to up to 750 mg/m^3 JP-5 vapor (Gaworski et al. 1984). However, final body weight of male rats exposed to 150 or 750 mg/m^3 JP-5 vapor was reduced 15–19% (Gaworski et al. 1984). Intermittent whole-body exposure of male Sprague-Dawley rats to 1,000 mg/m^3 JP-8 vapors

for 6 weeks resulted in body weights lower than controls during the exposure period, but the difference between the groups was not statistically significant (Witzmann et al. 2000). Male F344 rats continuously exposed to airborne JP-8 vapor (500 or 1,000 mg/m^3) for 90 days followed by a 21-month recovery period showed a 5–8% reduction in body weight relative to controls during the exposure period (Mattie et al. 1991). However, at the end of the 21-month recovery period, body weights were reduced 14–16% in both exposed groups relative to controls. Female body weights were not significantly affected by exposure to JP-8 (Mattie et al. 1991). There was no change in body weight gain in rats or dogs exposed to up to 100 mg/m^3 deodorized kerosene vapor 6 hours/day, 5 days/week for 13 weeks (Carpenter et al. 1976).

Metabolic Effects. There were no alterations in blood glucose in either of two individuals following a 1-hour exposure to unknown concentrations of JP-5 vapor while flying a small airplane (Porter 1990). No relevant information was located for JP-8 or Jet A fuels.

Serum levels of glucose and electrolytes were not significantly altered in rats or dogs exposed continuously to up to 750 mg/m^3 JP-5 vapor for 90 days (Gaworski et al. 1984).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans exposed to JP-5, JP-8, or Jet A fuels.

Harris and associates at the University of Arizona conducted a number of studies designed to assess the immunotoxic potential of JP-8 (Harris et al. 1997a, 1997b, 1997c, 2000a, 2000b, 2000c, 2007a, 2007c, 2008). As discussed in Section 3.2.1, there are a number of limitations to these studies; the primary limitation was the inaccurate measurement of the test atmosphere because only the aerosol component of the aerosolized JP-8 was measured. Thus, the reported concentrations underestimated the JP-8 exposure levels and the data are not considered suitable for concentration-response analysis. Additionally, the animals may have been exposed to plasticizing chemicals from the breakdown of the plastic cups used to hold the JP-8 during aerosolization (Mattie 2013). The results of the University of Arizona studies discussed in this paragraph are considered supporting studies and are not presented in Table 3-1 or Figure 3-1. Most of the immunotoxicity studies conducted by this group involved nose-only exposure of male and female C57Bl/6 mice to aerosolized JP-8 1 hour/day for 7 days. The studies consistently found decreases in spleen and thymus weights and decreases in the number of viable immune cells in these organs (Harris et al. 1997a, 1997b, 1997c); the effects on thymus immune cell numbers were observed at

the lowest concentrations tested. Multiphasic alterations in the number of viable immune cells were observed in other tissues. In the lymph nodes and peripheral blood, low concentrations of aerosolized JP-8 resulted in decreases in cell numbers, mid-range concentrations increased cell numbers, and high concentrations decreased cell numbers (Harris et al. 1997a, 1997b). In the bone marrow, increases in cell numbers were observed at low concentrations and decreases were observed at a mid-range concentration. A number of alterations in immunocompetence were also observed. Impaired immune responses were found in mice exposed to aerosolized JP-8 following stimulation with the T-cell mitogen concanavalin A or the T-cell growth factor interleukin-2 (IL-2) (Harris et al. 1997a). Exposure to aerosolized JP-8+100 also resulted in a suppressed response to concanavalin A (Harris et al. 2000b). Harris et al. (2008) showed that a 7-day exposure to aerosolized JP-8 could reduce immunocompetence, evidenced by decreased immune cell viability, decreased immune proliferative responses to mitogens, and the loss of $CD3^+$, $CD4^+$, and $CD8^+$ T cells from the lymph nodes, but not from the spleen. Exposure of mice to aerosolized JP-8 for 7 days before intravenous injection of B16 tumor cells induced an approximately 8.7-fold increase in tumor formation in the lungs, whereas mice exposed to JP-8 at the time of tumor induction showed a 5.6-fold increase in the number of tumors (Harris et al. 2007c). Although the results were not statistically analyzed, the findings were interpreted as a suppressive effect of JP-8 exposure on the immune system, leading to increased tumor formation and metastases. A 7-day exposure to aerosolized JP-8 also increased the severity of a viral infection (mice were exposed to A/Hong Kong/8/68 influenza virus 1 day post-JP-8 exposure) (Harris et al. 2008). A study of the time course of JP-8-induced effects showed that a 1-hour exposure caused significant spleen and thymus weight loss and loss on viable cells in the spleen within 2 hours of the exposure (Harris et al. 2002). It was also shown that immune function, as assessed by the response to mitogens, was impaired 1 hour after exposure and did not recover within 24 hours. Harris et al. (1997c) found that the decreases in immune organ weights and decreased immune function persisted for 4 weeks post-exposure to aerosolized JP-8. Harris and associates also examined the possible mechanisms of immunotoxicity in mice exposed to aerosolized JP-8. The studies showed that substance P, a small peptide thought to be involved in airway reactivity and in maintaining pulmonary epithelial integrity, could protect the immune system from JP-8-induced damage and also reverse the damage if administered at appropriate times before and/or after JP-8 exposure (Harris et al. 1997b, 2000c). They also showed that exposure to JP-8 rapidly increased serum levels of two immunosuppressive agents, interleukin-10 (IL-10) and prostaglandin E2 (PGE2) (Harris et al. 2007a). Since treatment with a PGE2 inhibitor did not completely reverse the effects of JP-8, the increased levels of IL-10 and PGE2 could only partially explain all of the effects of JP-8 exposure on immune function. Another study showed that exposure to aerosolized JP-8 almost completely inhibited natural killer (NK) cell activity, significantly suppressed the generation of lymphokine-activated killer (LAK) cell activity,

suppressed the generation of cytotoxic T lymphocyte cells from precursor T cells, and inhibited helper T cell activity (Harris et al. 2000a).

A more recent study conducted at the University of Arizona by Hilgaertner et al. (2011) used a different system for generating aerosolized JP-8, and both the aerosol and vapor components of the test atmosphere were measured. This study found significant decreases in spleen and thymus weights in C57BL/6 mice exposed to 1,000, 4,000, or 8,000 mg/m^3 (aerosol and vapor components) aerosolized JP-8 1 hour/day for 7 days; there were no changes in spleen weights at 2,000 mg/m^3. Thymus weights were significantly decreased at ≥1,000 mg/m^3; slight but statistically significant decreases in body weight were also observed at ≥1,000 mg/m^3. However, the body weights at all concentrations were within 10% of controls. Viable cell levels were significantly decreased in the bone marrow at 8,000 mg/m^3, in the spleen and peripheral blood at 4,000 mg/m^3, and in the thymus at ≥2,000 mg/m^3; significant increases in bone marrow and peripheral blood viable cell levels were observed at 4,000 and 1,000 mg/m^3, respectively. Assessment of immune function by proliferative responses to mitogens showed significant suppression by exposure to JP-8 fuel (about 70% at 1,000 mg/m^3).

Two 14-day studies in rats did not find concentration-related alterations in splenic lymphocyte phenotypes at Jet A vapor and aerosol levels up to 1,980 mg/m^3 (Sweeney et al. 2013). Harris et al. (2000b) also conducted a study in mice exposed to Jet A-1 fuel 1 hour/day for 7 days; similar to the JP-8 studies conducted by this group, only the aerosol component of the test atmosphere was measured. The study found no alteration in splenic lymphocyte populations, but did find significant increases in double negative thymocytes and a concomitant decrease in double positive thymocytes. A significant suppression of the response to concanavalin A was also observed in this study.

A study of unadditized jet fuel kerosene vapor (a composite blend of unadditized Jet A fuel) (500 mg/m^3 exposure level) or aerosol/vapor (1,000 or 2,000 mg/m^3 exposure levels) in which female B6C3F1 mice and female Crl:CD rats were exposed nose-only 6 hours/day, 7 days/week for 28 days did not find significant alterations in spleen or thymus weight, the T-dependent antibody-forming cell response, or the delay-type hypersensitivity response at exposure levels as high as 2,000 mg/m^3 (White et al. 2013). For the most part, spleen cell numbers and phenotypes were unaffected by exposure to kerosene; however, some non-concentration-related alterations were observed, including increased number of absolute NK cells in mice exposed to 500 or 1,000 mg/m^3, increased percentage of helper T-cells in mice exposed to 1,000 or 2,000 mg.m^3, reduced spleen cell number in rats exposed to 1,000 mg/m^3, and reduced absolute number of splenic B cells in rats exposed to 1,000 mg/m^3. NK cell activity was not affected in mice, and

no assessment could be done in rats due to an unusually low response in all groups. The results of this study suggested that, at least in part, the performance additives in JP-8 fuel could be responsible for the effects observed on cell-mediated immunity following exposure to JP-8.

No gross or microscopic alterations in the thymus, spleen, and/or lymph nodes were induced after continuous exposure of rats, mice, or dogs to ≤750 mg/m^3 JP-5 vapor for 90 days (Gaworski et al. 1984), continuous exposure of rats to ≤1,000 mg/m^3 JP-8 vapor (Mattie et al. 1991), exposure of rats to ≤1,980 mg/m^3 Jet A aerosols and vapors 4 hours/day, 5 days/week for 14 days (Sweeney et al. 2013), or exposures of rats or dogs to 100 mg/m^3 deodorized kerosene vapor for 6 hours/day, 5 days/week (Carpenter et al. 1976). Immune function was not assessed in these studies.

The highest NOAEL values and all LOAEL values from each reliable study for immunological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.4 Neurological Effects

Limited information was located regarding neurological effects in humans resulting from acute exposure to jet fuels. Coordination and concentration difficulties and fatigue were noted in two individuals following exposure to JP-5 in the cockpit of an unpressurized aircraft for one hour (Porter 1990). The odor of JP-5 in the cockpit at the end of the flight was described as overwhelming; however, it is not known whether JP-5 was the causative agent. 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.

A study of 27 U.S. Air Force employees examined the association between exposure to JP-8 and postural balance (Smith et al. 1997). The subjects had been exposed to JP-8 for at least 6 months. Although exposure concentrations could not be calculated in mg/m^3 because of insufficient data, mean 8-hour breathing zone samples 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 a statistical association between sway length and cumulative JP-8 benzene, which implied a subtle influence on vestibular/proprioception functionalities. However, a recent study of 37 active duty Air Force personnel found that workday exposure to JP-8 was not significantly associated with postural sway (Maule et al. 2013). Instead, increases in workday postural sway were associated with demographic variables including younger age, being a current smoker, and higher body mass index. In

this study, exposure was assessed by personal breathing zone levels of naphthalene and total hydrocarbons and urinary levels of 1- and 2-naphthol. A study of 63 Air National Guard personnel found that subjects exposed to JP-8 performed significantly poorer than a sample of unexposed (n=50) age- and education-matched individuals in 20 out of 47 measures of information processing and other neurocognitive tests (Tu et al. 2004). Exposure was assessed by daily breath analyses. Total JP-8 concentrations among the exposed workers before work ranged from 0 to 7.6 mg/m^3, whereas at the end of the workday, exposures ranged from 0.2 to 11.5 mg/m^3. In the unexposed subjects, total hydrocarbon concentrations at the beginning of the day ranged from 0.3 to 2.1 mg/m^3 and did not change significantly during the course of the day. A neurobehavioral assessment of 117 Air Force personnel exposed to JP-8 (primarily fuel cell maintenance workers) found significantly lower performance on digit span, symbol digit latency, and tapping tests that were conducted prior to the day's exposure; a group of 165 Air Force personnel with minimal exposure to JP-8 served as the control group (Air Force 2001). The investigators suggested that this was indicative of a carry-over or non-resolving effect associated with JP-8 exposure. A more recent study examined the potential neurotoxicity of JP-8 in 38 active duty Air Force personnel who performed job tasks that involved regular and routine individual personal exposure to JP-8 (high exposure group) and 36 Air Force personnel with low or no exposure to JP-8 (Proctor et al. 2011). The 8-hour geometric mean time-weighted average total hydrocarbon concentrations were 0.53 mg/m^3 (range of 0.24–22.01 mg/m^3) and 2.65 mg/m^3 (range of 0.24–73.93 mg/m^3) in the low- and high-exposure groups, respectively. Neuropsychological battery testing performed on days 1, 2, 4, and 6 were designed to assess attention, reaction time, psychomotor speed and efficiency, memory, and balance. When compared to normative, reference group data from groups of healthy adults (obtained from clinical test manuals or published studies), there were no significant alterations in performance on neuropsychological tests in the study participants (all groups combined), with the exception of lower performance scores on the Total Recall, Delayed Recall, and retention task tests among 20–29-year-old study participants. Interpretation of the results of this study is limited by the lack of comparison between the two exposure groups. Bell et al. (2005) exposed several groups of veterans to clean air or 0.00057 ppm JP-8 vapor for 7 minutes once a week for 3 weeks. Faster central reaction and peripheral reaction times were observed on a test of visual divided attention in the JP-8-exposed veterans compared to the air exposed veterans.

Studies in laboratory animals provide information regarding neurobehavioral and neurochemical effects as well as effects on hearing. Exposure of male Long-Evans rats exposed nose-only to 1,000 mg/m^3 JP-8, which was mostly in the vapor phase (1–5% aerosol) (only concentration tested), for 4 hours did not result in auditory impairment as assessed by decreased hair cell function, as measured by distortion product otoacoustic emissions (DPOAE), or loss of outer hair cells (Fechter et al. 2007). A subsequent 4-hour

exposure to noise with a 105 dB_{lin} sound intensity in the octave band of 8 Hz resulted in a depression of DPOAE amplitude, which was greater than in rats exposed only to noise. A subsequent 4-hour exposure to 97 dB or 1-hour exposure to 102 dB noise (8 Hz) resulted in further decreases in DPOAE amplitude, as compared to noise-only or JP-8-only exposed rats (Fechter et al. 2007). A significant increase in the auditory threshold, as measured by recording compound action potentials (CAPs) from the round window, was observed in rats exposed to JP-8 once, followed by a 4-hour exposure to noise at 105 dB; no alterations in auditory threshold were observed in the rats repeatedly exposed to JP-8 and noise (Fechter et al. 2007). In a subsequent study, no alterations in DPOAE were observed in rats exposed to up to 1,000 mg/m^3 JP-8 vapor 4 hours/day for 5 days (Fechter et al. 2010). At 2,000 mg/m^3, an initial loss in DPOAE amplitude at test frequencies above those predicted to be affected from noise-only exposure was observed 4 days after exposure termination; however, 4 weeks post-exposure, the DPOAE amplitude was similar to controls. When the rats were exposed to noise with a 97–99 dB_A intensity in the 8-Hz octave range for 1 hour immediately after each JP-8 exposure, there were significant decreases in DPOAE amplitude in the 1,000 and 2,000 mg/m^3 groups. No alterations in pure tone auditory threshold were observed in the JP-8 or JP-8 plus noise groups.

Fechter et al. (2012) found similar results in rats exposed to JP-8 (mostly vapor) 6 hours/day, 5 days/week for 4 weeks. No significant alterations in DPOAE amplitude, pure tone auditory threshold, or the number of cochlear outer hair cells were observed in rats exposed only to up to 1,500 mg/m^3 JP-8. In rats simultaneously exposed to 1,500 mg/m^3 JP-8 and noise with a 85 dB intensity (a noise intensity that is considered non-damaging) and octave band centered on 8 Hz, there were marked decreases in DPOAE amplitude measured 10 days and 4 weeks post-exposure and increases in pure tone auditory threshold; no alterations were observed at the two lower JP-8 concentrations. A decrease in DPOAE amplitude was also observed in rats exposed to JP-8 and intermittent noise (102 dB intensity for 15 minutes/hour), as compared to controls; however, there was no difference when compared to rats only exposed to intermittent noise. Some losses of cochlear outer hair cells were observed in rats exposed to 1,500 mg/m^3 JP-8 and continuous or intermittent noise were observed; however, the total loss was <1%. In contrast to these findings, Guthrie et al. (2014, 2015) found significant central auditory processing dysfunction in rats exposed to 1,000 mg/m^3 JP-8 (mostly vapor) 6 hours/day, 5 days/week for 4 weeks. The dysfunction was manifested as impaired brainstem encoding of stimulus intensity and was observed in rats exposed to JP-8 and JP-8 with noise (85 dB intensity 6 hours/day, 5 days/week for 4 weeks). No alterations in peripheral auditory function or loss of hair cochlear outer cells were found.

A study that tested both JP-5 and JP-8 reported slightly different results for the two fuels (Rossi et al. 2001). Male Sprague-Dawley rats were exposed to 1,200 mg/m^3 JP-5 vapor or 1,000 mg/m^3 JP-8 vapor 6 hours/day, 5 days/week for 6 weeks. Neurobehavioral toxicity assessment battery tests were conducted 65 days post-exposure. At termination, levels of neurotransmitters and their metabolites were determined in serum and in five brain regions. In rats exposed to JP-5, significant alterations in performance on battery tests were limited to an increase in forelimb grip strength. The only significant alteration in serum neurotransmitter levels was an increase in 5-hydroxyindoleacetic acid, a serotonin metabolite. Significant decreases in dihydroxyphenylacetic acid (DOPAC, a major metabolite of dopamine) levels in the cortex, increases in dopamine levels in the hippocampus, and decreases in homovanillic acid in the hippocampus were also observed. In rats exposed to JP-8, a significant alteration in performance on the novel appetitive stimulus test (hypothesized to quantify dopamine system sensitization) was observed. Evaluation of serum neurotransmitter levels showed a significant decrease in the serotonin metabolite 5-hydroxyindoleacetic acid levels. DOPAC levels were significantly decreased in the cerebellum and brainstem. Using the same exposure protocol, the same group of investigators showed that exposure to 1,000 mg/m^3 JP-8 had no significant effect on the performance of simple operant tasks (Ritchie et al. 2001). Although no significant differences in performance on the more difficult tasks between the controls and exposed groups were observed, significant decreases in performance were observed between the low- and high-exposure groups in the two most difficult tasks. Levels of dopamine in the cerebral cortex and DOPAC levels in the brain were significantly higher in both exposure groups, as compared to controls.

Studies in male F-344 rats conducted at the University of Arizona (see Section 3.2.1 for a discussion of study limitations) also examined the neurotoxicity of aerosolized JP-8. Intermittent nose-only exposure to aerosolized JP-8 for 4 weeks did not affect learning and memory for spatial location in a swim task in rats, nor did it influence visual discrimination learning (Baldwin et al. 2001). However, increased central nervous system excitability was observed. Greater hyperlocomotive behavior and increased arousal levels were observed in functional observational battery tests and faster swim speeds during spatial testing in the Morris swim task were observed (Baldwin et al. 2001). According to the investigators, the effects on arousal levels and locomotor activity are consistent with stimulation of the mesolimbic dopaminergic system. Evaluation of levels of neurotransmitters and their metabolites in various brain areas showed a significant increase in DOPAC levels in the hippocampal region in exposed rats relative to controls, which was more pronounced as the duration of exposure increased. This suggested increase in dopamine release and metabolism (Baldwin et al. 2007).

Continuous exposure of rats, mice, or dogs to up to 750 mg/m^3 JP-5 vapor for 90 days (Gaworski et al. 1984) or intermittent exposure of rats or dogs to ≥100 mg/m^3 deodorized kerosene vapor 6 hours/day, 5 days/week for 13 weeks (Carpenter et al. 1975, 1976) did not induce gross or microscopic alterations in the brain or sciatic nerve.

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 3-1 and plotted in Figure 3-1.

3.2.1.5 Reproductive Effects

A study of 170 military and civilian women recruited from 10 U.S. Air Force bases found that women working in occupations involving fuel handling did not have significantly higher odds of menstrual disorders in adjusted analyses (Army 2001; Reutman et al. 2002). In the study, exposure was characterized by measuring aliphatic hydrocarbons (total C6–C16) and total benzene, toluene, ethylbenzene, and xylene in exhaled breath. However, the study did find a significant (p=0.007) reverse association between preovulatory luteinizing hormone (LH) and breath aliphatic hydrocarbons. The mechanism by which aliphatic hydrocarbons could lower LH is unknown, but the investigators suggested that LH levels could potentially be lowered by effects on the pituitary gland, hypothalamus, or extrahypothalamic central nervous system inputs. Although not clearly stated, the assumption appeared to be that exposure was mainly to JP-8, but exposure to other products such as a gasoline, diesel fuels, and the products of their complete and incomplete combustion was not totally ruled out.

Continuous exposure of rats, mice, or dogs to up to 750 mg/m^3 JP-5 vapors for 90 days did not induce gross or microscopic alterations in the reproductive organs (Gaworski et al. 1984). Similarly, no histological alterations were observed in reproductive organs of female rats exposed to up to 1,980 mg/m^3 Jet A vapor and aerosol 4 hours/day, 5 days/week for 14 days (Sweeney et al. 2013). No other reproductive end point was assessed in these studies.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to JP-5, JP-8, or Jet A fuels.

Information on the developmental toxicity of JP-5, JP-8, or Jet A fuels in laboratory animals is limited to a study conducted by the University of Arizona (Harris et al. 2007b). As noted previously (see

Section 3.2.1 for discussion of the University of Arizona studies), interpretation of these studies is limited by an underestimation of the exposure concentration and possible exposure to plasticizers. Nose-only exposure of pregnant C57Bl/6 mice to aerosolized JP-8 (1 hour/day on GDs 7–21 or 15–21) resulted in significant decreases in thymus and spleen weight, viable immune cells from these organs, and suppressed immune function at 6–8 weeks old, regardless of the duration of maternal exposure (Harris et al. 2007b). It appeared that male pups were more severely affected than female pups. Since mothers displaying the most severe effect gave birth to pups that were the most affected by JP-8 exposure, the investigators suggested that susceptibility to the effects of JP-8 might be, at least in part, genetically determined. Average litter size was also significantly reduced in the exposed groups.

3.2.1.7 Cancer

There are limited data on the carcinogenicity of JP-5, JP-8, and Jet A fuels. A few studies have examined cancer incidence and/or mortality among workers exposed to jet fuels; however, in all of the studies, the workers were exposed to a number of types of jet fuels including JP-4. A large study by D'Este et al. (2008) found significantly higher incidences of cancer diagnoses among the 873 aircraft maintenance workers examined than in two large (>7,500 people) comparisons groups. As noted by the investigators, these maintenance workers were exposed to a number of compounds in addition to the jet fuels including hexavalent chromium, carbon black, ethylbenzene, and petroleum solvents; additionally, the workers were exposed to JP-4 fuel. A historical prospective cohort study of >2,000 men in the Swedish Air Force with exposure to aircraft fuel did not find an association between jet fuel exposure and the lymphatic malignancies (Seldén and Ahlborg 1991). The workers in this study were exposed to several types of jet fuels including JP-4 and Jet A-1. A population-based, case-referent study using a cohort of 3,726 cancer patients, of whom 43 individuals were exposed to jet fuel and 234 individuals were exposed to kerosene found a significant association between jet fuel exposure and kidney cancer (odds ratio [OR] 3.1; 90% confidence interval [CI] 1.5–6.6). 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 follow-up of this study (Parent et al. 2000) examined the ORs between renal cell cancers and selected substances and found that of the 142 cases of renal cell cancer examined, 6 individuals were exposed to jet fuel and 4 were exposed to jet fuel engine emissions. The ORs (adjusted for age, smoking, and body mass index) were 3.9 (95% CI 1.6–9.8) and 2.7 (05% CI 0.9–8.1), respectively. Although a statistically significant

association between renal cell cancer and jet fuel exposure was found, the study does not prove causality and the type of jet fuel was not specified.

Several studies have also examined the carcinogenicity of kerosene in humans. 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. Zheng et al. (1992) examined the possible association between the use of kerosene stoves and exposure to "petroleum products," and oral or pharyngeal cancer. Significantly more male cancer 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. In a matched case-control study examining risk factors for two common types of brain tumors in children, astrocytic glioma and primitive neuroectodermal tumor (PNET), a significant association (OR 8.9; 95% CI 1.l–71.1) was found 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-nitroso compounds, and possibly pesticides.

No studies were located regarding carcinogenicity in laboratory animals following inhalation exposure to JP-5, JP-8, or Jet A fuels.

3.2.2 Oral Exposure

3.2.2.1 Death

No reports of deaths in humans due to ingestion of JP-5, JP-8, or Jet A fuels were located. Numerous case studies have described death following the accidental ingestion of kerosene, particularly by children (usually under the age of 5, but as old as 15 years). Kerosene ingestion is one of the most common forms of acute childhood poisoning in many developing countries. Kerosene is used for cooking, heating, and lighting and is typically stored in containers and places easily accessible to children. Deaths following ingestion of kerosene were usually attributed to lipoid 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), respiratory failure (Abu-Ekteish 2002), and pneumonitis (Balme et al. 2012; 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). Many other studies have reported deaths due to ingestion of kerosene without providing a specific cause of death (i.e., Chun 1998; Gupta et al. 1998; Lang et al. 2008; Simmank et al. 1998). Estimated ingested doses of kerosene associated with death are approximately 1,900 mg/kg based on the ingestion of 30 mL of kerosene by a 2-year-old child, and approximately 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 <5,300 mg/kg kerosene resulted in the death of a 10-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. 1991). 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).

A single oral dose of 22,400 mg/kg kerosene killed 4/5 adult rats, 10/15 5-week-old rats, and 15/15 10-day-old rats in 1–3 days, suggesting increased susceptibility in younger animals (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 after receiving a single dose of ≤29,944 mg/kg JP-5 (Parker et al. 1981). An LD_{50} of >48,000 mg/kg was noted in rats receiving a single oral dose by gavage 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. No deaths were observed in groups of male and female Fischer 344 rats administered a single gavage dose of 5,000 mg/kg JP-8 or JP-8+100 (Wolfe et al. 1996) or in male and female Sprague-Dawley rats administered a single gavage dose of 25,000 mg/kg Jet A fuel (Vernot et al. 1990b).

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. Gavage administration of 6,400 mg/kg/day kerosene for 7–10 days was lethal to four of five 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.

Lethal dose in rats from the Parker et al. (1981) study and for rats, rabbits and guinea pigs from the Deichmann et al. (1994) study are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

No studies were located regarding ocular or metabolic effects in humans or laboratory animals after oral exposure to JP-5, JP-8, or Jet A fuels. The highest NOAEL and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Respiratory Effects. No studies were located regarding respiratory effects in humans following oral exposure to JP-5, JP-8, or Jet A fuels.

A number of studies have reported respiratory effects in humans ingesting kerosene. Even if kerosene is initially ingested, the respiratory toxicity is usually attributable to the aspiration of kerosene into the lungs during vomiting (Coruh and Inal 1966; Majeed et al. 1981; Nomi and Al-Rahim 1970). Based on reports 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 (Abu-Ekteish 2002; Akamaguna and Odita 1983; Aldy et al. 1978; Annobil 1983; Annobil and Ogunbiyi 1991; Balme et al. 2012; Benois et al. 2009; Chun 1998; Lang et al. 2008; Lucas 1994; Mahdi 1988; Santhanakrishnan and Chithra 1978; Shotar 2005; Simmank et al. 1998; St. John 1982). Pneumonitis, pulmonary edema, and/or pneumonia were reported for children and adults who had ingested kerosene (Subcommittee on Accidental Poisoning 1962). A follow-up study

Table 3-2 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (G)				47280 M (2/6 rats died during the study)	Parker et al. 1981 JP-5	
Systemic								
2	Rat (Sprague-Dawley)	10 d Gd 6-15 1 x/d (G)	Bd Wt	500 F		1000 F (31% reduced weight gain on Gd 5-20)	Cooper and Mattie 1996 JP-8	
3	Rat (Sprague-Dawley)	once (G)	Hemato		18912 M (2-3-fold increase in white cell count)		Parker et al. 1981 JP-5	
			Hepatic		18912 M (hepatocyte vacuolization)			
			Bd Wt		18912 M (10-16% weight loss)			
			Metab	18912 M				
4	Rat (Sprague-Dawley)	once (G)	Hepatic	37824 M	47280 M (cytoplasmic vacuolization of hepatocytes)		Parker et al. 1981 JP-5	Observed renal effects are not relevant to humans
			Renal	37824 M	47280 M (hyaline droplets in tubular epithelial cells)			
			Dermal		18912 M (ventral alopecia)			
5	Rat (Fischer- 344)	once (G)	Bd Wt	5000			Wolfe et al. 1996 JP-8	

Table 3-2 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
6	Rat (Fischer- 344)	once (G)	Bd Wt	5000			Wolfe et al. 1996 JP-8+100	
7	Mouse (B6C3F1)	7 d 1 x/d (GO)	Hepatic		1000 F (increased relative liver weight)		Dudley et al. 2001 JP-8	
8	Mouse (B6C3F1)	14 d 1 x/d (GO)	Hemato	2500 F			Keil et al. 2004 JP-8	No histological examination.
			Hepatic	750 F	1000 F (increased relative liver weight)			
			Renal	2500 F				
			Bd Wt	2500 F				
9	Mouse (B6C3F1)	14 d 1 x/d (GO)	Hemato	1000 F			Peden-Adams et al. 2001 JP-8	No histological examination.
			Hepatic	500 F	1000 F (significantly increased relative liver weight)			
			Renal	1000 F				
			Bd Wt	1000 F				
Immuno/ Lymphoret								
10	Mouse (B6C3F1)	7 d 1 x/d (GO)			1000 F (suppressed humoral immunity)		Dudley et al. 2001 JP-8	Similar effects seen in AhR-nonresponsive mice.

Table 3-2 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
11	Mouse (B6C3F1)	14 d 1 x/d (GO)		250[b] F	500 F (decreased humoral immunity)		Keil et al. 2004 JP-8	
12	Mouse (B6C3F1)	14 d 1 x/d (GO)			500 F (suppressed plaque-forming cell response)		Peden-Adams et al. 2001 JP-8	
Developmental								
13	Rat (Sprague-Dawley)	10 d Gd 6-15 1 x/d (G)		500	1000 (4-6% decreased fetal weight)		Cooper and Mattie 1996 JP-8	Maternal weight was decreased 31%.
14	Mouse (C57BL/6N)	Gd 6-15 1 x/d (GO)			1000 (decrease IgM PFC response to SRBC in offspring)		Keil et al. 2003 JP-8	

Table 3-2 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE								
Systemic								
15	Rat (Sprague-Dawley)	90 d 1 x/d (GO)	Resp	3000 M			Mattie et al. 1995 JP-8	Observed renal effects are not relevant to humans
			Cardio	3000 M				
			Gastro		750 M (stomach hyperplasia)			
			Hemato		750 M (decreased lymphocytes; increased neutrophils)			
			Musc/skel	3000 M				
			Hepatic		750 M (about 2-fold increase in ALT and AST activities)			
			Renal		750 M (hyaline droplet formation)			
			Endocr	3000 M				
			Dermal		750 M (perianal dermatitis)			
			Bd Wt	750 M	1500 M (15% reduction in final body weight)	3000 M (34% reduced final body weight)		
			Metab		750 M (hypoglycemia)			

Table 3-2 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
16	Rat (Sprague-Dawley)	21 wk 1 x/d (G)	Gastro	325 F	750 F (stomach hyperplasia)		Mattie et al. 2000 JP-8	
			Hemato	1500 F				
			Dermal	750 F	1500 F (perianal dermatitis)			
			Bd Wt	750 F	1500 F (10-20% reduced body weight)			
			Metab	1500 F				
17	Rat (Sprague-Dawley)	90 d 1 x/d (G)	Bd Wt	750 M	1500 M (15% reduction in final body weight)	3000 M (significant body weight loss)	Mattie et al. 2000 JP-8	
18	Rat (Sprague-Dawley)	90 d (GO)	Resp	500 F			Smith et al. 1999 Jet A	
			Cardio	500 F				
			Gastro	20 F	100 F (increased salivation and shoveling behavior which may be indicative of mouth irritation)			
			Hemato	500 F				
			Hepatic	100 F	500 F (increased liver weight and enlarged livers)			
			Renal	500 F				
			Endocr	500 F				
			Bd Wt	500 F				

Table 3-2 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
19	Mouse (C57BL/6N)	90 d (GO)	Resp	500 M			Smith et al. 1999 Jet A	
			Cardio	500 M				
			Gastro	500 M				
			Hemato	500 M				
			Renal	500 M				
			Endocr	500 M				
			Bd Wt	500 M				
Immuno/ Lymphoret								
20	Rat (Sprague-Dawley)	90 d 1 x/d (GO)		3000 M			Mattie et al. 1995 JP-8	NOAEL is for histology of lymphoreticular organs.
Neurological								
21	Rat (Sprague-Dawley)	90 d 1 x/d (GO)		3000 M			Mattie et al. 1995 JP-8	NOAEL is for histology of the brain and sciatic nerve.
22	Rat (Sprague-Dawley)	90 d (GO)		100 F	500 F (lethargy)		Smith et al. 1999 Jet A	
23	Mouse (C57BL/6N)	90 d (GO)		20 M	100 M (lethargy and hunched posture)		Smith et al. 1999 Jet A	
Reproductive								
24	Rat (Sprague-Dawley)	90 d 1 x/d (GO)		3000 M			Mattie et al. 1995 JP-8	NOAEL is for histology of the testes.

Table 3-2 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
25	Rat (Sprague-Dawley)	21 wk 1 x/d (G)		1500 F			Mattie et al. 2000 JP-8	NOAEL is for female fertility.
26	Rat (Sprague-Dawley)	90 d 1 x/d (G)		3000 M			Mattie et al. 2000 JP-8	NOAEL is for male fertility and sperm parameters.
Developmental								
27	Rat (Sprague-Dawley)	21 wk 1 x/d (G)		750	1500 (11% decrease pup's weight on PND 4)		Mattie et al. 2000 JP-8	
28	Rat (Sprague-Dawley)	21 wk 1 x/d (G)			325[c] (decreased scores in a swimming test)		Mattie et al. 2001 JP-8	

a The number corresponds to entries in Figure 3-2.

b Used to derive an acute-duration MRL of 3 mg/kg/day for JP-8. The NOAEL was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

c Used to derive an intermediate-duration MRL of 0.3 mg/kg/day for JP-8. The LOAEL was divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

ALT = alanine aminotransferase; AST = asparate aminotransferase; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GO) = gavage in oil; Hemato = hematological; IgM = immunoglobulin M; Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolism; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; PFC = plaque forming cells; PND = post-natal day; Resp = respiratory; SRBC = sheep red blood cell; x = time(s); wk = week(s)

Figure 3-2 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Oral

Acute (≤14 days)

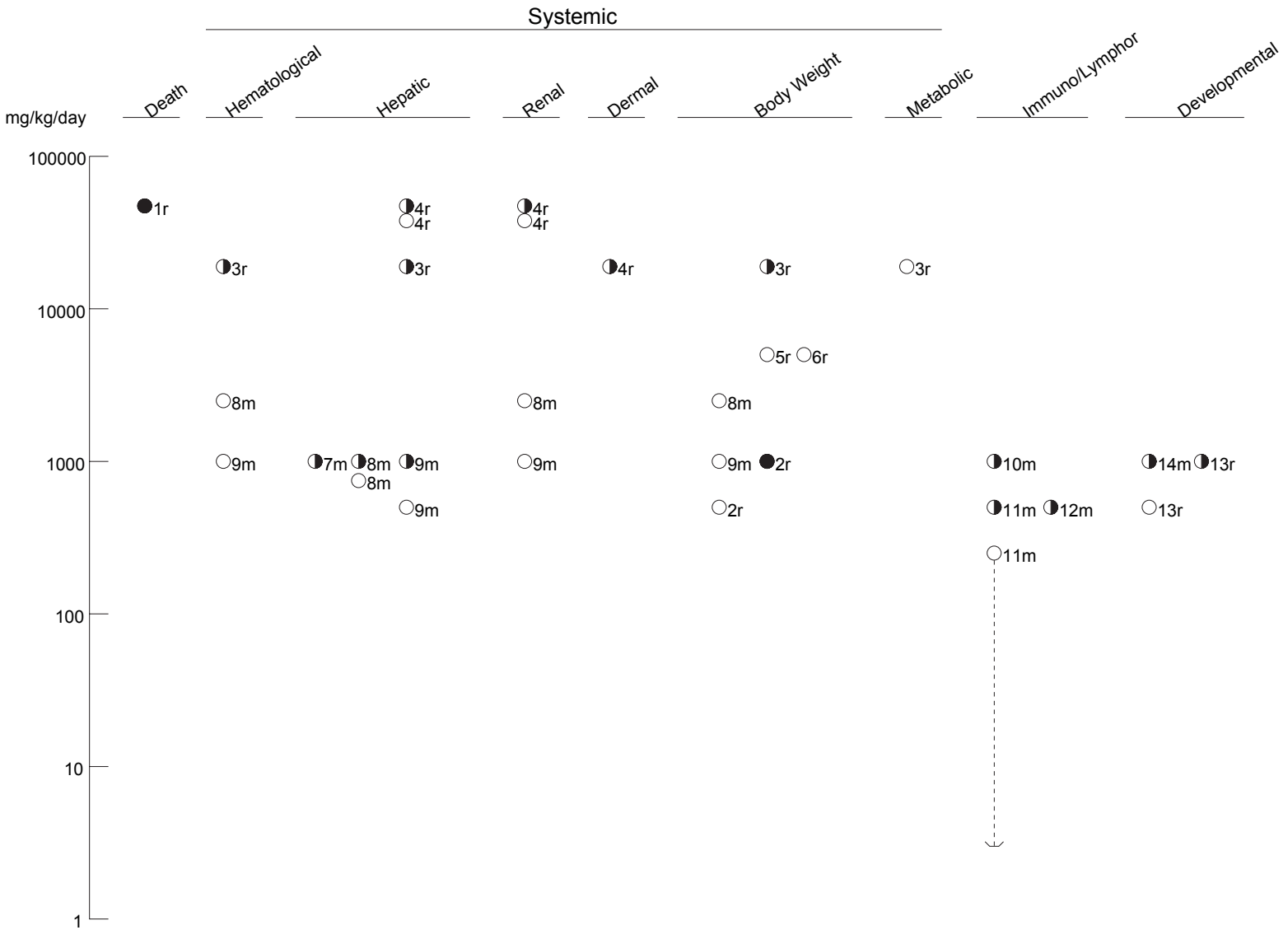


Figure 3-2 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Oral *(Continued)*

Intermediate (15-364 days)

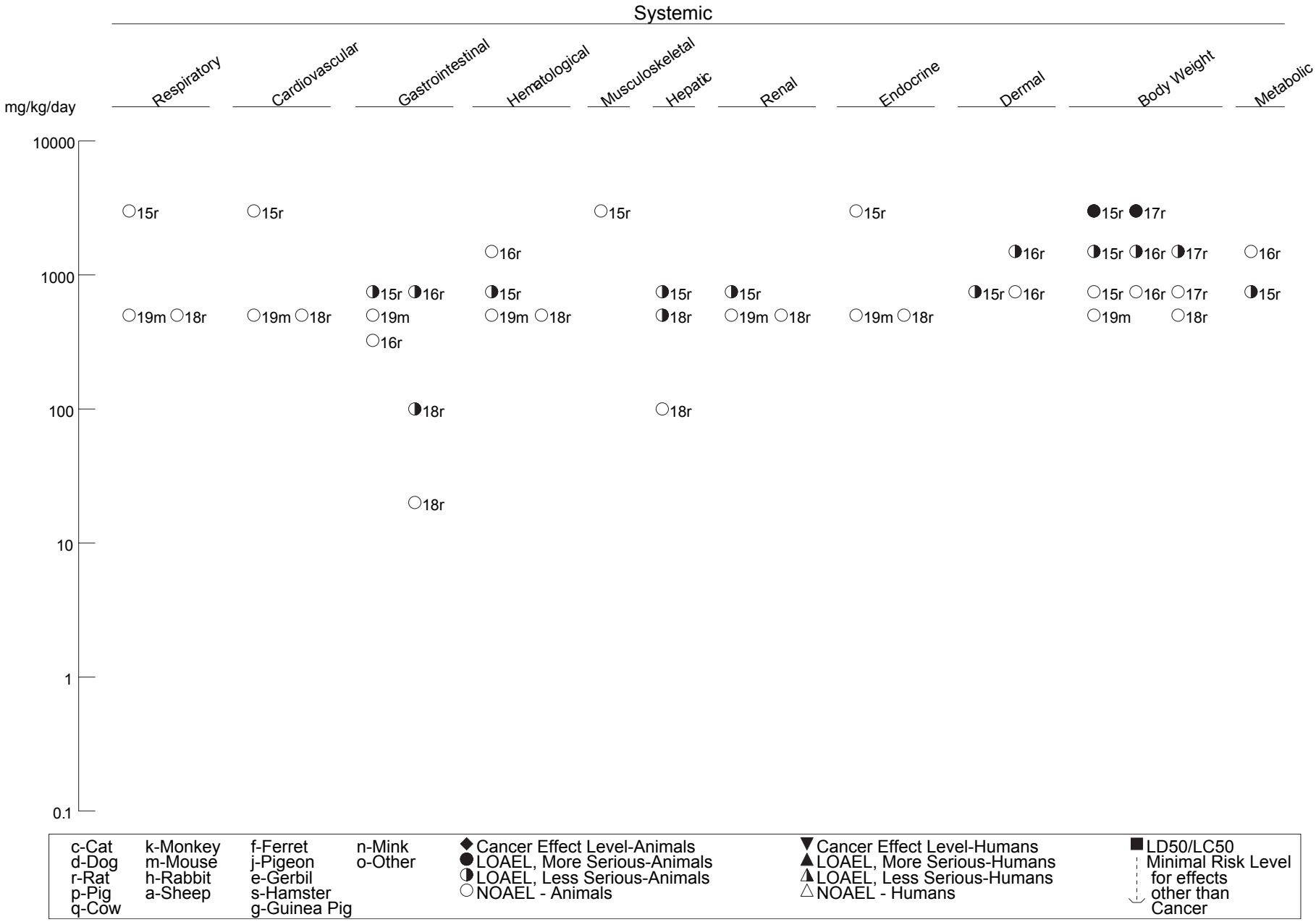
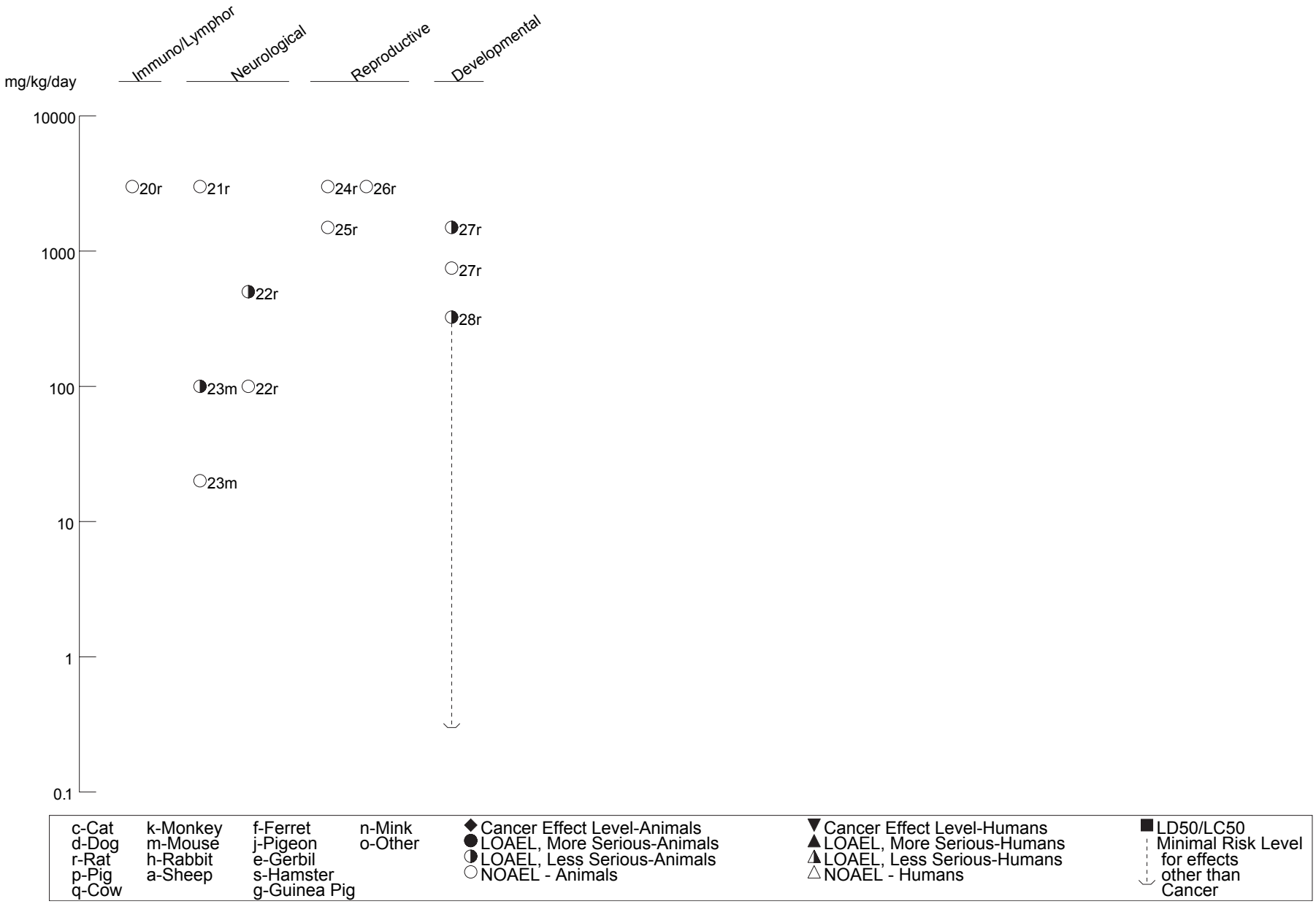


Figure 3-2 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Oral *(Continued)*

Intermediate (15-364 days)



conducted on children who had been diagnosed with pneumonitis due to kerosene ingestion 10 years earlier and who had abnormal chest radiographs at the time of diagnosis 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 (Tal et al. 1984). Simmank et al. (1998) conducted a similar, although much shorter, follow-up on a group of 57 children with clinical signs of pneumonitis. The exposed children and 41 controls were evaluated every 2 weeks for 3 months after the accident. The results showed that kerosene ingestion was not associated with increased respiratory morbidity in the 3 months following the accident, regardless of the child's nutritional status or the severity of the initial kerosene pneumonitis.

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. 1991; 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 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, in two study populations, as many as 56% of the cases studied were asymptomatic (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 respiratory signs or symptoms of toxicity are seen following ingestion.

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) or in a study in which female Sprague-Dawley rats or male C57BL/6 mice were administered via gavage up to 500 mg/kg/day Jet A fuel in corn oil for 90 days (Smith et al. 1999).

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 (Nouri 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.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following oral exposure to JP-5, JP-8, or Jet A fuels. 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).

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) or female Sprague-Dawley rats and male C57BL/6 mice were administered up to 500 mg/kg/day Jet A fuel for 90 days (Smith et al. 1999). Decreases in heart rate and mean arterial blood pressure occurred in dogs following aspiration of 0.5 mL/kg kerosene, but 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.

Gastrointestinal Effects. No information was located regarding gastrointestinal effects in humans following oral exposure to JP-5, JP-8, or Jet A fuels. The most commonly reported gastrointestinal effect in children following acute ingestion of kerosene is vomiting (Akamaguna and Odita 1983; Aldy et al. 1978; Benois et al. 2009; Chun 1998; Lucas 1994; Mahdi 1988; Majeed et al. 1981; Nouri and Al-Rahim 1970; Saksena 1969; Shotar 2005; St. John 1982), including bloody vomit (Nomi 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). Reliable doses are not available in these reports.

Stomach irritation and hyperplasia were observed in male Sprague-Dawley rats treated with ≥750 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. Gastritis may have resulted from contact irritation of the JP-8, since it was administered to the animals without a vehicle. A NOAEL for these effects was not established in the study. Squamous hyperplasia in the stomach was also reported in female Sprague-Dawley rats administered 750 mg/kg JP8-8 fuel daily by gavage for 21 weeks (Mattie et al. 2000); the NOAEL was 325 mg/kg/day.

Increased salivation was observed in female Sprague-Dawley rats administered via gavage 100 or 500 mg/kg/day Jet A fuel in corn oil for 90 days; shoveling behavior was also observed at these dose levels (Smith et al. 1999). Neither effect was observed in rats administered 20 mg/kg/day. The investigators suggested that the salivation and shoveling behavior were consistent with an irritation response in the mouth. These signs of irritation were not observed in similarly exposed male C57BL/6 mice (Smith et al. 1999).

Hematological Effects. No information was located regarding hematological effects in humans following oral exposure to JP-5, JP-8, or Jet A fuels. Several case studies reported hematological effects in children following acute ingestion of kerosene. The increased incidence of leukocytosis ranged from 8.6% to 80% of the respective study populations (Abu-Ekteisch 2002; Chun 1998; 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 or provide reliable dosing information.

Administration of a single gavage dose of 18,912 mg/kg (only dose tested) petroleum-derived JP-5 fuel to male Sprague-Dawley rats resulted in a statistically significant reduction in the hematocrit 48 hours after dosing, although it was still within normal limits (Parker et al. 1981). Red blood cell count was also significantly reduced in rats killed 24 hours after dosing, but still was within normal limits. White cell count was significantly increased (2–3-fold) in rats sacrificed 24 and 48 hours after dosing relative to controls. There were no significant alterations in other hematological parameters. Administration of up to 1,000 mg/kg/day of JP-8 to female B6C3F1 mice by gavage in olive oil for 14 days did not significantly alter erythrocyte or leukocyte number (total and differential counts), hemoglobin, or hematocrit (Peden-Adams et al. 2001). In a similar study, treatment of female B6C3F1 mice with doses between 250 and 2,500 mg/kg/day JP-8 fuel by gavage for 14 days reduced mean hemoglobin levels, hematocrit levels, and red blood cell counts and increased mean corpuscular volume at 2,500 mg/kg/day; mean corpuscular volume was also increased at 1,500 and 2,000 mg/kg/day (Keil et al. 2004). Considering that the mean values differed ≤7% from control values and that each dose group consisted of only 4–6 mice, these hematological changes are probably of little or no toxicological significance.

In male Sprague-Dawley rats administered neat JP-8 by gavage for 90 days, there were no significant changes in red blood cell count at doses as high as 3,000 mg/kg/day, but there was a significant increase in neutrophils and a significant decrease in lymphocytes at ≥750 mg/kg/day, as compared to controls (Mattie et al. 1995). The increase in neutrophils could have been a response to the renal nephropathy observed in this study, but the cause of the decrease in lymphocytes was unclear and may be related to the body weight effects. Platelets were increased at 3,000 mg/kg/day compared to controls. In contrast, administration of up to 1,500 mg/kg/day to female Sprague-Dawley rats by gavage for 21 weeks (90 days followed by cohabitation, gestation, delivery, and lactation) did not significantly alter a comprehensive number of hematological parameters, including those examined in the male study (Mattie et al. 2000).

Significant decreases in red blood cell levels were observed in female Sprague-Dawley rat administered via gavage Jet A fuel in corn oil for 90 days (Smith et al. 1999). Decreases in hemoglobin and hematocrit levels were also observed at 100 and 500 mg/kg/day. Although the hematological alterations are considered to be treatment-related, the magnitudes of the changes were minimal and were not considered biologically relevant. No treatment-related alterations in hematological parameters were observed in similarly exposed male C57BL/6 mice (Smith et al. 1999).

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

No histological alterations were observed in skeletal muscle or bone of male Sprague-Dawley rats treated with up to 3,000 mg/kg neat JP-8 for 90 days (Mattie et al. 1995) or female Sprague-Dawley rats and male C57BL/6 mice treated with up to 500 mg/kg/day Jet A fuel in corn oil for 90 days (Smith et al. 1999).

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

Administration of a single gavage dose of 18,912 mg/kg JP-5 fuel (only dose tested) to male Sprague-Dawley rats resulted in increases in serum lactate dehydrogenase, AST, and ALT within 3 days after dosing (Parker et al. 1981). Microscopic examination of the liver showed vacuolization of periportal hepatocytes in rats killed on day 2. Liver lesions were also described in male Sprague-Dawley rats 14 days after receiving single doses of JP-5 ranging from 18,912 to 47,280 mg/kg (Parker et al. 1981).

However, it is not clear at what dose level the lesions appeared; therefore, this effect is not listed in Table 3-2. Rats receiving a single dose of 24 mL JP-5/kg by gavage (approximately 19.2 mg/kg) exhibited a transient increase in serum levels of ALT and AST (Bogo et al. 1983; Mehm and Feser 1984). It was noted that the elevated levels of ALT and AST 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).

Three acute studies in B6C3F1 mice reported significant increases in relative liver weight (23–29%) following gavage administration of 1,000 mg/kg/day JP-8 fuel for 7–14 days (Dudley et al. 2001; Keil et al. 2004; Peden-Adams et al. 2001). However, none of these studies conducted tests for liver function or examined the liver microscopically.

Male Sprague-Dawley rats that received 750, 1,500, or 3,000 mg/kg neat JP-8 by gavage once a day for 90 days had significant increases in serum ALT and AST activities in all treated groups (about 2-fold, but not dose-related), decreased triglycerides in high-dose rats, and increased total bilirubin in all treated groups (Mattie et al. 1995). Microscopic examination of the liver did not show treatment-related alterations.

Significant increases in absolute and relative liver weight were observed in female Sprague-Dawley rats administered via gavage 500 mg/kg/day Jet A fuel in corn oil for 90 days (Smith et al. 1999); enlarged livers were also observed during the gross necropsy examination in the 500 mg/kg/day group. No alterations in liver weight or appearance were observed at 100 mg/kg/day, and no histological alterations were observed at 500 mg/kg/day. No hepatic effects were observed in similarly exposed male C57BL/6 mice exposed to up to 500 mg/kg/day for 90 days (Smith et al. 1999).

Renal Effects. No information was located regarding renal effects in humans following oral exposure to JP-5, JP-8, Jet A fuels. 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); the studies did not provide reliable information on the amount of kerosene ingested.

Acute- and intermediate-duration studies that tested male rats described the formation of hyaline droplets in the cytoplasm of epithelial cells in the proximal tubules in the kidneys. Parker et al. (1981) observed

this in male rats after a single dose of 18,912 mg/kg JP-5 fuel (only dose level tested). Similar observations were made in male rats administered single doses ≥19,200 mg/kg JP-5 fuel (Bogo et al. 1983) and a 90-day study in rats administered doses ≥750 mg/kg/day JP-8 fuel (Mattie et al. 1995). As indicated in Section 3.2.1.2 (renal effects by inhalation exposure), the nephropathy characterized by the buildup of alpha$_{2u}$-globulin-containing hyaline droplets is unique to mature male rats and has no toxicological relevance for humans. A significant increase in relative kidney weight was observed in female Sprague-Dawley rats following gavage administration of 500 mg/kg/day Jet A fuel for 90 days; no histological alterations were observed (Smith et al. 1999).

Relative kidney weight was not significantly affected in female B6C3F1 mice dosed by gavage with up to 2,500 mg/kg JP-8 fuel for 14 consecutive days; no other renal end points were assessed (Keil et al. 2004; Peden-Adams et al. 2001). No alterations in kidney weight or morphology were observed in male C57BL/6 mice administered via gavage 500 mg/kg/day Jet A fuel in corn oil for 90 days (Smith et al. 1999).

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

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 for 90 days (Mattie et al. 1995) or in female Sprague-Dawley rats and male C57BL/6 mice administered up to 500 mg/kg/day Jet A fuel for 90 days.

Dermal Effects. No studies were located regarding dermal effects in humans following oral exposure to JP-5, JP-8, or Jet A fuels.

Ventral alopecia was consistently seen in Sprague-Dawley rats following gavage administration of single doses ≥19,200 mg/kg JP-5 and observed for 14 days (Parker et al. 1981). Perianal dermatitis was reported in male Sprague-Dawley rats dosed daily by gavage with ≥750, 1,500, or 3,000 mg/kg neat JP-8 (Mattie et al. 1995). The incidence of the lesion was similar in all the treated groups. The same type of lesion was reported in female Sprague-Dawley rats dosed with 1,500 mg/kg/day JP-8 fuel for 21 weeks, but not in rats dosed with 750 mg/kg/day (Mattie et al. 2000).

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

Several studies provide information regarding body weight in laboratory animals exposed to jet fuels, but data on food consumption were generally not available. A single dose of 18,912 mg/kg JP-5 induced weight losses of 10–16% in Sprague-Dawley rats within 3 days of dosing (Parker et al. 1981). Single doses of up to 5,000 mg/kg JP-8 or JP-8+100 did not significantly affect body weight of male or female F-344 rats during a 14-day observation period (Wolfe et al. 1996). However, treatment of pregnant rats with 1,000 mg/kg JP-8 fuel on GDs 6–15 reduced body weight gain by 31% during GDs 5–20; the NOAEL was 500 mg/kg/day (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. In 14-day gavage studies in female B6C3F1 mice, a dose of up to 2,500 mg/kg/day JP-8 (highest dose tested) did not significantly affect body weight (Keil et al. 2004; Peden-Adams et al. 2001).

In intermediate-duration gavage studies with JP-8 in male and female Sprague-Dawley rats, the NOAEL for body weight effects was 500 mg/kg/day (Mattie et al. 1995, 2000). In these studies, doses of 1,500 mg/kg/day JP-8 reduced final body weight 10–20% relative to controls. No alterations in body weight gain were observed in female Sprague-Dawley rats or male C57BL/6 mice receiving gavage doses of 500 mg/kg/day Jet A fuel in corn oil for 90 days (Smith et al. 1999).

Metabolic Effects. No studies were located regarding metabolic effects in humans following oral exposure to JP-5, JP-8, or Jet A fuels.

In an acute study of male Sprague-Dawley rats, a single dose of 18,912 mg/kg JP-5 did not significantly affect serum levels of sodium or potassium (Parker et al. 1981). In a 90-day gavage study of male Sprague-Dawley rats administered 750, 1,500, or 3,000 mg/kg/day JP-8, significant metabolic alterations included increased serum sodium (2.8%) and chlorine (4.8%) in high-dose rats and decreased glucose in all treated groups (26% in low-dose rats) (Mattie et al. 1995). However, administration of up to 1,500 mg/kg/day neat JP-8 (highest dose tested) by gavage to female Sprague-Dawley rats for 90 days before mating and continuing through gestation and lactation did not induce significant alterations in serum levels of glucose or electrolytes (Mattie et al. 2000).

Other Effects. Fever was commonly reported in children following ingestion of kerosene (Abu-Ekteisch 2002; Akamaguna and Odita 1983; Aldy et al. 1978; Benois et al. 2009; Chun 1998; Dudin et al.

1991; Lang et al. 2008; Lucas 1994; Mahdi 1988; Majeed et al. 1981; Nouri and Al-Rahim 1970; Saksena 1969; Shotar 2005; Simmank et al. 1998; St. John 1982).

3.2.2.3 Immunological and Lymphoreticular Effects

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

Three acute-duration studies of female B6C3F1 mice provide information regarding immune competence following gavage exposure to JP-8 fuel. Peden-Adams et al. (2001) administered 0, 500, or 1,000 mg/kg/day JP-8 by gavage in olive oil to the mice for 14 days before immunosuppression was assessed. End points examined included spleen and thymus weight and organ cellularity, NK cell activity, cytotoxic T-cell activity, mitogen-induced lymphocyte proliferation, nitrogen production by peritoneal macrophages, plaque-forming cell response to SRBCs, delayed type hypersensitivity, and susceptibility to tumor B16F10 or *Listeria monocytogenes* challenges. Of all of the end points measured, only the plaque-forming cell response was significantly reduced at both JP-8 dose levels; the decrease was dose-related. Dudley et al. (2001) tested the hypothesis that JP-8 may exert immunosuppression by acting through the aryl hydrocarbon receptor (AhR). Tests conducted in the wild B6C3F1 strain of mice and the Ah-nonresponsive DBA/2 mouse strain showed that both strains were equally sensitive to JP-8's toxicity. In both mouse strains, administration via gavage of 2,000 mg/kg/day JP-8 for 7 days resulted in decreases in thymus weight and cellularity; administration of 1,000 or 2,000 mg/kg/day resulted in decreases in plaque-forming cell response to SRBCs. JP-8 did not induce CYP1A1 or promote down-regulation of the AhR, suggesting that JP-8 may exert immunotoxicity via an AhR-independent mechanism. In the third study, administration of JP-8 resulted in decreases in thymic cellularity at ≥2,000 mg/kg/day and decreases in thymic CD8+, CD4+, and CD4+/CD8+ T-cell subpopulations at 2,000 mg/kg/day; no changes in the CD4/CD8 ratios or the relative percentages of T-cell subpopulations were observed (Keil et al. 2004). In the spleen, cellularity and absolute values of T-cell phenotypes were not affected; an increase in the percentage of CD4+ cells was observed at 1,000 and 2,000 mg/kg/day. In the bone marrow, there was a 47% increase in colony-forming units at 2,000 mg/kg/day, but no alteration in total bone marrow cellularity. Alterations in immune function were also observed; suppression of the antibody plaque-forming cell response to SRBCs was observed at ≥500 mg/kg/day. However, serum levels of anti-SRBC IgM were not altered when measured by either the enzyme-linked immunosorbent assay (ELISA) or hemagglutination (Keil et al. 2004). The NOAEL for immunological effects in the study was 250 mg/kg/day.

Gavage administration of up to 3,000 mg/kg of neat JP-8 to Sprague-Dawley rats once/day for 90 days did not cause histopathological changes in the spleen, thymus, or lymph nodes (Mattie et al. 1995).

3.2.2.4 Neurological Effects

No information was located regarding neurological effects in humans following ingestion of JP-5, JP-8, or Jet A fuels.

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 (Abu-Ekteisch 2002; Akamaguna and Odita 1983; Aldy et al. 1978; Benois et al. 2009; Chun 1998; Coruh and Inal 1966; Dudin et al. 1991; Lang et al. 2008; Lucas 1994; Mahdi 1988; Majeed et al. 1981; Nouri and Al-Rahim 1970; Saksena 1969; Santhanakrishnan and Chithra 1978; Shotar 2005; 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. 1981; Nouri and Al-Rahim 1970; Saksena 1969; Santhanakrishnan and Chithra 1978). Of 78 children (aged 11–48 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; 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 126–1,754 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; Shotar 2005).

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 up to 3,000 mg/kg neat JP-8 by gavage for 90 days (Mattie et al. 1995). This NOAEL is recorded in Table 3-2 and plotted in Figure 3-2.

Lethargy was observed in approximately 50% of the female Sprague-Dawley rats receiving gavage doses of 500 mg/kg/day Jet A fuel in corn oil for 90 days, but was not observed at the lower doses (20 and 100 mg/kg/day). It was observed on exposure days 5–7 and there were nine incidences among the seven affected rats. Lethargy was also observed in 33, 80, and 100% of male C57BL/6 mice administered 20, 100, or 500 mg/kg/day Jet A fuel for 90 days (Smith et al. 1999). In the 15 mice exposed to 20 mg/kg/day, lethargy was observed in 5 mice, and only on exposure day 23 (5 incidences among the 5 mice affected). At 100 mg/kg/day, lethargy was observed on days 21–43 and there were 44 incidences. At 500 mg/kg/day, there were 417 incidences of lethargy among the 15 mice and they occurred on days 6–62. Hunched posture was also observed in 80, 80, and 100% of the mice in the 20, 100 and 500 mg/kg/day groups; as compared to 27% in the controls.

3.2.2.5 Reproductive Effects

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

Very limited information was located regarding reproductive effects in laboratory animals. Gavage administration of up to 3,000 neat JP-8 to male Sprague-Dawley rats for 90 days did not induce histological alterations in the testes (Mattie et al. 1995). The same group of investigators also reported that administration of up to 3,000 mg/kg/day neat JP-8 by gavage to male Sprague-Dawley rats for 70 days before mating with untreated females had no significant effect on fertility or sperm parameters measured in epididymal sperm samples (sperm concentration, motile sperm concentration, percent motility, velocity, linearity, maximum amplitude of lateral head displacement [ALH], mean ALH, and beat/cross frequency) (Mattie et al. 2000).

Administration of up to 1,500 mg/kg/day neat JP-8 by gavage to female Sprague-Dawley rats for 90-day before mating and continuing throughout gestation did not significantly affect pregnancy rate, gestation length, or litter size (Mattie et al. 2000).

NOAELs for reproductive effects from the Mattie et al. (1995, 2000) studies are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

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

In a gestational exposure study, pregnant Sprague-Dawley rats were treated by gavage with 0, 500, 1,000, 1,500, or 2,000 mg/kg JP-8 during GDs 6–15 and were sacrificed on GD 20 (Cooper and Mattie 1996). Maternal weight gain on GDs 5–20 was significantly reduced in all treated groups (31% at 1,000 mg/kg/day). Maternal deaths occurred during the study in groups dosed with ≥1,000 mg/kg/day, and the cause was found to be related to the presence of JP-8 in the lungs. Fetal weight was significantly reduced in a dose-related manner (about 4–6% at 1,000 mg/kg/day). There were no significant alterations in other developmental parameters examined, including incidences of fetal malformations and variations. The developmental NOAEL was 500 mg/kg/day and the LOAEL was 1,000 mg/kg/day.

Developmental effects were also examined in a study in which female Sprague-Dawley rats were administered 325, 750, and 1,500 mg/kg/day JP-8 for 90 days before mating and continuing throughout gestation and lactation (Mattie et al. 2000). There were no significant effects on pregnancy rate, gestation length, litter size, or percent live pups. However, pup weights were significantly lower in the high-dose group on PNDs 4 and 14 (11 and 10%, respectively). Neurodevelopmental testing of these pups showed a significant alteration in the total score for the swimming development test at ≥325 mg/kg/day on PND 8 and ≥750 mg/kg/day on PND 14; however, no significant alterations in total score were observed on PNDs 10, 12, 16, 18, or 20 (Mattie et al. 2001). The alterations in the total scores were primarily due to swimming direction scores; significant decreases in direction scores were observed on PND 6 (≥750 mg/kg/day), PND 8 (≥325 mg/kg/day), and PND 14 (≥750 mg/kg/day); no alterations in angle of head or limb usage scores were observed at any time point. No significant alterations in surface righting (tested on PND 4), negative geotaxis (tested on PND 5), or water maze performance (tested on PNDs 70 and 77) were observed. The investigators suggested that the results in the swimming development test were indicative of a possible developmental delay in motor coordination; however, the delay did not affect motor ability at later ages. The developmental LOAEL was 325 mg/kg/day for alterations in swimming behavior; a developmental NOAEL was not defined.

Keil et al. (2003) studied immune parameters, host resistance, body and organ weights (spleen, thymus, and liver), hematology parameters, and thyroid hormones in C57BL/6 mice offspring from dams administered 0, 1,000, or 2,000 mg/kg JP-8 fuel by gavage in olive oil on GDs 6–15. Evaluations were conducted at 3 and 8 weeks of age. Exposure to JP-8 fuel resulted in a significant decrease in thymic cellularity and an increase in spleen weight at 8 weeks of age. Hematological parameters were not significantly affected by gestational exposure to JP-8. There were no dose-related alterations in thymic or splenic lymphocytic subpopulations at weaning or in adult offspring. A significant decrease in B-cell lymphocyte proliferation was reported in high-dose offspring at weaning; T-lymphocyte proliferation was not affected at weaning or in adult offspring. Exposure to JP-8 did not induce compound-related alterations in macrophage parameters. Significant dose-related decreases in the IgM plaque-forming cell response to SRBCs occurred in adult offspring from both dose groups (46 and 81% decreases with the respective dosages). Exposure to JP-8 did not significantly affect bone marrow cellularity, stem cell proliferation, or splenic NK cell function. Adult offspring exposed to JP-8 showed no significant change in susceptibility to infection with *L. monocytogenes*, but susceptibility to B16F10 tumor challenge was decreased in both dose groups. Finally, serum T4 levels were significantly reduced (38%) in high-dose adult offspring.

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

3.2.2.7 Cancer

No studies were located regarding cancer in humans or laboratory animals after oral exposure to JP-5, JP-8, or Jet A fuels. However, a single study provided information regarding cancer from exposure to kerosene in animals. Male and female Sprague-Dawley rats (50/sex/group) were exposed to 0, 500, or 800 mg/kg kerosene by gavage in olive oil 4 days/week for 104 weeks (Maltoni et al. 1997). The study was terminated after 123 weeks, at which time survivors underwent complete necropsy and all major organs and tissues were prepared for microscopic examination. It should be noted that no statistical analyses of the results were performed. It appeared that the percent of animals bearing malignant tumors may have been increased in the high-dose group; a Fisher Exact test conducted by ATSDR showed that the increase in malignant tumors in the high-dose group was not statistically significant (p=0.0623). Exposure to kerosene did not seem to increase the percent of females bearing mammary cancers (6, 6, and 10% in the control, low-, and high-dose groups, respectively). In addition, kerosene did not seem to increase the percent of animals bearing various head cancers (Zymbal gland, ear duct, nasal cavity, oral

cavity, and head). Finally, the percent of females bearing malignant tumors of the uterus and vagina appeared elevated in the exposed groups, but there was no dose-response relationship (2, 14, and 10% in the control, low-, and high-dose groups, respectively).

3.2.3 Dermal Exposure

3.2.3.1 Death

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

No deaths were observed in groups of male and female New Zealand White rabbits following a 4-hour application of 2,000 mg/kg JP-8 or JP-8+100 under occluded conditions (Wolfe et al. 1996). A 24-hour exposure to 5,000 mg/kg Jet A under occluded conditions also did not result in deaths in male and female New Zealand White rabbits (Vernot et al. 1990b). Daily dermal exposures to 0.1 mL kerosene for 1 week were not lethal to male mice (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 application of 5,000–20,000 mg/kg JP-5 for 14 days (NTP/NIH 1986). Dermal application of 2,000–8,000 mg/kg JP-5 5 days/week for 13 weeks (NTP/NIH 1986) or 42.2 mg JP-5 3 times/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/kg JP-5 5 days/week for 13 weeks (NTP/NIH 1986) or 21.1 mg JP-5 2 or 3 times/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 dermatitis 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 is possible that oral exposure may have contributed to the observed effects; NTP/NIH (1986) did not specify 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 could have substantially affected the study results.

LOAEL values for lethality from each reliable study for death in each species and duration category are recorded in Table 3-3.

3.2.3.2 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 3-3.

Respiratory Effects. No studies were located regarding respiratory effects in humans following dermal exposure to JP-5, JP-8, or Jet A fuels.

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/kg JP-5 (five applications per week), or chronic exposures (five dermal applications per week for 103 weeks) to 250 or 500 mg/kg JP-5 (NTP/NIH 1986).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following dermal exposure to JP-5, JP-8, or Jet A fuels.

Application of 300 µL of JP-8 to a clipped area of the neck of male Long-Evans rats 7 days/week resulted in slight and predominantly perivascular lymphocyte infiltration in the heart (Larabee et al. 2005). Approximately 80% of the myocardial fibers showed fat infiltration, and edema or swelling was observed in 80–90% of the heart section. It should be noted that the study did not provide incidence data. In addition to the morphological changes, an increase in the levels of inducible heat shock protein 70 was observed in the heart. No histopathological changes were noted in the cardiovascular system of mice dermally exposed to 2,000–8,000 mg/kg JP-5 for 13 weeks (five applications per week) or mice chronically exposed (five applications per week for 103 weeks) to 250 or 500 mg/kg JP-5 (NTP/NIH 1986).

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

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).

Table 3-3 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL				Reference Chemical Form	Comments
				Less Serious		Serious			
ACUTE EXPOSURE									
Death									
Mouse B6C3F1	2 wk 7 d/wk					30000 M mg/kg/day	(100% mortality)	NTP/NIH 1986 JP-5	
Systemic									
Rat (Fischer- 344)	7 d 1 x/d	Dermal		0.156 M mL	(gross and microscopic alterations of the skin)			Baker et al. 1999 JP-8	
		Bd Wt	0.156 M mL						
Rat (Fischer- 344)	7 d 1 x/d	Dermal		0.156 M mL	(gross and microscopic alterations of the skin)			Baker et al. 1999 JP-8+100	
		Bd Wt	0.156 M mL						
Rat (Sprague-Dawley)	1 hr	Dermal		0.23 mL	(increased transepidermal water loss and skin inflammation)			Chatterjee et al. 2006 JP-8	
Rat (Long- Evans)	7 d 1 x/d	Dermal		0.3 M mL	(thickened epidermis and inflammatory infiltration)			Gallucci et al. 2004 JP-8	

Table 3-3 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
Rat (Fischer- 344)	1 hr	Dermal		0.25 M mL	(morphological and biochemical alterations in the skin)		Kabbur et al. 2001 JP-8	
Rat SD hairless	5 d 4 x/d	Dermal		0.014 M mL	(Moderate-to-severe erythema and moderate edema under occluded conditions)		Kanikkannan et al. 2002 Jet A	
Rat SD hairless	5 d 4 x/d	Dermal		0.014 M mL	(altered skin morphology and function)		Kanikkannan et al. 2002 JP-8	
Rat SD hairless	5 d 4 x/d	Dermal		0.014 M mL	(altered skin morphology and function)		Kanikkannan et al. 2002 JP-8+100	
Rat (Long- Evans)	7 d 1 x/d	Cardio		0.3 M mL	(alteration of myocardial fibers)		Larabee et al. 2005 JP-8	
		Hepatic		0.3 M mL	(isolated hepatic cell death)			
		Renal		0.3 M mL	(some renal tubular cell death)			

Table 3-3 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
Mouse B6C3F1	2 wk 7 d/wk	Bd Wt	5000 mg/kg/day	10000 mg/kg/day	(17% decrease in body weight gain)		NTP/NIH 1986 JP-5	
Rabbit (New Zealand)	4 hr	Dermal		0.5 mL	(moderately irritating under occluded conditions)		Hurley et al. 2011 JP-8	Slightly irritating under semi-occluded exposure.
		Bd Wt	0.5 mL					
Rabbit (New Zealand)	24 hr	Dermal		0.05 M mL	(altered stratum corneum barrier function)		Singh and Singh 2004 JP-8	
Rabbit (New Zealand)	4 hr	Dermal		0.5 M mL	(slight skin irritation)		Sterner et al. 2014 JP-8	
Rabbit New Zealand	24 hr	Ocular		0.1 mL	(minimal eye irritation)		Vernot et al. 1990b Jet A	
Rabbit New Zealand	24 hr	Dermal		0.5 mL	(miild dermal irritation)		Vernot et al. 1990b Jet A	

Table 3-3 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form	Comments
				Less Serious	Serious		
Rabbit (New Zealand)	4 hr	Dermal	0.5 M mL			Wolfe et al. 1996 JP-8	NOAEL is for skin irritation.
Rabbit (New Zealand)	24 hr	Dermal		2000 B mg/kg (mild erythema)		Wolfe et al. 1996 JP-8	
		Bd Wt	2000 B mg/kg				
Rabbit (New Zealand)	4 hr	Dermal	0.5 M mL			Wolfe et al. 1996 JP-8+100	NOAEL is for skin irritation.
Rabbit (New Zealand)	24 hr	Dermal		2000 B mg/kg (mild erythema)		Wolfe et al. 1996 JP-8+100	
		Bd Wt	2000 B mg/kg				
Pig Yucatan	24 hr	Dermal		0.25 M mL (disruption of barrier function of the skin)		Kanikkannan et al. 2001 JP-8	

Table 3-3 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
Pig Yorkshire	4 d 1 x/d	Dermal	0.025 F mL	0.335 F mL	(slight to moderate erythema and slight edema under occluded test conditions)		Monteiro-Riviere et al. 2001 Jet A	
Pig Yorkshire	4 d 1 x/d	Dermal	0.025 F mL	0.335 F mL	(erythema, edema, epidermal hyperplasia)		Monteiro-Riviere et al. 2001 JP-8	Chemical was applied via a fuel-soaked fabric.
Pig Yorkshire	4 d 1 x/d	Dermal	0.025 F mL	0.335 F mL	(erythema, edema, epidermal hyperplasia)		Monteiro-Riviere et al. 2001 JP-8+100	Chemical was applied via a fuel-soaked fabric.
Pig Yorkshire	4 d 1 x/d	Dermal		0.335 mL	(morphological alterations in the skin)		Monteiro-Riviere et al. 2004 Jet A	
Pig Yorkshire	4 d 1 x/d	Dermal		0.335 mL	(morphological alterations to the skin)		Monteiro-Riviere et al. 2004 JP-8	Fuel was applied in a fuel-soaked cotton fabric.
Pig Yorkshire	4 d 1 x/d	Dermal		0.335 mL	(morphological alterations in the skin)		Monteiro-Riviere et al. 2004 JP-8+100	Fuel was applied in a fuel-soaked cotton fabric.
Immuno/ Lymphoret								
Mouse CBA/Ca	once		0.025 F mL				Kanikkannan et al. 2000 Jet A	

Table 3-3 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form	Comments
				Less Serious	Serious		
Mouse CBA/Ca	once			0.025 F mL (weak skin sensitization)		Kanikkannan et al. 2000 JP-8	
Mouse CBA/Ca	once		0.025 F mL			Kanikkannan et al. 2000 JP-8+100	NOAEL is for skin sensitization.
Mouse (C57BL/6N)	once			0.3 mL (suppressed contact hypersensitivity)		Limon-Flores et al. 2009 JP-8	
Mouse C3H/HeNCr	4 d 1 x/d			0.025 F mL (suppressed immune memory)		Ramos et al. 2002 Jet A	
Mouse C3H/HeNCr	once			0.075 F mL (immune suppression)		Ramos et al. 2002 Jet A	
Mouse C3H/HeNCr	4 d 1 x/d		0.01 F mL	0.025 F mL (suppressed immunological memory)		Ramos et al. 2002 JP-8	
Mouse C3H/HeNCr	once			0.3 F mL (suppressed delayed-type hypersensitivity response)		Ramos et al. 2007 JP-8	

Table 3-3 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
Mouse CH3/HeNCr	1-5 d 1 x/d			0.05 F mL (suppressed contact hypersensitivity)		Ullrich 1999 JP-8	
Mouse CH3/HeNCr	once		0.05 F mL	0.1 F mL (suppressed contact hypersensitivity)		Ullrich and Lyons 2000 JP-8	
Gn Pig (New Zealand)	4 d 1 x/d		0.1 M mL			Wolfe et al. 1996 JP-8	NOAEL is for lack of sensitization.
Gn Pig (New Zealand)	4 d 1 x/d		0.1 M mL			Wolfe et al. 1996 JP-8+100	NOAEL is for lack of sensitization.
INTERMEDIATE EXPOSURE							
Death							
Mouse B6C3F1	13 wk 7 d/wk				2000 F mg/kg/day (60% mortality)	NTP/NIH 1986 JP-5	
Mouse BALB/C	40 wk 3 x/wk				42.2 F mg/kg/day (40% mortality)	Schultz et al. 1981 JP-5	
Mouse BALB/C	40 wk 3 x/wk				41.5 F mg/kg/day (27% mortality)	Schultz et al. 1981 JP-8	

Table 3-3 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL				Reference Chemical Form	Comments
				Less Serious		Serious			
Systemic									
Rat (Fischer- 344)	28 d 1 x/d	Dermal		0.156 M mL	(gross and microscopic alterations of the skin)			Baker et al. 1999 JP-8	
		Bd Wt	0.156 M mL						
Rat (Fischer- 344)	28 d 1 x/d	Dermal		0.156 M mL	(gross and microscopic alterations of the skin)			Baker et al. 1999 JP-8+100	
		Bd Wt	0.156 M mL						
Rat (Sprague-Dawley)	28 d	Dermal				500 F mg/kg/day	(severe skin irritation)	Mann et al. 2008 Jet A	
Rat (Sprague-Dawley)	28 d	Dermal		165 F mg/kg/day	(transient skin irritation)			Mann et al. 2008 Jet A	
Mouse (C3H)	2 x/wk 13 wk	Dermal	10 M %volume	50 M %volume	(skin irritation)			Freeman et al. 1990 Jet A	
Mouse (CD-1)	2 x/wk 52 wk	Dermal		100 M %volume	(moderate irritation)			Nessel et al. 1999 Jet A	

Table 3-3 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form	Comments
				Less Serious	Serious		
Mouse (CD-1)	7 x/wk 52 wk	Dermal	28.6 M %volume			Nessel et al. 1999 Jet A	
Mouse B6C3F1	13 wk 7 d/wk	Resp	8000 mg/kg/day			NTP/NIH 1986 JP-5	
		Cardio	8000 mg/kg/day				
		Gastro	8000 mg/kg/day				
		Hemato		500 mg/kg/day (splenic hematopoiesis)			
		Hepatic		500 mg/kg/day (karyomegaly)			
		Renal	8000 mg/kg/day				
		Dermal		500 mg/kg/day (slight to moderate dermatosis)			
		Bd Wt	2000 mg/kg/day	4000 mg/kg/day (decrease in body weight gain)			

Table 3-3 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
Mouse BALC/C	40 wk 3 x/wk	Hepatic	42.2 mg/kg/day			Schultz et al. 1981 JP-5	
		Renal		21.1 M mg/kg/day (increased kidney weight)			
				21.1 F mg/kg/day (decreased kidney weight)			
		Bd Wt		21.1 mg/kg/day (7-11% decrease in body weight)			
Mouse BALC/C	40 wk 3 x/wk	Hepatic	41.5 mg/kg/day			Schultz et al. 1981 JP-8	
		Renal		21.1 M mg/kg/day (decreased kidney weight)			
				21.1 F mg/kg/day (increased kidney weight)			
		Bd Wt		21.1 mg/kg/day (7-11% decrease in body weight)			
Immuno/ Lymphoret							
Rat (Sprague-Dawley)	28 d		495 F mg/kg/day			Mann et al. 2008 Jet A	

Table 3-3 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
Gn Pig Hartley	3 wk 1 d/wk 6 hr/d	Dermal	0.5 mL			Vernot et al. 1990b Jet A	
Neurological							
Mouse B6C3F1	13 wk 7 d/wk		8000 M mg/kg/day			NTP/NIH 1986 JP-5	
Reproductive							
Mouse B6C3F1	13 wk 7 d/wk		8000 mg/kg/day			NTP/NIH 1986 JP-5	
Cancer							
Mouse (CD-1)	2 x/wk 52 wk				100 M %volume (increased tumor incidence)	Nessel et al. 1999 Jet A	
CHRONIC EXPOSURE							
Death							
Mouse C3H/HeN	3 x/wk 62 wk				25 B mg/app (50% mortality)	Clark et al. 1988 Jet A	
Mouse B6C3F1	90-103 wk 5 d/wk				250 M mg/kg/day (34% mortality)	NTP/NIH 1986 JP-5	
					250 F mg/kg/day (30% mortality)		

Table 3-3 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
Systemic								
Mouse C3H/HeN	3 x/wk 62 wk	Dermal				25 B mg/app (skin irritation, inflammation, and necrosis)	Clark et al. 1988 Jet A	

Table 3-3 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
Mouse B6C3F1	90-103 wk 5 d/wk	Resp	500 mg/kg/day			NTP/NIH 1986 JP-5	
		Cardio	500 mg/kg/day				
		Gastro	500 mg/kg/day				
		Hemato	250 mg/kg/day	500 mg/kg/day (amyloid deposits in spleen)			
		Musc/skel	500 mg/kg/day				
		Hepatic	250 mg/kg/day	500 mg/kg/day (amyloid deposits in liver)			
		Renal	250 mg/kg/day	500 mg/kg/day (amyloid deposits in kidney)			
		Dermal			250 mg/kg/day (ulcers; dermatitis)		
		Bd Wt	250 mg/kg/day	500 mg/kg/day (12-25% decrease in body weight gain)			

Table 3-3 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL				Reference Chemical Form	Comments
				Less Serious		Serious			
Immuno/ Lymphoret									
Mouse B6C3F1	90-103 wk 5 d/wk		250 mg/kg/day	500 mg/kg/day	(granulocyte hyperplasia in the bone marrow; hyperplasia in the lymph nodes)			NTP/NIH 1986 JP-5	
Neurological									
Mouse B6C3F1	90-103 wk 5 d/wk		500 mg/kg/day					NTP/NIH 1986 JP-5	
Reproductive									
Mouse B6C3F1	90-103 wk 5 d/wk		500 mg/kg/day					NTP/NIH 1986 JP-5	
Cancer									
Mouse C3H/HeN	3 x/wk 56-62 wk					25 B mg/app	(fibromas, sarcomas)	Clark et al. 1988 Jet A	

B = both sexes; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); F = Female; Gastro = gastrointestinal; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; x = time(s); wk = week(s)

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

Hematopoiesis by the spleen (extramedullary hematopoiesis) was noted in mice receiving 8,000 mg/kg JP-5 by dermal administration 5 days/week for 13 weeks or 500 mg/kg JP-5 for 103 weeks (NTP/NIH 1986). Extramedullary hematopoiesis may be indicative of a 1% hematological effect.

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

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

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

Application of 300 µL of JP-8 to a clipped area of the neck of male Long-Evans rats 7 days/week resulted in spotty, isolated hepatic cell death and loss of cytoplasm with shrinking nuclei in 1% of hepatic cells (Larabee et al. 2005). It should be noted that only a qualitative description of the results was provided. Slight hepatic karyomegaly was noted in mice receiving 500–8,000 mg/kg JP-5 dermally 5 times/week for 13 weeks (NTP/NIH 1986). Amyloidosis of the liver occurred in mice following the dermal administration of 500 mg/kg JP-5, 5 times/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, JP-8, or Jet A fuels.

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/kg JP-5 5 times/week for 13 weeks (NTP/NIH 1986). Repeated application of 300 µL of JP-8 to a clipped area of the neck of male Long-Evans rats 7 days/week induced renal tubular cell death in approximately 10% of the proximal tubules (Larabee et al. 2005). This was not observed in control preparations, but quantitative data were not provided. 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/kg JP-5 (NTP/NIH 1986).

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

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. No studies were located regarding dermal effects in humans following dermal exposure to JP-5, JP-8, and Jet A fuels.

Information is available regarding dermal exposure of humans to kerosene. 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 a single 90-minute exposure to 1 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 corneum 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 kerosene 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 20-minute dermal exposure to kerosene (Mosconi et al. 1988). Three males (2–15 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).

Numerous studies have examined the effect of jet fuels on the skin of animals, as dermal exposure is a relevant occupational route of exposure. Application of 250 µL of JP-8 fuel to the clipped skin of male Fischer-344 rats for 1 hour under occluded conditions resulted in evidence of dermal inflammation (Kabbur et al. 2001). Morphological changes (increase in extravascular dermal granulocytes) were observed as early as 2 hours after exposure started and were more prominent 6 hours after exposure started. The morphological changes were preceded by an increase in biomarkers of inflammation, such as interleukin (IL)-1α and inducible nitric oxide synthase protein and nitrite levels in the skin. Exposure to a lower concentration (156 µL/cm^2) JP-8 for 1 hour did not result in visible damage to the skin of rats (McDougal et al. 2007). However, alterations in gene expression in the epidermis showed that shortly after exposure, there was activation of several signaling pathways related to inflammation, apoptosis, cell growth, and proliferation. Similar results were reported by Gallucci et al. (2004), who noted that unoccluded application of 300 µL JP-8 to the clipped area of the skin of male Long-Evans rats for 7 days induced thickened epidermis and profound inflammatory infiltration. This was associated with changes in the expression of numerous proinflammatory cytokines. Occluded application of 230 µL JP-8 to the skin of hairless rats for 1 hour significantly increased the cytokine IL-1α in blood and TNFα in the skin 24 hours after dosing (Chatterjee et al. 2006). Once daily unoccluded application of 0.156 mL JP-8 or JP-8+100 to the skin of Fischer rats under non-occluded conditions for 7–28 days resulted in erythema and edema, characterized as very slight during the first few days of exposure and well-defined by the end of the first week of exposure (Baker et al. 1999). Histopathological alterations observed in the skin included spongiosis, orthokeratosis, parakeratosis, hyperplasia, hypergranulosis, dyskeratosis, inflammatory infiltrates, edema, and vasodilation. In animals exposed for 28 days and allowed to recover for 7–28 days, the histopathological alterations were limited to hypergranulosis. Studies in rats also showed significant increases in transepidermal water loss (TEWL, a measure of stratum corneum barrier function) as a result of nonocclusive application of 14 µL JP-8, JP-8+100, or Jet A fuels 4 times/day for 5 days (Kanikkannan et al. 2002). Dermal exposure to these fuels also resulted in slight erythema under non-occluded conditions and moderate-to-severe erythema and moderate edema under occluded conditions (Kanikkannan et al. 2002). An intermediate-duration study with Jet A showed that the concentration and/or vehicle strongly influence the extent of skin damage (Mann et al. 2008). Unoccluded application of 500 mg/kg/day of neat Jet A resulted in severe irritation in Sprague-Dawley

rats; the study was terminated after 5 days due to morbidity. Application of 500 mg/kg/day as 50% Jet A in mineral oil resulted in mild-to-moderate erythema and desquamation after 28 days of exposure. More severe irritation was observed when the Jet A was diluted to 50% using a 4:1 acetone:olive oil vehicle. Another study by Mann et al. (2008) reported transient skin irritation in Sprague-Dawley rats dermally exposed to 165 or 330 mg/kg/day Jet A in mineral oil for 28 days; at 495 mg/kg/day, erythema, edema, and eschar were observed.

In New Zealand White rabbits, application of 500 µL JP-8 to clipped skin for 4 hours resulted in moderate irritation when tested under occluded conditions and slight irritation when tested under semi-occluded conditions (Hurley et al. 2011). Another study found mild erythema in New Zealand White rabbits administered 500 µL JP-8 under semi-occluded conditions for 4 hours (Wolfe et al. 1996). Mild erythema was also found following administration of one of two formulations of JP-8+100 (Wolfe et al. 1996). The primary skin index for all three fuels was less than 1, indicating that it is not a skin irritant. Another study reported that application of 500 µL undiluted JP-5 or JP-8 to a clipped and occluded area of the skin of rabbits for 4 hours did not induce skin irritation (Schultz et al. 1981). However, similar application of 500 µL of JP-8 to male New Zealand White rabbits for 4 hours under occluded or semi-occluded skin conditions resulted in slight skin irritation (Sterner et al. 2014). Mild dermal irritation was reported in New Zealand White rabbits exposed to 500 µL Jet A for 24 hours under occluded conditions (Vernot et al. 1990b).

Repeated application of 335 µL of JP-8 fuel to the clipped skin of female weanling Yorkshire pigs by means of a fuel-soaked fabric induced slight erythema at 5 hours and increased erythema at 5 days (Monteiro-Riviere et al. 2001). Jet A fuel was slightly more irritating than JP-8; slight to moderate erythema and slight edema were observed (Monteiro-Riviere et al. 2001). Light microscopy showed slight intracellular epidermal edema at 5 and 24 hours and at 5 days post-dosing with JP-8 or Jet A fuels. Application sites also had intra-corneal micro-abscesses filled with inflammatory cells, and epidermal thickening was evident. Further studies using electron microscopy showed that the primary ultrastructural changes after JP-8 or Jet A fuel exposure involve alterations in the lipid bilayers of the skin that would likely affect the epidermal-dermal barrier in a manner that would allow further fuel absorption (Monteiro-Riviere et al. 2004). The results from an additional study from this group of investigators indicated that individual aliphatic hydrocarbons, such as tridecane, tetradecane, and pentadecane, are the principal source of JP-8-induced irritation (Muhammad et al. 2005b). Kanikkannan et al. (2001) showed that a 24-hour skin treatment with 250 µL JP-8 in male Yucatan minipigs significantly increased TEWL at 2 and 24 hours after exposure and caused moderate erythema and moderate to severe edema 1 hour after

exposure. Singh and Singh (2004) reported an increase in TEWL in male New Zealand White rabbits after application of 50 µL JP-8 to the shaved back and left covered for 1 hour; this was due to the rupture of the skin barrier and an increase in temperature. Chatterjee et al. (2006) also reported an increase in TEWL in hairless rats applied 230 µL JP-8 for 1 hour.

Acute dermal exposures (14 days) to unspecified concentrations of JP-5 induced dermatitis (acanthosis, scaly skin, hair loss, inflammation, parakeratosis, and/or hyperkeratosis of the skin) in mice (NTP/NIH 1986). Intermediate exposure (five dermal applications per week for 14 weeks) to 500–8,000 mg/kg JP-5 induced slight-to-moderate dermatosis, which increased with dose in mice (NTP/NIH 1986). Chronic dermal application of 250 or 500 mg/kg JP-5 5 times/week for 103 weeks induced dermatitis and ulcerations of the skin of 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 burn. Similarly, the incidence of ulcers induced by the chronic application of JP-5 was dose-dependent. Repeated exposure studies in mice exposed to Jet A also reported dermal irritation. Minimal skin irritation was observed following application of 50% Jet A mineral oil 2 times/week for 13 weeks (Freeman et al. 1990). Moderate irritation was observed following application of 100% Jet A applied 2 times/week for 52 weeks (Nessel et al. 1999). No irritation was observed when 28.6% Jet A in mineral oil was applied 7 times/week for 52 weeks (Nessel et al. 1999). A 62-week exposure (3 times/week) of mice to 25 mg neat Jet A resulted in skin irritation, inflammation, and necrosis (Clark et al. 1988); inflammation was observed in the female mice 2 months prior to the appearance in males.

Ocular Effects. No studies were located regarding ocular effects in humans following dermal exposure to JP-5, JP-8, or Jet A fuels.

No signs of ocular irritation were noted in rabbits exposed to JP-5 or JP-8 in several studies (Cowan and Jenkins 1981; Schultz et al. 1981), although Draize scores were not reported by some of the investigators (Cowan and Jenkins 1981). Minimal eye irritation was observed in rabbits following application of 0.1 mL Jet A (Vernot et al. 1990b).

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

Occluded or semi-occluded application of 0.5 mL JP-8 to the skin of male New Zealand White rabbits for 4 hours and observed for up to 14 days caused no remarkable changes in body weight according to the

investigators (Sterner et al. 2014); however, because there were only three rabbits per group and no controls were used, no meaningful conclusions can be drawn from these results. Application of 0.156 mL of JP-8 or JP-8+100 fuels onto the skin of F-344 rats for up to 28 days did not affect body weight (Baker et al. 1999). In rabbits, a single 4-hour topical exposure to 2,000 mg/kg JP-8 or JP-8+100 did not significantly affect body weight during a subsequent 14-day period (Wolfe et al. 1996). 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). However, in a study in mice exposed to 5,000–40,000 mg/kg JP-5, 7 days/week for 2 weeks, exposure to at least 10,000, but not 5,000 mg/kg JP-5 induced a 17% decrease in body weight gain (NTP/NIH 1986).

Mice treated dermally with JP-5 (at 500, 1,000, 2,000, 4,000, or 8,000 mg/kg) 5 times/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 not significantly affected by the dermal treatment with JP-5 in this study. Dermal application of JP-5 three times per week for 40 weeks produced significant weight reduction in mice (Schultz et al. 1981); total weekly doses were 126.6 and 63.3 mg of JP-5. Chronic dermal exposures (dermal application 3 times/week for 103 weeks) to 500 mg/kg JP-5 induced decreases in body weight relative to controls (NTP/NIH 1986).

3.2.3.3 Immunological and Lymphoreticular Effects

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

Acute dermal treatment (“patch test”) with 1% JP-5 induced mild dermal sensitization in guinea pigs (Cowan and Jenkins 1981). 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). Negative results were observed in a skin sensitization test of JP-8 and JP-8+100 in male Hartley guinea pigs that exhibited edema (Wolfe et al. 1996). Similarly, skin sensitization was not observed in male Hartley guinea pigs following application of 0.5 mL Jet A (Vernot et al. 1990b).

Other studies have also shown that JP-8 and Jet A are not skin sensitizers. Application of 25 µL of JP-8 on the back of the ear of female CBA/Ca mice for 3 consecutive days induced local lymph node

proliferative activity; a stimulation index of 3.17 was determined, indicating that JP-8 was a weak skin sensitizer (Kanikkannan et al. 2000); the threshold definition for a skin sensitizer in this assay is a stimulation index of 3. Adding butylated hydroxytoluene (BHT, an antioxidant additive) to the JP-8 resulted in a lower stimulation index (2.83), although the difference was not statistically significant. The investigators speculated that BHT may inhibit the formation of oxidative products and free radicals from JP-8. Kanikkannan et al. (2000) also tested JP-8+100 and Jet A in using the mouse local lymph node assay; the stimulation indices were 2.38 and 2.44, respectively, indicating that neither fuel was a skin sensitizer.

Application of 50 µL JP-8 to the shaved back of adult female C3H/HeN mice for 4–5 days resulted in significant inhibition of contact and delayed-type hypersensitivity, but application for ≤3 days was without significant effect (Ullrich 1999). This occurred regardless of whether the contact allergen was applied directly to the JP-8 treated site or at a distant untreated site. A single exposure to 150, 240, or 300 µL JP-8 resulted in suppressed delayed-type hypersensitivity to *Candida albicans* in female C3H/HeN mice (Ramos et al. 2002, 2004, 2007, 2009); repeated exposure to 25 µL JP-8 over 4 consecutive days also resulted in suppression of delayed-type hypersensitivity (Ramos et al. 2002). Similarly, a single exposure to ≥75 µL Jet A or repeated exposure to ≥25 µL Jet A over 4 days resulted in suppression of delayed-type hypersensitivity in mice (Ramos et al. 2002, 2004). Exposure to 300 µL JP-8 significantly depressed the ability of splenic T lymphocytes to proliferate in response to plate-bound monoclonal antiCD3 (Ullrich 1999). JP-8 (300 µL) also significantly increased serum levels of the cytokine IL-10. Ullrich and Lyons (2000) showed that immune suppressive cytokines, presumably produced by JP-8-treated epidermal cells, are responsible for the immune suppression seen in JP-8-treated mice, and that blocking and/or neutralizing their production *in vivo* overcomes the immunotoxic effects of JP-8. In a more recent study, application of 300 µL of JP-8 to the skin of C57BL/6 mice resulted in significant suppression of contact hypersensitivity (Limón-Flores et al. 2009). However, no immune suppression was observed in treated mice that were mast cell deficient, suggesting that mast cells mediate immune suppression. Additional experiments showed that PGE2 is the critical mast cell product activating immune suppression and suggested that mast cells migrate from the skin to draining lymph nodes, thereby transmitting the immunosuppressive signal from the skin to the immune system (Limón-Flores et al. 2009). Ramos et al. (2009) showed that JP-8 activated reactive oxygen species and nuclear factor kappa B (NF-κB), which resulted in an upregulation of cyclooxygenase (COX)-2, an enzyme that regulates prostaglandin synthesis. Ramos et al. (2007) suggested that the aromatic hydrocarbons present in JP-8 were the immunosuppressive agents. S-8 synthetic fuel, which is devoid of aromatic hydrocarbons, did not result in suppression of delayed-type hypersensitivity; however,

immunosuppression was observed when a mixture of hydrocarbons (benzene, toluene, ethylbenzene, xylene, 1,2,4-trimethylbenzene, cyclohexylbenzene, and dimethylnaphthalene) was added to the S-8.

Intermediate-duration exposure of Sprague-Dawley rats to 495 mg/kg/day Jet A (60% dilution in mineral oil) did not result in alterations in spleen or thymus weights, spleen lymphocyte population, splenic B-cell or T-cell phenotypes, splenic IgM antibody response to SRBCs or anti CD3 antibody, stimulated T-cell proliferation, or NK cell activity (Mann et al. 2008). Chronic dermal application of 500 mg/kg JP-5 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 with 500 mg/kg JP-5 five times per week for 103 weeks; this effect was not noted following dermal application of 250 mg/kg JP-5 (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 3-3.

3.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans following dermal exposure to JP-5, JP-8, or Jet A fuels.

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 up to 8,000 mg/kg JP-5 5 times/week for 13 weeks or mice chronically exposed (five applications per week for 103 weeks) to up to 500 mg/kg JP-5 (NTP/NIH 1986).

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

3.2.3.5 Reproductive Effects

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

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

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

3.2.3.6 Developmental Effects

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

3.2.3.7 Cancer

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

An increase in skin tumors (squamous cell carcinoma and fibrosarcomas) was observed in C3H/HeN mice following dermal application of 25 mg neat Jet A 3 times/week for 62 weeks (Clark et al. 1988). This concentration was also associated with significant skin damage including inflammation and necrosis. A tumor promotion study demonstrated that damage to the skin was necessary for the induction of tumors (Nessel et al. 1999). In this study, CD-1 mice were exposed to dimethylbenzanthracene (DMBA), which is a tumor initiator, prior to exposure to Jet A. Application of neat Jet A 2 times/week for 52 weeks resulted in a significant increase in skin tumors in CD-1 mice (Nessel et al. 1999); the tumor incidence was 11/30, as compared to 1/30 in the controls. Moderate dermal irritation was also observed at this concentration. However, no skin tumors were observed following the application of 28.6% Jet A in mineral oil 7 times/week for 52 weeks; this concentration did not result in skin irritation. The weekly Jet A doses were the same in both studies (25 µL) and the investigators suggested that the fuel did not induce tumors in the absence of skin irritation.

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. 1981). Tumors were more prevalent in females than in 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 treated dermally with 250 or 500 mg/kg JP-5 five times/week for 103 weeks

(NTP/NIH 1986). Malignant lymphomas were noted in 39% of females treated with 250 mg/kg JP-5, 11% of females at 500 mg/kg JP-5, and 15% of females in the control group. 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/kg JP-5 and 2% at 500 mg/kg JP-5. Significant dermal damage (ulceration and dermatitis) was observed at both JP-5 concentrations.

3.3 GENOTOXICITY

Limited information is available regarding genotoxicity in humans due to exposure to jet fuels. A study of Turkey Air Force personnel exposed to JP-8 found significant increases in the occurrence of sister chromatid exchanges in peripheral lymphocytes; when the personnel were divided by smoking status, only the occurrence in smokers was statistically significant (Erdem et al. 2012). No significant alterations in occurrence of high frequency of sister chromatid exchange cells or in micronuclei frequency were observed. In a study of DNA damage among U.S. Air Force personnel, no significant differences in mean comet assay measurements in leukocytes between different JP-8 exposure categories (high, medium, or low potential exposure) were observed (Krieg et al. 2012). Because the high-exposure workers wore respirators, it is presumed that dermal contact was the primary route of exposure. No associations were found for benzene or naphthalene work shift air levels and DNA damage. However, significant associations were found between pre-shift breath benzene levels and mean tail DNA damage and mean tail (Olive) moment (there was a statistically significant increase in mean tail DNA and mean tail (Olive) moment as the concentration of benzene in breath increased preshift); but the number of cells with highly damaged DNA was statistically decreased as pre-shift benzene breath levels increased. In contrast, mean tail DNA and mean tail (Olive) moment decreased as post-shift breath benzene levels increased. Pre- and post-shift naphthalene breath levels were not significantly associated with DNA damage. However, there was a statistically significant decrease in mean tail DNA as the concentration of naphthalene in end of shift increased. The post-shift number of cells with highly damaged DNA was significantly associated with urinary levels of (2-methoxyethoxy) acetic acid (MEAA), a metabolite of 2-(2-methoxyethoxy) ethanol; however, the association was no longer statistically significant when MEAA levels were adjusted for creatinine levels.

Significant increases in the frequency of micronuclei were observed in peripheral blood polychromatic erythrocytes following application of 240 mg JP-8 or Jet A to the shaved backs of female C3H/HeNCr (MTV-) mice (Vijayalaxmi et al. 2004). Although an increase in micronuclei frequency was also

observed in bone marrow cells for both fuels, the difference over controls was not statistically significant. However, when the experiment was repeated with JP-8 and Jet A, no statistically significant alterations in micronuclei frequency were observed in the peripheral blood or bone marrow (Vijayalaxmi et al. 2006). Additionally, a 3-day repeated dermal exposure to 240 mg/day JP-8 or Jet A did not result in increases in micronuclei formation. Kerosene administered intraperitoneally did not increase the frequency of chromosomal aberrations in bone marrow cells harvested from male or female Sprague-Dawley rats following a one-time exposure to 0.04, 0.13, or 0.4 mL or a 5-day exposure to 0.02, 0.06, or 0.18 mL/day (Conaway et al. 1984). JP-8 did not induce significant dominant lethal effects either in mice at dietary doses of 0.13, 0.4, or 1.3 mL/kg or in rats at gavage doses of 0.1, 0.3, or 1.0 mL/kg (Air Force 1978a). Table 3-4 summarizes the results of *in vivo* genotoxicity studies.

Several studies have examined the genotoxicity of jet fuels using *in vitro* assays. JP-5 was not mutagenic in the Ames assay in *Salmonella typhimurium* TA98 when incubated with or without metabolic activation (Schultz et al. 1981). Similarly, JP-5 was not mutagenic in various strains of *S. typhimurium* preincubation assays with or without metabolic activation (NTP/NIH 1986). Negative results were also reported for JP-8 in several *Salmonella* strains and the yeast *Saccharomyces cerevisiae* D4 (Air Force 1978a). Hydrotreated kerosene was not mutagenic in *S. typhimurium* TA98 with or without activation in a study conducted by Blackburn et al. (1986). Similar results were reported for kerosene in various *Salmonell*a strains incubated with or without metabolic activation (Conaway et al. 1984). In *in vitro* studies with mammalian cells, neither JP-8 nor kerosene was mutagenic in the L5178Y mouse lymphoma assay with or without activation (Air Force 1978a; Conaway et al. 1984). DNA damage assessed by increased unscheduled DNA synthesis was reported in WI-38 cells derived from human embryonic lung following incubation with JP-8 (Air Force 1978a). Two more recent studies of jet fuels also yielded positive results. Using the Comet Assay, Grant et al. (2001) showed that JP-8 induced DNA damage in H4IIE rat hepatoma cells when incubated for 4–8 hours with JP-8 in concentrations ranging from 3 to 20 μg/mL. In this concentration range, JP-8 did not induce cytotoxicity or significant apoptosis. Using the same assay, Jackman et al. (2002) reported that JP-8, JP-5, and JP8+100 induced significant DNA damage in human peripheral blood lymphocytes. JP-8+100 was the most potent, inducing DNA damage at the lowest concentration tested (1/500 dilution). JP-8+100 and JP-8 were considerably more potent than JP-5. Table 3-5 summarizes the genotoxicity of jet fuels in *in vitro* assays.

Overall, the studies of genotoxicity of JP-5, JP-8, and kerosene yielded mixed results. The only two occupational studies located did not provide evidence of genotoxicity, but additional studies are necessary

Table 3-4. Genotoxicity of JP-8, Jet A, and Kerosene *In Vivo*

Species (exposure route)	End point	Results	Reference
JP-8 fuel			
Human (inhalation)	Sister chromatid exchange (peripheral lymphocytes)	+	Erdem et al. 2012
Human (inhalation)	Micronuclei (peripheral lymphocytes)	–	Erdem et al. 2012
Human (dermal)	DNA damage	–	Krieg et al. 2012
Mice (dermal)	Micronuclei (polychromatic erythrocytes)	+	Vijayalaxmi et al. 2004
Mice (dermal)	Micronuclei (bone marrow)	–	Vijayalaxmi et al. 2004
Mice (dermal)	Micronuclei (polychromatic erythrocytes)	–	Vijayalaxmi et al. 2006
Mice (dermal)	Micronuclei (bone marrow)	–	Vijayalaxmi et al. 2006
Mice (oral)	Dominant lethal (germ cells)	–	Air Force 1978a
Rats (oral)	Dominant lethal (germ cells)	–	Air Force 1978a
Jet A fuel			
Mice (dermal)	Micronuclei (polychromatic erythrocytes)	+	Vijayalaxmi et al. 2004
Mice (dermal)	Micronuclei (bone marrow)	–	Vijayalaxmi et al. 2004
Mice (dermal)	Micronuclei (polychromatic erythrocytes)	–	Vijayalaxmi et al. 2006
Mice (dermal)	Micronuclei (bone marrow)	–	Vijayalaxmi et al. 2006
Kerosene			
Rat (intraperitoneal)	Chromosomal aberrations (bone marrow)	–	Conaway et al. 1984

– = negative result; + = positive result

Table 3-5. Genotoxicity of JP-5, JP-8 and Kerosene *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				
Human lymphocytes	DNA damage	No data	+	Jackman et al. 2002
JP-8 fuel				
Prokaryotic organisms				
S. typhimurium (TA98, TA100, TA1535, TA1537, TA1538	Gene mutation	–	–	Air Force 1978a
Saccharomyces cerevisiae D4	Gene mutation	–	–	Air Force 1978a
Mammalian cells				
Mouse lymphoma (L5178Y)	Gene mutation	–	–	Air Force 1978a
WI-38 cells (derived from human embryonic lung)	DNA damage	+	+	Air Force 1978a
Human lymphocytes	DNA damage	No data	+	Jackman et al. 2002
H4IIE rat hepatoma cells	DNA damage	No data	+	Grant et al. 2001
JP-8+100 fuel				
Mammalian cells				
Human lymphocytes	DNA damage	No data	+	Jackman et al. 2002
Kerosene				
Prokaryotic organisms				
S. typhimurium (TA98)	Gene mutation	–	–	Blackburn et al. 1986
S. typhimurium (TA1535, TA1537, TA1538, TA98, TA100)	Gene mutation	–	–	Conaway et al. 1984
Mammalian cells				
Mouse lymphoma (L5178Y)	Gene mutation	–	–	Conaway et al. 1984

— = negative result; + = positive result; DNA = deoxyribonucleic acid

to draw firm conclusions regarding occupational exposures. Examination of mammalian cells from animals exposed to JP-8 or kerosene provided negative results, as did studies of mutagenicity in prokaryotic organisms. However, two more recent studies with mammalian cells *in vitro* showed that JP-5, JP-8, and JP-8+100 can cause DNA damage.

3.4 TOXICOKINETICS

Few data were available concerning the absorption, distribution, metabolism, and excretion of JP-5, JP-8, or Jet A fuels. Information on the toxicokinetics of some components of jet fuel is available (see toxicological profiles for benzene [ATSDR 2007a]; toluene [ATSDR 2015b]; total xylenes [ATSDR 2007b]; ethylbenzene [ATSDR 2010); and naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene [ATSDR 2005]); it should be noted, however, that the interaction of these compounds may influence their individual toxicokinetic properties. Indirect evidence suggests that JP-5, JP-8, and Jet A fuel components may be absorbed through the respiratory tract and the gastrointestinal tract in humans and laboratory animals (see Section 3.4.1). Experimental studies in humans and animals, as well as *in vitro* studies using human or animal skin models, have demonstrated the dermal absorption of JP-8 components. No data were located concerning the metabolism of JP-5, JP-8, or Jet A fuel in humans or laboratory animals. No quantitative data were found regarding the excretion of JP-5, JP-8, or Jet A fuel.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No studies were located specifically regarding the absorption of JP-5, JP-8, or Jet A fuel components in humans or laboratory animals after inhalation exposure. However, adverse health effects including systemic toxicity and neurotoxicity observed in humans (Air Force 2001; Proctor et al. 2011; Tu et al. 2004) or laboratory animals (Gaworski et al. 1984; Hanas et al. 2010; Mattie et al. 1991; Ritchie et al. 2001; Rossi et al. 2001) exposed to jet fuels by inhalation provide indirect evidence for inhalation absorption.

3.4.1.2 Oral Exposure

No studies were located specifically regarding the absorption of JP-5, JP-8, or Jet A fuel components in humans after oral exposure. Indirect evidence of oral absorption of jet fuel components comes from studies reporting non-portal of entry effects in animals exposed to JP-5 (Bogo et al. 1983; Parker et al.

1981), JP-8 (Cooper and Mattie 1996; Dudley et al. 2001; Keil et al. 2004; Mattie et al. 1995, 2000; Peden-Adams et al. 2001), or Jet A (Smith et al. 1999).

3.4.1.3 Dermal Exposure

Information on the absorption of JP-8 components through the skin comes from an occupational exposure study (Chao et al. 2005), short-duration experimental studies in humans (Chao and Nylander-French 2004; Mattorano et al. 2004), modeling studies (Kim et al. 2006a, 2006b, 2007), and *in vitro* studies using human or animal skin models (Baynes et al. 2001; Kanikkannan et al. 2001; McDougal et al. 2000; Muhammad et al. 2005a; Riviere et al. 1999). Using a tape-stripping method that used naphthalene as a marker of JP-8 exposure, Nylander-French and associates (Chao and Nylander-French 2004; Mattorano et al. 2004) demonstrated the dermal absorption of JP-8 through human skin following exposure to liquid jet fuel for ≤30 minutes. The amount of naphthalene removed in the tape strips was inversely related to the post-exposure time. Mattorano et al. (2004) estimated that 5 minutes after exposure, 70% of the naphthalene remained on the skin of fuel cell maintenance workers; after 10 minutes, only 33% remained on the skin and after 20 minutes, approximately 1% remained. A study of Air Force fuel-cell maintenance workers routinely working with JP-8 found a significant relationship between exposure category (high, moderate, or low exposure based on job titles) and naphthalene levels detected via tape stripping in various areas of the body (Chao et al. 2005). Multivariate linear regression models also showed that skin irritation and increasing duration of exposure increased JP-8 component dermal absorption.

Subsequent studies attempted to quantify the absorption and penetration of several aromatic and aliphatic components of JP-8. Kim et al. (2006b) estimated that the aromatic components penetrated faster than the aliphatic components after a single 30-minute dermal-only exposure to JP-8. The rank order of the apparent permeability coefficients (K_P) of aromatic and aliphatic components of JP-8 was naphthalene > 1-methyl naphthalene = 2-methyl naphthalene > decane > dodecane > undecane. Kim et al. (2006a) calculated apparent permeability coefficients of $5.3x10^{-5}$, $2.9x10^{-5}$, $3.2x10^{-5}$, $6.5x10^{-6}$, $4.5x10^{-7}$, and $1.6x10^{-6}$ cm/hour for naphthalene, 1-methyl naphthalene, 2-methyl naphthalene, decane, undecane, and dodecane, respectively.

A data-based, four-compartment model developed by Kim et al. (2006a) accurately predicted the time-course of absorption and appearance in the blood of six components of JP-8 (naphthalene, 1-methyl naphthalene, 2-methyl naphthalene, n-decane, n-undecane, and n-dodecane) in humans following

administration of JP-8 to the forearm. The four compartments were the stratum corneum, viable epidermis, blood, and a fat storage compartment. The diffusion rate constant across the stratum corneum was predicted to be about 4 orders of magnitude less than diffusion across the viable epidermis. The model was used to estimate the cumulative internal dose of naphthalene resulting from dermal exposure to JP-8 at three different concentrations: 344, 483, and 4,188 ng/m^2 for 4 hours; the cumulative doses were 1.61, 2.26, and 19.56 ng-minute/mL, respectively. A subsequent study used a mathematical model and tape-stripping data in humans to calculate diffusion coefficients for five JP-8 components (Kim et al. 2008). The diffusion coefficients were 4.2, 4.6, 4.5, 4.2, and 5.0 cm^2/minute $x10^{-8}$ for naphthalene, 1-methylnaphthalene, 2-methylnaphthalene, undecane, and dodecane, respectively.

In vitro studies using human (Kanikkannan et al. 2001), pig (Kanikkannan et al. 2001; Riviere et al. 1999), or rat (McDougal et al. 2000) skin have demonstrated the penetration and absorption of JP-8 components. Using rat skin, McDougal et al. (2000) showed that 13 components of JP-8 penetrated the skin after a 3.5-hour exposure; the components included diethylene glycol monomethyl ether, decane, methyl naphthalenes, trimethyl benzenes, undecane, naphthalene, xylene, dimethyl naphthalenes, toluene, dodecane, nonane, ethylbenzene, and tridecane. The aromatic hydrocarbon components penetrated the skin better than the aliphatic components. The permeability coefficients ranged from $8.0x10^{-2}$ for diethylene glycol monomethyl ether to $1.4x10^{-5}$ for dodecane. The components with lower octanol/water partition coefficients were found to have the larger permeability coefficients. The permeability coefficients of tridecane, nonane, naphthalene, and toluene from JP-8 across human skin ($6.699x10^{-5}$, $7.239x10^{-5}$, $2.170x10^{-4}$, $1.968x10^{-4}$, respectively) were similar to the values calculated using pig ear skin ($6.982x10^{-5}$, $5.410x10^{-5}$, $1.808x10^{-4}$, $2.470x10^{-4}$, respectively) (Kanikkannan et al. 2001). Riviere et al. (1999), using pig skin, estimated that 1.17, 0.63, and 0.18% (measured as the percentage of the dose) of radiolabelled naphthalene, dodecane, and hexadecane from JP-8 were absorbed. Similarly, Baynes et al. (2001) found that approximately 1% of naphthalene and 0.6% of dodecane dose was absorbed through porcine skin flaps. In an *in vivo* study in weanling pigs, a 30-minute exposure to radiolabelled hexadecane, heptane, and xylene in a JP-8 vehicle resulted in 0.34, 0.18, and 0.12% of the dose being detected at the application site (Singh et al. 2003). Previous *in vivo* exposure to JP-8 for 1 or 4 days resulted in an increased absorption of aromatic hydrocarbons such as naphthalene, ethylbenzene, o-xylene, and trimethylbenzene following *in vitro* pig skin exposure (Muhammad et al. 2005a). For some aliphatic compounds (undecane, dodecane, and tridecane), a 1-day *in vivo* exposure did not affect the absorption following a subsequent *in vitro* exposure; however, a 4-day exposure did result in significant increase in absorption in the *in vitro* exposure phase of the study. The investigators suggested that the increased absorption was due to lipid extraction from the stratum corneum by the JP-8 components.

At the end of a 3.5-hour *in vitro* exposure of rat skin, only six JP-8 components were detected in the skin; all were aliphatic compounds with high octanol/water partition coefficients: nonane, decane, undecane, dodecane, tridecane, and tetradecane (McDougal et al. 2000). An *in vivo* study in rats also showed that the amount of aliphatic compounds absorbed was influenced by the concentration of kerosene per unit area of skin exposed rather than the amount of skin that was exposed (Tsujino et al. 2003).

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No studies were located regarding the distribution of JP-5, JP-8, or Jet A fuel in humans after inhalation exposure. A study by Martin et al. (2012) demonstrated that one component of JP-8 (toluene) was detected in the blood, fat, brain, lung, and liver following a 4-hour exposure to 2,700 mg/m^3 JP-8 aerosols or 900 mg/m^3 JP-8 vapor.

3.4.2.2 Oral Exposure

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

Limited animal data indicate that kerosene is absorbed and the components are 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).

3.4.2.3 Dermal Exposure

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

3.4.3 Metabolism

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

3.4.4 Elimination and Excretion

There are limited data on the excretion of JP-5, JP-8, or Jet A fuels following inhalation, oral, or dermal exposure in humans or laboratory animals. A study of workers exposed to JP-8, found higher post-shift 1-naphthol and 2-naphthol urinary levels, as compared to pre-shift levels (Maule et al. 2013).

3.4.5 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 parameterization, (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) are 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.

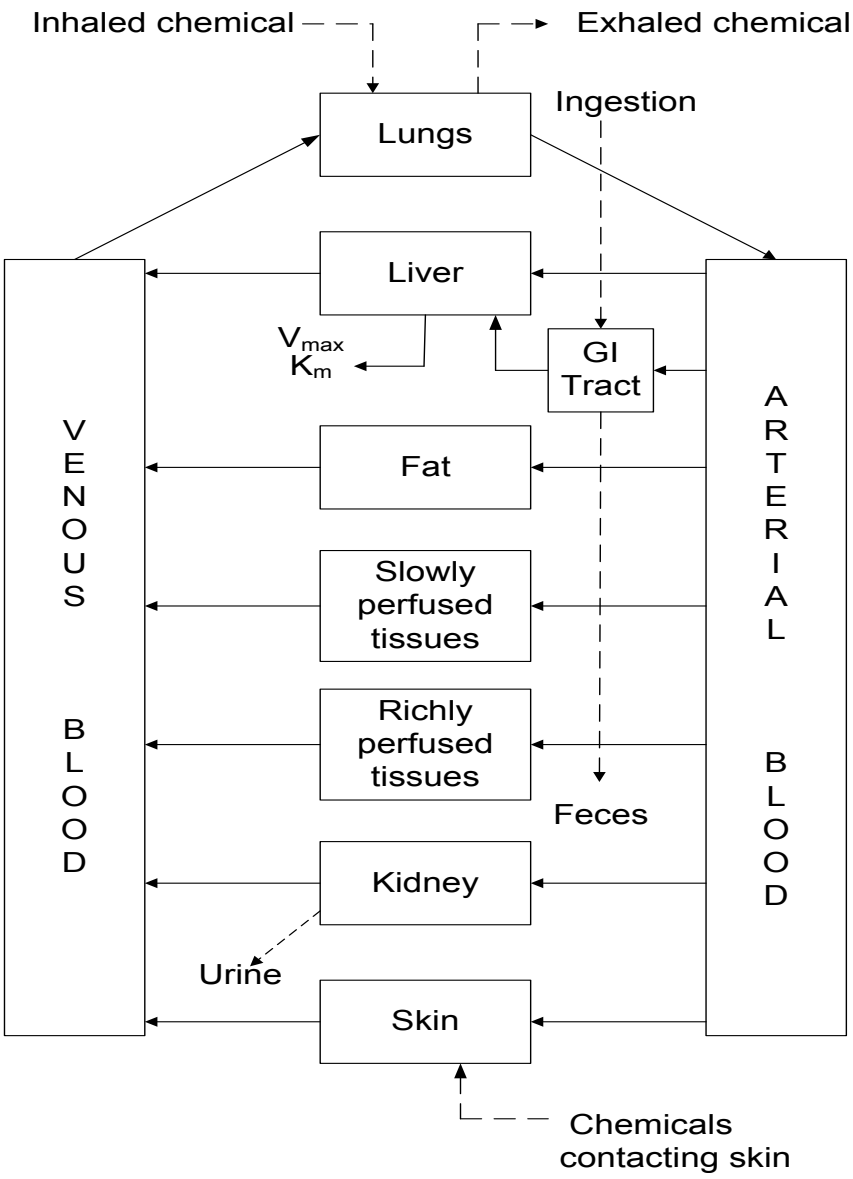
PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in 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 3-3 shows a conceptualized representation of a PBPK model.

If PBPK models for JP-5, JP-8, and Jet A fuels 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.

Kim et al. (2006a) developed a four-compartment dermatotoxicokinetic model that accurately predicted the time-course of absorption and appearance in the blood of six components of JP-8 (naphthalene, 1-methyl naphthalene, 2-methyl naphthalene, n-decane, n-undecane, and n-dodecane) in humans following administration of JP-8 to the forearm. The mean apparent permeability coefficients for the six components are $5.3x0^{-5}$, $3.2x10^{-5}$, $2.9x10^{-5}$, $6.5x10^{-6}$, $1.6x10^{-6}$, and $4.5x10^{-7}$ for naphthalene, 2-methylnaphthalene, 1-methylnaphthalene, decane, dodecane, and undecane, respectively.

With the goal of developing a PBPK model for inhaled JP-8, Campbell and Fisher (2007) examined the metabolic interactions of two JP-8 components, m-xylene and ethylbenzene. At low JP-8 concentrations

Figure 3-3. 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.

Source: adapted from Krishnan and Andersen 1994

(<400 mg/m^3), minimal or no metabolic interactions were found. At the highest concentration (2,700 mg/m^3), a 40 and 46% increase in the area-under-the-concentration curve values for blood xylene and ethylbenzene, respectively, was found. Martin et al. (2012) developed a PBPK model for JP-8 that could predict the dosimetry following inhalation of aerosol and vapor jet fuel. The model was developed using submodels for six aliphatic and aromatic hydrocarbon markers (n-octane, n-decane, n-tetradecane, toluene, ethylbenzene, and m-xylene), plus three submodels that represent the lumped fractions in fuel based on physical property similarities (aromatic hydrocarbons, 8–10-carbon hydrocarbon aliphatics, and heavier aliphatic hydrocarbons). The investigators noted that additional refinements of this model will include submodels for other jet fuel components.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

No studies were identified concerning the pharmacokinetic mechanisms of JP-5, JP-8, or Jet A fuels.

3.5.2 Mechanisms of Toxicity

A number of acute inhalation studies involving mixed exposure to JP-8 aerosols and vapors have identified the respiratory tract as a target of toxicity. The observed effects include increased respiratory permeability, increases in inspiratory resistance and dynamic compliance, interstitial edema and thickening of the bronchiolar epithelium, and deterioration of the alveolar-capillary barrier (Hays et al. 1995; Herrin et al. 2006; Pfaff et al. 1995, 1996; Robledo and Witten 1998, 1999; Robledo et al. 2000; Wang et al. 2001; Wong et al. 2004, 2008). The molecular mechanisms responsible for these effects have not been established.

In vivo and *in vitro* studies have found that alveolar type II cells and alveolar macrophages are targets of JP-8 toxicity. In the alveolar type II cells, exposure to lower JP-8 concentrations results in an increase in the density of lamellar bodies (Espinoza et al. 2007; Hays et al. 1995, 2003; Herrin et al. 2006; Wong et al. 2008), which is indicative of an increase in the production and secretion of surfactant (Hays et al. 2003). At higher JP-8 concentrations, lysis of alveolar type II cells has been observed (Hays et al. 2003; Pfaff et al. 1995). Robb et al. (2010) demonstrated a gradual decline in cultured alveolar type II cell viability with increasing JP-8 concentrations. It is likely that the cell death is due to apoptosis rather than necrosis (Boulares et al. 2002; Stoica et al. 2001); this is supported by the finding of DNA fragmentation

and increased cystolic cytochrome C levels, which is indicative of mitochondrial damage (Stoica et al. 2001).

The damage to respiratory cells may be related to increased levels of reactive oxygen species (ROS) generated during phase 1 metabolism of JP-8 components and the subsequent depletion of glutathione (Hays et al. 2003). Glutathione depletion could result in airway cell necrosis and dilation of bronchial airway junctions and ultimately to increased respiratory permeability via exfoliation of the airways. This theory is supported by the finding of increased ROS generation (Espinoza et al. 2007) and decreased glutathione levels in alveolar macrophages exposed to high JP-8 concentrations (Boulares et al. 2002). At lower JP-8 concentrations, intracellular glutathione levels were not affected; however, there was a decrease in manganese superoxide dismutase levels, which may result in increases in nitric oxide and peroxynitrite formation (Espinoza et al. 2007). The generation of these reactive nitrogen species induced the expression of a number of proinflammatory mediators in alveolar macrophages including interleukin-1 (IL-1), COX-2, inducible nitric oxide synthase (iNOS), and poly(ADP-ribose) polymerase (PARP-1) (Espinoza et al. 2006, 2007; Sun et al. 2007).

3.5.3 Animal-to-Human Extrapolations

The available toxicological studies do not allow determining which species would be a suitable model to predict health outcomes in humans exposed to JP-5, JP-8, or Jet A fuels.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists

agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

There is no evidence from human or animal studies suggesting that JP-5, JP-8, or Jet A fuels might be endocrine disruptors following inhalation, oral, or dermal exposure. In addition, no *in vitro* studies were located regarding endocrine disruption of JP-5, JP-8, or Jet A fuels.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when most biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age

(Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). Past literature has described the fetal/infant blood-barrier as leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at this stage of development, and the restrictive intracellular junctions that exist at the blood-CNS interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the brain, there are differences between fetuses/infants and adults which are toxicologically important. These differences mainly involve variations in physiological transport systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult. Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; as it raises a very important toxicological question as to whether these mechanisms provide protection for the developing brain or render it more vulnerable to toxic injury. Each instance of chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who typically have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

There are no studies of children exposed to JP-5, JP-8, or Jet A fuels, which reflects the fact that exposure to these fuels occurs almost exclusively at work during their manufacture or use. However, exposure to kerosene via ingestion is one of the most common forms of acute childhood poisoning in many developing countries, since kerosene is used for cooking, heating and lightning and is usually stored in containers and places easily accessible to children. Detailed information regarding effects reported in children following ingestion of kerosene as well as original references have been presented in Section 3.2.2, Oral Exposure, and will not be repeated here. Instead, an overview is presented below.

Ingestion of kerosene caused death in children due to lipoid pneumonia from aspiration of kerosene into the lungs during vomiting. One report estimated a lethal dose of approximately 1,900 mg/kg based on the ingestion of 30 mL of kerosene by a 2-year-old child. Based on reports 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. Some studies reported long-lasting respiratory effects following acute poisoning, but others have not. The amount ingested, timing, and quality of initial care may affect the course of adverse health effects from exposure. Vomiting, possibly due to gastric irritation, is frequently reported in acute

poisoning. Leukocytosis and fever are also commonly seen. In reports of multiple cases, the neurological effects noted most frequently were unconsciousness or semiconsciousness, drowsiness, restlessness, and irritability. Coma and convulsions were also noted in numerous studies, but were usually evident in only one or two individuals per study population. 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.

Developmental studies in animals have shown that inhalation or oral exposure of pregnant mice to JP-8 can result in altered immune competence in the pups (Harris et al. 2007b; Keil et al. 2003). Oral exposure of pregnant rats to JP-8 resulted in alterations in a swimming test in the pups indicative of possible developmental delay in motor coordination; however, the delay did not affect motor ability at later ages (Mattie et al. 2001). Reduced fetal and pup weights were reported in developmental studies in rats exposed to JP-8 (Cooper and Mattie 1996; Mattie et al. 2001); however, no teratogenicity has been reported in developmental studies in animals exposed to JP-5, JP-8, or Jet A fuels.

An early study in rats reported that a single dose of 22,400 mg/kg of kerosene killed 4/15 adults, 10/15 juveniles, and 15/15 neonates in 3 days, suggesting increased susceptibility in younger animals compared to adults (Deichmann et al. 1944). A more recent study examined age-related differences in the toxicity JP-8 on various parameters of respiratory function (pulmonary mechanics, respiratory permeability, lavaged cell profile, and chemical mediators in BALF) in mice aged 3.5 or 12 months (Wang et al. 2001). The mice were exposed nose-only to aerosolized JP-8 1 hour/day for 7 days. The results showed similar responses in both groups of mice; however, it appeared that the inflammatory mechanisms might have been different. No further information was located to determine whether there are age-related susceptibilities to jet fuels in humans or in animals.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance

itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to JP-5, JP-8, and Jet A fuels are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by JP-5, JP-8, and Jet A fuels are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to JP-5, JP-8, and Jet A Fuels

A study of Air Force personnel exposed to high (fuel cell maintenance workers), moderate (regular contact with jet fuel via fuel handling, distribution, recovery, and testing), and low (subjects without direct contact) levels of JP-8 found exposure-related increases in benzene and naphthalene levels in expired air (Egeghy et al. 2003). Multivariate analysis found a high correlation between airborne naphthalene and *a priori* JP-8 exposure categories and was not highly influenced by background sources and cigarette smoking. It contrast, benzene levels in post-exposure breath were significantly related to

pre-exposure breath benzene levels and recent smoking, suggesting that breath benzene levels may not be a good biomarker of JP-8 exposure. Pleil et al. (2000) found increases in breath levels of "JP-8 fingerprint compounds" (nonane, decane, undecane, and dodecane) in after-work breath samples of fuel maintenance workers, as compared to before-work samples. Similar to the Egeghy et al. (2003) study, Pleil et al. (2000) found that benzene in expired air was not a good biomarker of exposure to JP-8 because smoking can result in a 400% increase in the benzene mean body burden.

Several studies have examined the possible association between exposure to JP-8 in Air Force fuel cell maintenance workers and urinary excretion of several potential biomarkers, particularly 1- and 2-naphthol. Urinary levels of naphthalene, 1-naphthol, and/or 2-naphthol were higher in workers with high levels of JP-8 exposure as compared to workers with low levels of exposure (Serdar et al. 2003; Smith et al. 2012) and the levels of 1- and 2-naphthol in urine were correlated with naphthalene air levels (Serdar et al. 2004; Smith et al. 2012). Other studies of Air Force fuel cell maintenance workers found a statistical association between urinary 2-naphthol levels and dermal exposure to JP-8; however, no association was found for urinary 1-naphthol levels (Chao and Nylander-French 2004; Chao et al. 2006). However, exhaled breath naphthalene and breathing zone naphthalene levels significantly predicted urinary 1-naphthol and 2-naphthol levels (Chao et al. 2006). Regression analysis showed that breathing zone naphthalene levels was a significant predictor of urinary 1-naphthol levels (after controlling for smoking status, pre-shift 1- and 2-naphthol levels, and post-shift creatinine levels), but did not predict urinary 2-naphthol levels; time spent in the fuel tank was a significant predictor of 1- and 2-naphthol levels (Smith et al. 2012). High levels of urinary benzene were also found in the high-exposure workers; however, the levels were similar to levels found in smokers (Serdar et al. 2003).

Urinary level of MEAA, a metabolite of 2-(2-methoxyethoxy)ethanol, which is added to JP-8, was shown to be a suitable biomarker of JP-8 exposure in oral and dermal exposure studies in mice (B'Hymer et al. 2005). In Air Force personnel, MEAA was detected in 94% of the urine samples of personnel in the high-exposure group, 34% in the medium-exposure group, and 3% in the low-exposure group (B'Hymer et al. 2012b). The mean urinary MEAA level (both unadjusted and adjusted for creatinine) in the high-exposure group was significantly higher than the medium- and low-exposure groups and the mean of the medium-exposure group was significantly higher than the low-exposure group. B'Hymer et al. (2012a) compared two other potential biomarkers of JP-8 exposure in Air Force personnel: *S*-benzylmercapturic acid (BMA), a metabolite of toluene, and *S*-phenylmercapturic acid (PMA), a metabolite of benzene, to the results from the B'Hymer et al. (2012b) study of MEAA. BMA was detected in almost all urine samples from personnel in the high- (98%), medium- (97%), and low- (95%) exposure categories, and the

mean levels were significantly higher in the high-exposure group, as compared to the low-exposure group, but no difference was found between the high- and medium-exposure groups. When BMA levels were adjusted for creatinine levels, no significant differences were found between the groups. PMA was detected in 34, 24, and 20% of the personnel in the high-, medium-, and low-exposure groups, respectively. Mean levels of PMA were significantly higher in the high-exposure group, as compared to the medium- and low-exposure groups; however, when the PMA levels were adjusted for creatinine levels, no significant differences were found between the three exposure categories. Based on these results, B'Hymer et al. (2012a) concluded that MEAA is a suitable biomarker of JP-8 exposure because it appears to be relatively specific for JP-8 exposure and it is easily detected at levels that allow for distinguishing differences in exposure levels.

Kang-Sickel et al. (2011) examined the potential use of naphthyl-keratin adduct levels in the skin as a potential biomarker of dermal exposure to JP-8 among Air Force fuel maintenance workers. Naphthyl-keratin adduct levels correlated with urine naphthalene levels, but did not correlate with dermal, breath, or breathing zone naphthalene levels or with urinary 1-naphthol, 2-naphthol, or total naphthol levels. However, regression analyses showed that log-transformed dermal naphthalene levels and age were inversely associated with skin naphthyl-keratin adduct levels and that naphthyl levels increased with exposure duration (on sampling day). The investigators noted that as more naphthalene was absorbed into the stratum corneum and metabolized by keratinocytes to form keratin adducts, less would remain on the surface of the stratum corneum for sampling by tape-stripping, which may explain the inverse association between dermal naphthalene levels and adduct levels.

A recent study examined the possibility that volatile organic compounds (VOCs) in blood could be used as biomarkers of exposure to JP-8 (Maule et al. 2016). The study comprised 69 active duty U.S. Air Force personnel in jobs tasks that involved potential exposure to different levels of airborne JP-8. The study controlled for potential confounders, most importantly, cigarette smoking. Blood samples collected at the end of shift on day 5 of the week-long sampling investigation were analyzed for 11 VOCs. Multiple linear regression models were used to examine the association between blood VOCs and JP-8 exposure. Of the VOCs measured, *o*- and *m/p*-xylene appeared to be the most appropriate blood biomarkers of JP-8 exposure based on their strong correlation with THCs in personal air and evidence that THCs concentration was a significant predictor of *o*- and *m/p*-xylene. The results also showed that self-reported work shift exposure to JP-8 was a good predictor of *o*- and *m/p*-xylene. Finally, the concentration of THCs in the personal breathing zone measured over a work shift was a better predictor

of ethylbenzene and toluene than self-reported exposure, which the investigators suggested could indicate a source of VOC exposure other than JP-8 fuel.

3.8.2 Biomarkers Used to Characterize Effects Caused by JP-5, JP-8, and Jet A Fuels

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

3.9 INTERACTIONS WITH OTHER CHEMICALS

The only information regarding interaction of jet fuels with other chemicals is from a study examining immunotoxicity induced in female mice by single and concurrent exposure to *N,N*-diethyl-*m*-toluamide (DEET), pyridostigmine bromide (PYR), and JP-8 (Peden-Adams et al. 2001). Co-exposure to these chemicals was common among U.S. service personnel in the Persian Gulf War. JP-8 and PYR were administered orally to mice, whereas DEET was administered by subcutaneous injection singly or as a tertiary mixture for 14 days. Most of a comprehensive number of immune end points examined were not altered by the single or tertiary mixture of compounds (500 or 1,000 mg/kg JP-8; 15.5 or 31 mg/kg DEET; 2 or 5 mg/kg PYR). However, there was synergism with PYR, DEET, and JP-8, resulting in immune suppression of delayed-type hypersensitivity. While all individual agents suppressed humoral immunity, the effect was not exacerbated by the simultaneous exposure to PYR, DEET, and JP-8.

Kerosene vapor has been shown to increase hexobarbital-induced sleeping time 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.

It should be kept in mind that any effect of JP-5, JP-8, or kerosene is the result of unknown interactions between the individual components in these fuels.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to JP-5, JP-8, and Jet A fuels than will most persons exposed to the same level of JP-5, JP-8, and Jet A fuels 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, JP-8, and Jet A fuels, or compromised function of organs affected by JP-5, JP-8, and Jet A fuels. Populations who may be at greater risk due to their unusually high exposure to JP-5, JP-8, and Jet A fuels are discussed in Section 6.7, Populations with Potentially High Exposures.

No information was located regarding the toxicity of JP-5, JP-8, and Jet A fuels 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 did appear more likely to be accidentally orally exposed to kerosene than adults. In particular, children who were ≤5 years old often mistakenly drank kerosene because it was accessible.

Data from a single animal study 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 acute oral exposure 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 10-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.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to JP-5, JP-8, and Jet A fuels. 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, JP-8, and Jet A fuels. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide information about treatment following exposures hydrocarbon products, the main components of JP-5, JP-8, and Jet A fuels:

Gummin DD. 2015. Hydrocarbons. In: Hoffman RS, Howland MA, Lewin NA, et al., eds. Goldfrank's toxicologic emergencies. 10th ed. New York, NY: McGraw Hill Education, 1334-1345.

Shannon MW, Borron SW, Burns MJ, eds. 2007. Haddad and Winchester's clinical management of poisoning and drug overdose. 4th ed. Philadelphia, PA: WB Saunders Company, 1343-1346.

Wang RY. 2004. Hydrocarbon products. In: Dart RC, ed. Medical toxicology. 3rd ed. Philadelphia, PA: Lipincott Williams & Wilkins, 1328-1351.

3.11.1 Reducing Peak Absorption Following Exposure

The following information was extracted from the books listed above.

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, including 100% humidified supplemental oxygen as required. Contaminated clothing should be removed to avoid further exposure.

For poisoning by ingestion, the treatment protocol is more complex. As with inhalation, it is recommended that the patient receive prompt supportive medical care. 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. If unknown or large amounts (volumes >100 mL) have been ingested, then the decision as to how or if there is a need 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 intact gag reflexes and without spontaneous emesis, induced vomiting seems to be the preferred method of gastric emptying; otherwise, endotracheal intubation followed by gastric lavage can be employed.

Controversy also exists over whether or not to administer activated charcoal (to bind the hydrocarbon) or cathartics. Some people question the overall effectiveness of activated charcoal and cathartics. In addition, activated charcoal may cause vomiting, 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.

In general, the prophylactic administration of antibiotics or corticosteroids does not appear useful in treating hydrocarbon pneumonitis. The use of antibiotics is recommended only to only treat secondary lung infections.

If the skin is exposed to jet fuels, washing the area of contact with large amounts of soapy water is recommended. If blistering or skin loss occurs, then the use of sterile water alone is suggested. For ocular exposure, flushing the eyes liberally with water and, if necessary, using proparacaine hydrochloride to assist the irrigation, are the recommended treatment protocols.

A study was conducted to determine whether protection through the use of barrier skin creams or lotions was feasible, and whether a single application would provide sufficient and consistent protection before exposure to JP-8 (Wagner et al. 2009). The investigators tested a wide variety of over-the-counter (OTC) creams as well as some formulated creams *in vitro* using a Silastic® barrier or harvested pig skin and *in vivo* in rabbit skin. In the *in vivo* experiments, the barrier creams were scored in three ways: by visual scoring described by the Draize method, by colorimetry, and by histopathology. JP-8 was applied undiluted in amounts of 0.5 mL to shaved areas of the backs of rabbits by means of Hill Top Chambers for 4 hours. Application sites were scored 40 minutes after the chambers were removed and 24, 48, and 72 hours after exposure. While some OTC creams showed some effectiveness in preventing JP-8 absorption in the cell diffusion chambers, they did not prevent absorption and skin irritation in the live rabbits' skin. Some formulated creams worked better than OTC creams in the diffusion chamber, yet they did not perform when tested on the animal model. The investigators concluded that the best protection against dermal exposure to JP-8 is the use of personal protective equipment (PPE).

3.11.2 Reducing Body Burden

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

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Although the pulmonary 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.

3.12 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, JP-8, and Jet A fuels 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, JP-8, and Jet A fuels.

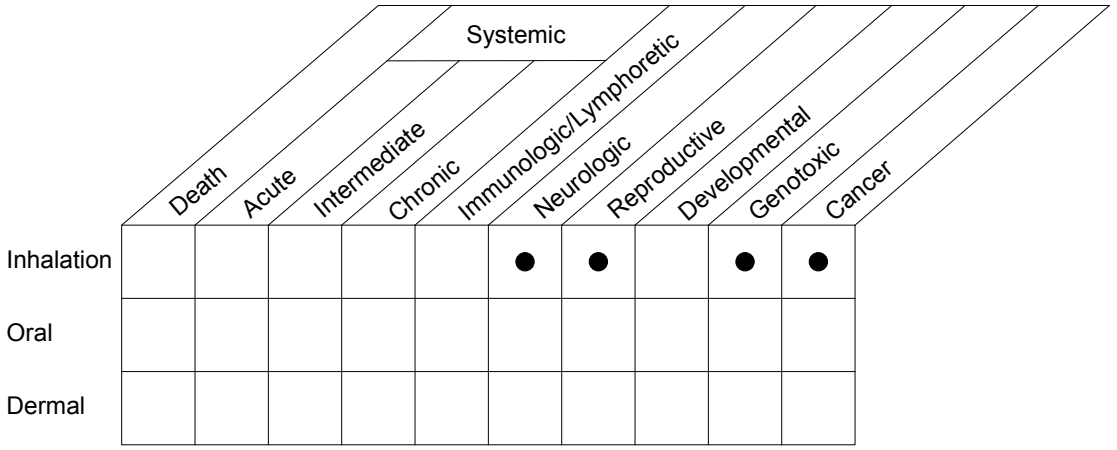
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean 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.

3.12.1 Existing Information on Health Effects of JP-5, JP-8, and Jet A fuels

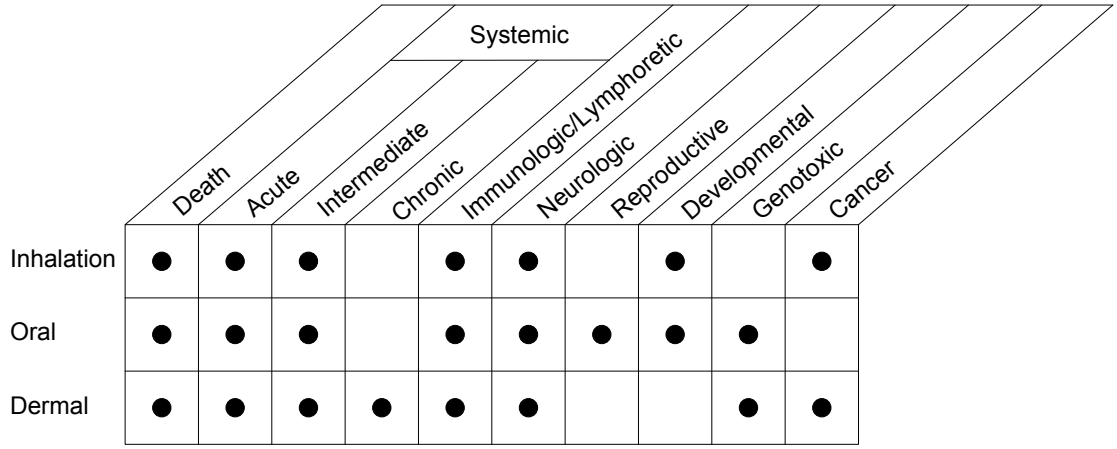
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to JP-5, JP-8, and Jet A fuels are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of JP-5, JP-8, and Jet A fuels. Each dot in 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.

There are limited data on the toxicity of JP-5, JP-8, or Jet A fuels in humans; the available studies have evaluated neurologic, reproductive, genotoxic, or carcinogenic end points following inhalation exposure. However, there are a number of studies and case-reports of humans exposed to kerosene, which has a similar composition to jet fuels. These kerosene studies have reported systemic effects following inhalation exposure, death, systemic, and neurological effects following oral exposure, and systemic effects following dermal exposure. Information is also available in laboratory animals on death and acute and intermediate systemic effects as well as on immunological, neurological, developmental, and

Figure 3-4. Existing Information on Health Effects of JP-5, JP-8, and Jet A Fuels



Human



Animal

● Existing Studies

carcinogenic effects following inhalation exposure to jet fuels; on death, acute and intermediate systemic effects, immunological, neurological, reproductive, developmental, and genotoxic effects following ingestion; and on death, acute, intermediate, and chronic systemic effects, immunological, neurological, and carcinogenic effects following dermal exposure.

Therefore, as Figure 3-4 shows, the majority of the data on health effects of jet fuels comes from animal studies with some limited data in humans exposed via inhalation exposure.

3.12.2 Identification of Data Needs

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

Acute-Duration Exposure. The only information available regarding effects in humans following acute inhalation exposure to the jet fuels is that from a report of accidental exposure to unknown concentrations of JP-5 vapors by two pilots flying a small airplane (Porter 1990). This report provided some information on systemic and neurological effects; limited conclusions can be drawn from data on two individuals. A study in six volunteers exposed to 140 mg/m^3 deodorized kerosene vapors for 15 minutes provided data on throat and eye irritation for this fuel (Carpenter et al. 1976). This information is insufficient to derive an acute inhalation MRL for JP-5, JP-8, or Jet A fuels based on human data. Studies in animals provided information on respiratory and ocular effects of JP-8 and JP-8+100 in rats (Wolfe et al. 1996), respiratory effects of JP-8 in mice (Herrin et al. 2006; Robledo and Witten 1998, 1999; Robledo et al. 2000; Wang et al. 2001; Wong et al. 2004, 2008), immunological effects of JP-8 in mice (Harris et al. 1997a, 1997b, 1997c, 2000a, 2000b, 2000c, 2007a, 2007c, 2008; Hilgaertner et al. 2011), and neurological effects in rats (Fechter et al. 2007, 2012). Of the studies in mice, only Herrin et al. (2006), Hilgaertner et al. (2011), and Wong et al. (2008) measured both aerosol and vapor components of the airborne JP-8. These studies were not considered suitable for development of an acute inhalation MRL for JP-8 because the daily exposure duration (1 hour) was short and there would be considerable uncertainty in extracting these data for continuous exposure. Additional studies are needed in which a variety of end points, including respiratory effects and immunotoxicity, are examined following exposure for at least 6 hours/day. No human acute-duration oral data were located

for JP-5, JP-8, or Jet A fuels. However, there are numerous case reports of accidental oral exposure to kerosene, particularly in children (Abu-Ekteish 2002; Akamaguna and Odita 1983; Aldy et al. 1978; Annobil 1983; Annobil and Ogunbiyi 1991; Balme et al. 2012; Benois et al. 2009; Chun 1998; Dudin et al. 1991; Lang et al. 2008; Lucas 1994; Mahdi 1988; Santhanakrishnan and Chithra 1978; Shotar 2005; Simmank et al. 1998; St. John 1982). These and many additional reports provide information regarding death, systemic, and neurological effects, but few provided estimates of the amounts ingested. The animal data provided information regarding death in various species (Deichmann et al. 1944; Parker et al.1981), immunological effects (Dudley et al. 2001; Keil et al. 2004; Peden-Adams et al. 2001), and developmental effects (Cooper and Mattie 1996; Keil et al. 2003). The database is lacking an adequate study examining systemic toxicity, which precludes identifying the most sensitive target of toxicity and derivation of an acute-duration oral MRL. A repeated-dose study in rats and mice that includes examination of major tissues and organs would be useful for determining the critical targets of toxicity. No acute-duration dermal studies in humans exposed to JP-5, JP-8, or Jet A fuels were found. However, a few studies showed that dermal exposure to kerosene can cause dermatitis and erythema in humans (Mosconi et al. 1988; Tagami and Ogino 1973). Numerous studies in animals provide information regarding dermal effects in various animal species (Baker et al. 1999; Chatterjee et al. 2006; Deichmann et al. 1944; Gallucci et al. 2004; Hurley et al. 2011; Kabbur et al. 2001; Kanikkannan et al. 2002; Monteiro-Riviere et al. 2001, 2004; Singh and Singh 2001; Sterner et al. 2014; Wolfe et al. 1996). Many of these studies described morphological and functional alterations of the skin. Additional studies describing skin alterations do not appear necessary, but further research on the mechanisms involved would provide valuable information. Acute dermal studies that described alterations in immune function in mice exposed to JP-8 are also available (Kanikkannan et al. 2000; Limón-Flores et al. 2009; Ramos et al. 2002, 2007; Ullrich 1999; Ullrich and Lyons 2000). Studies that examined the issue of skin sensitization in mice are also available (Kanikkannan et al. 2000; Wolfe et al. 1996).

Intermediate-Duration Exposure. No studies were located of humans exposed to JP-5, JP-8, or Jet A fuels for intermediate durations. Animal data are available for intermediate duration by the inhalation, oral, and dermal routes of exposure. Ninety-day studies are available for JP-8 in rats (Hanas et al. 2010; Mattie et al. 1991), JP-5 in rats, mice, and dogs (Gaworski et al. 1984), and kerosene in rats and dogs (Carpenter et al. 1976). These studies provided information mainly on systemic effects, specifically on histopathology of major organs and tissues. Other intermediate-duration inhalation studies provided data on neurological effects of JP-8 and JP-5 in rats (Ritchie et al. 2001; Rossi et al. 2001) and immunological effects of jet fuel kerosene in rats and mice (White et al. 2013). The lowest LOAEL identified was 150 mg/m^3 and it was for liver histopathology in mice exposed to JP-5 vapors (the lowest

exposure concentration tested) (Gaworski et al. 1984). The lowest LOAEL for JP-8 was 500 mg/m^3 (aerosol and vapor components) and it was for morphological alterations in the lungs, heart, liver, and bone marrow of rats; the NOAEL was 250 mg/m^3. As it appears that acute-duration inhalation studies (Herrin et al. 2006; Wong et al. 2008) identified ultrastructural alterations in the lungs of mice exposed to significantly lower exposure concentrations of JP-8 (45–53 mg/m^3), it would be appropriate to conduct intermediate-duration inhalation studies that examine the lungs of mice and rats with transmission electron microscopy and perform lung function tests in the animals. Intermediate-duration oral studies provided data on a wide range of systemic end points in rats exposed to JP-8 (Mattie et al. 1995, 2000). These studies also provided information on fertility in male and female rats. An additional study conducted neurobehavioral tests on the offspring of female rats that were exposed to JP-8 during cohabitation, gestation, delivery, and lactation (Mattie et al. 2001). The intermediate-duration oral database was considered inadequate for derivation of an MRL. Intermediate-duration inhalation studies have identified the liver as the most sensitive target of toxicity in mice and dogs; the LOAEL in mice is lower than the highest NOAEL in rats. An oral study in mice in which the major tissues and organs are examined would allow greater confidence in identifying the most sensitive target of toxicity. Intermediate-duration dermal studies reported lethal doses for JP-5 and JP-8 in mice (NTP/NIH 1986; Schulz et al. 1991) and provided information on systemic effects in mice following repeated dermal application of JP-5 for 13 weeks (NTP/NIH 1986). The latter study examined a wide range of systemic end points and reported hematological, hepatic, and dermal effects at the lowest dose tested, 500 mg/kg/day. No reliable intermediate-duration dermal studies with JP-8 were located. Since skin contact is an important route of occupational exposure to jet fuels, an intermediate-duration study with JP-8 that examines a wide range of end points seems warranted.

Chronic-Duration Exposure and Cancer. No studies were located regarding health effects in humans following chronic-duration exposure to JP-5 by any route of exposure. Very limited information is available for JP-8. Suggestive evidence of neurological alterations was presented in three studies of military personnel exposed to JP-8 (Proctor et al. 2011; Smith et al. 1997; Tu et al. 2004), but not in a more recent study (Maule et al. 2013). Another study of military personnel reported an association between JP-8 exposure and leukocytosis (Rhodes et al. 2003). No chronic-duration studies in animals were available for JP-8 by any route of exposure or for JP-5 by the inhalation and oral routes of exposure. Inhalation and dermal studies with JP-8 would be valuable since these are relevant routes of occupational exposure to JP-8. Results from the inhalation study could be used to derive a chronic-duration inhalation MRL for JP-8. A 103-week dermal bioassay for JP-5 in mice reported dermatitis at the lowest dose

tested, 250 mg/kg/day, and amyloid deposits in the spleen, liver and kidneys at 500 mg/kg/day (NTP/NIH 1986).

No studies were located regarding cancer in humans exposed to JP-5, JP-8, or Jet A fuels. Health screening of military personnel with past or current exposure to these fuels that included monitoring for cancer, particularly of the respiratory tract and the skin would be useful, as these are the sites with the most contact with the fuels in occupational settings and could provide useful information on the carcinogenic potential of jet fuel exposure. A few studies reported an association between kerosene and oral and pharyngeal cancer (Zheng et al. 1992), brain tumors (Bunin et al. 1994), and kidney cancer (Siemiatycki et al. 1987). The result of these studies should be interpreted with caution because, often, potential confounders were not well controlled, exposure concentrations were not available, and the possibility of simultaneous exposure to other chemicals could not be ruled out. There are no studies of cancer in animals exposed to JP-8 by any route of exposure or to JP-5 by inhalation or orally. Inhalation and dermal studies with JP-8 would be appropriate since these are relevant routes of occupational exposure. A dermal bioassay for JP-5 in mice did not find evidence of carcinogenicity (NTP/NIH 1986). However, dermal exposure of mice to undiluted kerosene resulted in an increased number of skin tumors (Nessel et al. 1998). In the latter study, it appeared that tumors developed only in the presence of skin irritation; further research into the possible mechanisms involved in dermal carcinogenicity would be valuable.

Genotoxicity. Studies of workers exposed to JP-8 did not provide evidence of *in vivo* genotoxicity (Erdem et al. 2012; Krieg et al. 2012). *In vivo* studies in animal also yielded negative results (Air Force 1978a; Conaway et al. 1984; Vijayalaxmi et al. 2006). *In vitro* studies in *Salmonella* or in mammalian cells incubated with JP-5, JP-8, or kerosene with or without metabolic activation yielded negative results (Blackburn et al. 1986; NTP/NIH 1986). However, three studies with mammalian cells *in vitro* reported that JP-8 induced DNA damage (Air Force 1978a; Grant et al. 2001; Jackman et al. 2002). One of these studies also showed that JP-5 and JP-8+100 could induce DNA damage (Jackman et al. 2002). Further occupational studies with enough statistical power and appropriate control of potential confounders are necessary to draw stronger conclusions.

Reproductive Toxicity. The only relevant information located is that from a study of military and civilian women from 10 U.S. Air Force bases who reported a significant inverse association between exposure to JP-8 and serum levels of LH (Army 2001; Reutman et al. 2002). No significant association was found between exposure to JP-8 and higher odds of menstrual disorders. Further studies of

reproductive end points in women exposed to jet fuels would be valuable. Conduction of fertility surveys among populations (males and females) with past or current occupational exposure to JP-8 or JP-5 to determine potential abnormalities would be useful. JP-8 did not affect fertility in male or female rats in intermediate-duration oral studies (Mattie et al. 2000). Other long-term studies with oral JP-8 exposure to rats (Mattie et al. 1995), JP-5 dermal exposure to mice (NTP/NIH 1986), or JP-5 vapor exposure to rats, mice, or dogs (Gaworski et al. 1984) did not report morphological alterations in the reproductive organs of the animals. It appears that although additional oral studies in animals are not necessary at this time, information is lacking from inhalation and dermal exposure, the two relevant routes of occupational exposure. It may be useful to conduct fertility surveys among populations (males and females) with past or current occupational exposure to JP-8 or JP-5 to determine potential abnormalities.

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 doses of JP-8 that also significantly reduced maternal weight gain (Cooper and Mattie 1996). No teratogenicity was observed in that study. Immune suppression was reported in offspring from mice exposed to airborne (Harris et al. 2007b) or oral JP-8 during gestation (Keil et al. 2003). In addition, transient neurobehavioral alterations were reported in offspring of rats exposed orally with JP-8 during pregnancy (Mattie et al. 2001). Results from the inhalation study suggested that there might be a genetic component involved in determining the immune response in the offspring exposed *in utero*; this possibility should be explored further. Standard developmental end points have not been examined following inhalation or dermal exposures, the two relevant routes of occupational exposure; therefore, studies by these routes may be warranted. It would be interesting to determine whether maternal immunotoxicity is necessary to observe immunotoxicity in the offspring. Monitoring women who were or are exposed to JP-5, JP-8, or Jet A fuels during pregnancy could provide valuable information regarding birth parameters.

Immunotoxicity. No information was found regarding immunotoxicity in humans exposed to JP-5, JP-8, or Jet A fuels. A series of studies examined immune function in mice acutely exposed to airborne JP-8 (Harris et al. 1997a, 1997b, 1997c, 2000a, 2000b, 2000c, 2007a, 2007c, 2008). However, in these studies, only the aerosol component (not the vapor component) was measured; therefore, the total exposure concentration of JP-8 was underestimated. It would be useful to replicate these studies to determine the true exposure level at which the various immune alterations occur. Several studies have tried to determine which component or components of the fuels are responsible for the immune effects

(Hilgaertner et al. 2011; Ramos et al. 2007; White et al. 2013). The results were not consistent between studies and further exploration of this line of research may be warranted.

Neurotoxicity. A few studies examined possible associations between occupational exposure to JP-8 and neurological effects. These studies reported an association between cumulative, but not daily, exposure to JP-8 and altered balance (Maule et al. 2013; Smith et al. 1997), and between exposure to JP-8 and alterations in neuropsychological tests (Proctor et al. 2011; Tu et al. 2004). Continued monitoring of these cohorts seems appropriate. Accidental ingestion of kerosene has resulted in neurological effects, including unconsciousness or semiconsciousness, drowsiness, restlessness, and irritability (Abu-Ekteisch 2002; Akamaguna and Odita 1983; Aldy et al. 1978; Benois et al. 2009; Chun 1998; Coruh and Inal 1966; Dudin et al. 1991; Lang et al. 2008; Lucas 1994; Mahdi 1988; Majeed et al. 1981; Nouri and Al-Rahim 1970; Saksena 1969; Santhanakrishnan and Chithra 1978; Shotar 2005; St. John 1982). Many of these cases occurred in other countries and may be difficult to follow-up. However, cases identified in the Unites States, where kerosene can be purchased for use, for example, in portable heaters, could be followed to determine whether acute exposure to a high amount of kerosene results in long-lasting neurological effects. This could also be studied in animal models. Intermediate-duration studies in rats showed that exposure to JP-5 or JP-8 vapors can induce neurobehavioral alterations, changes in the levels of neurotransmitter in brain areas, and hearing alterations (Guthrie et al. 2014, 2015; Ritchie et al. 2001; Rossi et al. 2001). However, this has not been examined in long-term, low-exposure studies that simulate occupational settings.

Epidemiological and Human Dosimetry Studies. A few studies have examined the effects of exposure to JP-8 on human health. These studies examined occupationally exposed subjects and provided some evidence suggesting that long-term exposure to JP-8 may be associated with adverse neurological effects (Proctor et al. 2011; Smith et al. 1997; Tu et al. 2004). An additional study reported that daily exposure to JP-8 was not associated with alterations in balance (Maule et al. 2013). Since those exposed at work may be subjected to the highest levels of exposure, continued monitoring of these groups is important to detect any emerging health condition associated with exposure to jet fuels. Studies in animals indicate that the respiratory tract may be a sensitive target for JP-8 toxicity; therefore, occupational studies should monitor respiratory function with appropriate tests. Exposure of the general population to JP-5 and JP-8 is likely to be limited to populations living on or near military installations where JP-5 and/or JP-8 are utilized. However, should unintentional exposure to JP-5 and JP-8 occur as a result of groundwater contamination from spilled jet fuels or contact with soils that have been contaminated with jet fuels, those exposed should be monitored for potential adverse health effects.

Biomarkers of Exposure and Effect.

Exposure. A number of studies examining biomarkers that could be used to identify and/or quantify exposure to JP-8 have focused on measuring the levels of specific components of JP-8 in expired air or metabolites of components in urine. Levels of naphthalene, nonane, decane, undecane, and dodecane in expired air have been shown to be elevated in fuel maintenance workers exposed to JP-8 (Egeghy et al. 2003; Pleil et al. 2000); however, the benzene level in expired air was heavily influenced by pre-exposure levels and smoking and was not a good biomarker (Egeghy et al. 2003; Pleil et al. 2000). Similarly, urinary levels of naphthalene, 1-naphthol, 2-naphthol, and MEAA have been shown to be elevated in workers exposed to JP-8 (B'Hymer et al. 2012a; Chao and Nylander-French 2004; Chao et al. 2006; Serdar et al. 2003; Smith et al. 2012). Levels of naphthalene, 1-naphthol, and 2-naphthol in urine were higher in workers with high exposure to JP-8, and the 1- and 2-naphthol levels were correlated with the naphthalene levels in air (Serdar et al. 2004; Smith et al. 2012). B'Hymer et al. (2012a) found significant differences in urinary levels of MEAA, a metabolite of a JP-8 additive, between workers with high, medium, and low JP-8 exposure levels; since it is relatively specific for JP-8 exposure and urinary levels appear to be related to air concentrations, MEAA appears to be a suitable biomarker of exposure. VOCs such as *o*- and *m/p*-xylene appeared to be appropriate blood biomarkers of JP-8 exposure in a recent study of U.S. Air Force personnel (Maule et al. 2016). Additional research is needed to establish a quantitative relationship between urinary levels and air concentrations.

Effect. No specific biomarkers of effect were identified for JP-5, JP-8, or Jet A fuels. 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. With the exception of dermal absorption data, no quantitative data were located regarding the absorption, distribution, metabolism, or excretion of jet fuels following inhalation, oral, or dermal exposure in humans. Observation of systemic effects following inhalation and oral exposure provide indirect evidence for the absorption of jet fuels. The dermal absorption of JP-8 has been demonstrated in humans and animals (Baynes et al. 2001; Chao and Nylander-French 2004; Kanikkannan et al. 2001; Kim et al. 2006a, 2006b, 2007; Mattorano et al. 2004; McDougal et al. 2000; Muhammad et al. 2005a; Riviere et al. 1999). As would be expected, the studies found large differences in the absorption of different JP-8 components, with the aromatics penetrating the skin faster than the aliphatic compounds (Kim et al. 2006b; McDougal et al. 2000); thus, the composition

of the dermally absorbed components will vary greatly from the composition of JP-8 (McDougal and Robinson 2002). Additional studies are needed to further examine the time course of dermal absorption of different jet fuel components and to determine other factors that could influence dermal absorption, such as prior exposure. 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 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; Gummin 2015; Shannon et al. 2007; Steele et al. 1972; Wolfsdorf and Kundig 1974). 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.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

There are no studies of children exposed to JP-5, JP-8, or Jet A fuels, which is not unexpected since exposure to these fuels is likely to occur mainly in occupational settings. However, as previously mentioned, exposure to kerosene via ingestion is one of the most common forms of acute childhood

poisoning in many developing countries since kerosene is used for cooking, heating and lighting and is usually stored in containers and places easily accessible to children. Accidental poisoning has resulted in respiratory, gastrointestinal, neurological, and hematological effects; fever has also been reported, and in some cases, death occurred (Abu-Ekteish 2002; Akamaguna and Odita 1983; Aldy et al. 1978; Annobil 1983; Annobil and Ogunbiyi 1991; Balme et al. 2012; Benois et al. 2009; Chun 1998; Dudin et al. 1991; Lang et al. 2008; Lucas 1994; Mahdi 1988; Santhanakrishnan and Chithra 1978; Shotar 2005; Simmank et al. 1998; St. John 1982). These and many other case reports do not provide enough information to determine whether or not children are more susceptible to kerosene than adults. It would be useful to follow-up children who have suffered poisoning with kerosene to determine whether high acute exposure results in long-term effects.

A study in animals showed that young rats are more susceptible to the effects of acute oral exposure to high doses of kerosene than adult rats (Deichmann et al. 1944). However, it would be inappropriate to predict what would occur in humans based on the results of a single study.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

No ongoing studies pertaining to JP-5 and JP-8 were identified in RePORTER (2014).

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4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identities of JP-5, JP-8, and Jet A fuels is located in Table 4-1. Nearly all jet fuel is made from kerosene derived from petroleum; however, a small percentage is made from oil sands (Chevron 2006). Kerosene is manufactured from the distillation of crude oil at atmospheric pressure (straight-run) or from catalytic, thermal, or steam cracking of heavier petroleum streams (cracked kerosene). Figure 4-1 depicts a general schematic of a refinery capable of producing jet fuels along with other light, middle, and heavy distillates of crude oil. The exact composition of any particular batch of jet fuels is dependent upon the crude oil from which it was derived and on the refinery processes used for its production. Regardless of the source and production process, kerosenes and jet fuels primarily consist of C9 to C16 hydrocarbons that boil in the range of 145–300°C (API 2010a). Analytical techniques are not capable of separating and characterizing each molecular species of these complex mixtures (likely >1,000 individual components); however, the predominant components of jet fuels are branched and linear paraffins and naphthenes (cycloalkanes) which usually account for over 70% of the components by volume (API 2010a; Chevron 2006). Aromatic hydrocarbons such as alkylbenzenes and naphthalenes do not exceed 25% of the total. Olefins represent an insignificant fraction of the total composition of JP-5, JP-8, and Jet A fuels. The final product must meet all of the performance and regulatory requirements of the specific fuel. ASTM International (formerly known as the American Society for Testing and Materials) and the U.K. Ministry of Defense publish specifications and test methods for commercial jet fuels and more information regarding these standards may be obtained from these organizations. These requirements, including a description on the different additives used in aviation fuels have been summarized in an ExxonMobil report on world jet fuel specifications (ExxonMobil 2005). The U.S. government and other nations' governments maintain specifications for jet fuels for military use (Chevron 2006).

Two important types of jet fuels exist for commercial aviation, Jet A and Jet A-1. Jet A is predominantly used in the continental United States while Jet A-1 is used throughout the rest of the world (ExxonMobile 2005). These fuels are nearly identical; however the most important difference between them is that Jet A-1 is refined to have a lower maximum freezing point (-47°C) than Jet A (-40°C). The lower freezing point makes Jet A-1 a better choice for international flights, especially on polar routes during the winter season (Chevron 2006). In addition, Jet A typically does not contain a static dissipator additive that may be required for Jet A-1 fuels (ExxonMobil 2005). Table 4-2 lists some compositional data for 14 different Jet A fuel samples provided by the American Petroleum Institute (API).

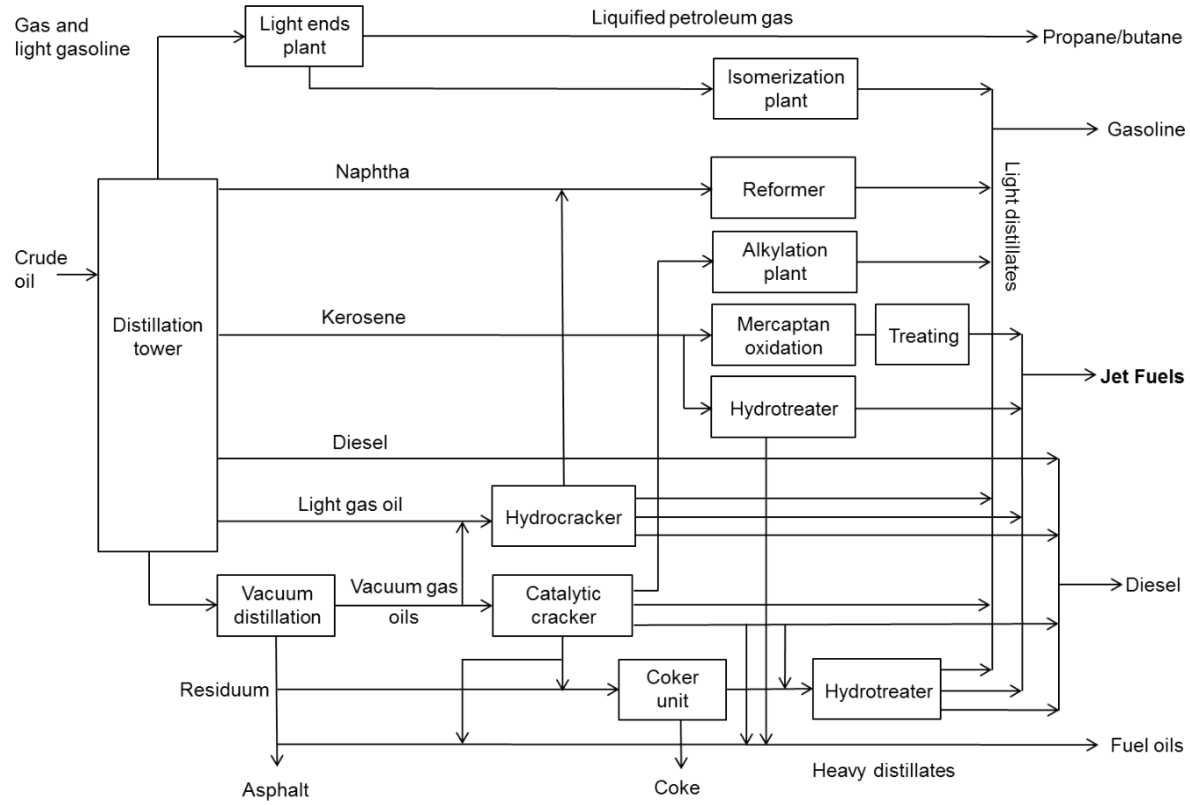
Table 4-1. Chemical Identity of JP-5, JP-8, and Jet A Fuels

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

[a]RTECS 1998
[b]HSDB 2012
[c]IARC 1989
[d]Army 1988
[e]DOD 2013
[f]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.
[g]NTP/NIH 1986
[h]OHM/TADS 1985

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = 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

Figure 4-1. Kerosene/Jet Fuel Processing



Adapted from API 2010a; Chevron 2006

Table 4-2. Compositional Analysis of 14 Samples of Jet A Fuel

Component	Average weight percentage	Minimum weight percentage	Maximum weight percentage
Hydrocarbon types by mass spectrometry ASTM Method D2425			
Paraffins	46.66	32.60	59.10
Monocycloparaffins	26.19	13.80	34.20
Dicycloparaffins	5.89	4.10	8.50
Tricycloparaffins	0.77	0.40	1.40
Benzenes	12.99	9.50	16.50
Indanes/tetralins	4.05	2.50	6.60
C_nH_{2n-10}	0.96	0.60	1.80
Naphthalene	0.44	0.00	1.10
Naphthalenes	1.46	0.90	2.00
C_nH_{2n-14}	0.34	0.20	0.50
C_nH_{2n-16}	0.23	0.00	0.50
C_nH_{2n-18}	0.00	0.00	0.00
Total aromatics	21.18	17.90	27.20
Total olefins	0.00	0.00	0.00
Total paraffins + napthenes	78.82	72.80	82.10
Total aromatics by gas chromatography/mass spectrometry ASTM Method D5769			
Benzene	0.01	0.00	0.02
Toluene	0.14	0.06	0.50
Ethylbenzene	0.15	0.08	0.26
m,p-xylene	0.54	0.24	1.25
1,2-Dimethylbenzene	0.27	0.11	0.51
Isopropylbenzene	0.07	0.05	0.11
Propylbenzene	0.14	0.06	0.25
1-Methyl-3-ethylbenzne	0.50	0.21	1.02
1-Methyl-4-ethylbenzne	0.13	0.04	0.24
1,3,5-Trimethylbenzene	0.25	0.11	0.65
1-Methyl-2-ethylbenzene	0.18	0.02	0.30
1,2,4-Trimethylbenzene	0.94	0.50	1.78
1,2,3-Trimethylbenzene	0.33	0.20	0.43
Indane	0.06	0.00	0.12
Alkyl Indanes	0.61	0.06	1.13
1,4-Diethyl + butylbenzene	0.32	0.11	0.50
1,2-Diethylbenzene	0.18	0.02	0.41
1,2,4,5-Trimethyl benzene	0.11	0.09	0.20
1,2,3,5-Tetramethylbenzene	0.46	0.08	0.72
Total C10 benzenes	1.34	0.08	2.76
Total C11 benzenes	2.88	0.10	4.53
Total C12 benzenes	0.18	0.69	0.34
Naphthalene	0.18	0.07	0.30

Table 4-2. Compositional Analysis of 14 Samples of Jet A Fuel

Component	Average weight percentage	Minimum weight percentage	Maximum weight percentage
2-Methylnaphthalene	0.38	0.18	0.57
1-Methylnaphthalene	0.28	0.13	0.37

Source: API (2010b)

The U.S. military uses two kerosene-based aircraft fuels, JP-5 and JP-8. JP-8 is the military equivalent of Jet A-1; however, it contains a corrosion inhibitor and anti-icing additive that is not required in the ASTM specification of Jet A-1. The primary difference between the two military fuels is that the flash point temperature for JP-5 is higher (60°C) as compared to JP-8 (38°C). The higher flash point for JP-5 is more suitable for safe handling and fueling practices aboard aircraft carriers and this is the primary fuel used by the U.S. Navy (Chevron 2006). An important additive for military fuels is enhanced thermal stability additives. Jet fuels act as a heat sink for modern aircraft engines. They absorb heat from engine oil, hydraulic fluid and air conditioning apparatus (Chevron 2006). Jet fuels used for high performance military aircraft engines have even greater need of thermal stability as compared to commercial aviation fuels. In the late 1990s, the U.S. Air Force began development of an additive to increase the thermal stability of jet fuels. JP-8 fuel containing this additive package is usually referred to as JP-8+100 because this additive increased the thermal stability of the fuel by 100°F; however, this particular additive is not currently approved for use in commercial aircraft fuels (Chevron 2006). Beginning in 2013, the U.S. Air Force began using Jet A (plus additives) rather than JP-8 for continental flight usage in order to save on fuel costs (Air Force 2013).

Potter and Simmons provided general compositional data for JP-5 and JP-8 fuels and these data are provided in Tables 4-3 and 4-4, respectively.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

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

In summary, the composition of Jet A/A-1, JP-5, and JP-8 are very similar. They consist predominantly of C9–C16 hydrocarbons that are a combination of n-paraffins, isoparaffins, naphthenes, and aromatics. The paraffin and napthene fraction typically compose over 70% of the fuels by weight, while the aromatic fraction is ≤25%. Olefins typically comprise <1% of the total. The important differences in the fuels relates to certain physical properties and the inclusion of particular additives to enhance performance. Jet A-1 has a lower maximum freezing point (-47°C) than Jet A (-40°C); JP-8 is the military equivalent to Jet A-1, but contains certain additives that are not required in Jet A-1; and JP-5 is formulated to have a higher flash point temperature (60°C) than JP-8 (38°C).

Table 4-3. Compositional Data for JP-5[a]

Compound	Weight percentage
Alkenes	
Tridecene	0.45
Alkyl aromatic	
m-xylene	0.13
o-xylene	0.090
1,2,4-Trimethylbenzene	0.37
1,2,3,4-Tetramethylbenzene	1.5
1,3-Diethylbenzene	0.61
1,4-Diethylbenzene	0.77
1,2,4-Triethylbenzene	0.72
1-tert-Butyl-3,4,5-trimethylbenzene	0.24
n-Heptylbenzene	0.27
n-Octylbenzene	0.78
1-Ethylpropylbenzene	1.2
Branched paraffins	
3-Methyloctane	0.070
2,4,6-Trimethylheptane	0.070
2-Methyldecane	0.61
4-Methyldecane	0.78
2,6-Dimethyldecane	0.72
2-Methylundecane	1.4
2,6-Dimethylundecane	2.0
Naphthenes	
1,1,3-Trimethylcyclohexane	0.050
1,3,5-Trimethylcyclohexane	0.090
n-Butylcyclohexane	0.90
Phenylcyclohexane	0.82
Heptylcyclohexane	0.99
Diaromatics excluding naphthalenes	
Biphenyl	0.70
n-Paraffins	
n-Octane	0.12
n-Nonane	0.38
n-Decane	1.8
n-Undecane	4.0
n-Dodecane	3.9
n-Tridecane	3.5
n-Tetradecane	2.7
n-Pentadecane	1.7
n-Hexadecane	1.1
n-Heptadecane	0.12

Table 4-3. Compositional Data for JP-5[a]

Compound	Weight percentage
Napthalenes	
Napthalene	0.57
1-Methylnapthalene	1.4
2-Methylnapthalene	1.4
1-Ethylnaphthalene	0.32
2,3-Dimethylnaphthalene	0.46
2,6-Dimethylnaphthalene	1.1

[a]Does not include all JP-5 fuel components.

Source: Potter and Simmons (1998)

Table 4-4. Compositional Data for JP-8[a]

Compound	Weight percentage
Alkenes	
Tridecene	0.73
Alkyl aromatic	
m-Xylene	0.060
o-Xylene	0.060
1,2,3-Trimethylbenzene	0.27
1,2,3,4-Tetramethylbenzene	1.1
1,3-Dimethyl-5-ethylbenzene	0.62
1-Methyl-2-isopropylbenzene	0.56
1,2,4-Triethylbenzene	0.99
1,3,5-Triethylbenzene	0.60
n-Heptylbenzene	0.25
n-Octylbenzene	0.61
1-Ethylpropylbenzene	0.99
Branched paraffins	
3-Methyloctane	0.040
2,4,6-Trimethylheptane	0.070
2-Methyldecane	0.41
2,6-Dimethyldecane	0.66
2-Methylundecane	1.2
2,6-Dimethylundecane	2.1
Naphthenes	
1,1,3-Trimethylcyclohexane	0.060
1,3,5-Trimethylcyclohexane	0.060
1-Methyl-4-ethylcyclohexane	0.10
Propylcyclohexane	0.14
n-Butylcyclohexane	0.74
Hexylxyxlohexane	0.93
Phenylcyclohexane	0.87
Heptylcyclohexane	1.0
Diaromatics excluding naphthalenes	
Biphenyl	0.63
n-Paraffins	
n-Heptane	0.030
n-Octane	0.090
n-Nonane	0.31
n-Decane	1.3
n-Undecane	4.1
n-Dodecane	4.7
n-Tridecane	4.4
n-Tetradecane	3.0

Table 4-4. Compositional Data for JP-8[a]

Compound	Weight percentage
n-Pentadecane	1.6
n-Hexadecane	0.45
n-Heptadecane	0.080
n-Octadecane	0.020
Napthalenes	
Napthalene	1.1
1-Methylnapthalene	1.8
2-Methylnapthalene	1.5
1-Ethylnaphthalene	0.33
2,3-Dimethylnaphthalene	0.36
2,6-Dimethylnaphthalene	1.3

[a]Does not include all JP-8 fuel components.

Source: Potter and Simmons (1998)

Table 4-5. Physical and Chemical Properties of Jet Fuels[a]

Property	JP-5	JP-8	Jet A[b]
Molecular weight[c]	No data	No data	No data
Color	Clear and bright[d]	Clear and bright[d]	Clear
Physical state	Liquid[e]	Liquid[e]	Liquid
Melting point	-46°C[d]	-52°C[d]	-40°C (Jet A); -47°C (Jet A-1)
Boiling point	170°C[f]; 150–290°C[g]	170°C[f]; 150–290°C[g]	145–300°C
Density at 15 °C	0.788–0.845 kg/L[f]	0.775–0.840 kg/L[f]	0.775–0.840 kg/L[h]
Odor	Kerosene-like[i] (kerosene)	Kerosene-like[i] (kerosene)	Kerosene-like[i] (kerosene)
Odor threshold (ppm):	1[j]; 0.082[k] (kerosene)	1[j]; 0.082[k] (kerosene)	0.082[k] (kerosene)
Solubility:			
Water at 20°C	~5 mg/L[e] (kerosene)	12.44 mg/L (unspecified temperature)[b] ~5 mg/L[e] (kerosene)	10.4 mg/L ~5 mg/L[e] (kerosene)
Organic solvents	Miscible with other petroleum solvents[k]	Miscible with other petroleum solvents[k]	Miscible with other petroleum solvents[k]
Partition coefficients:			
Log K_{ow}	3.3–7.06[e] (kerosene)	3.3–7.06[e] (kerosene)	3.3–7.06[e] (kerosene)
Log K_{oc}	$9.6x10^2$–$5.5x10^{6}$[e] (kerosene)	$9.6x10^2$–$5.5x10^{6}$[e] (kerosene)	$9.6x10^2$–$5.5x10^{6}$[e] (kerosene)
Vapor pressure at 21°C	2.25–25.1 mm Hg at 21°C[b] 1.12–26.4 mmHg[e] (kerosene)	2.25–25.1 mm Hg at 21°C[b] 1.12–26.4 mmHg[e](kerosene)	>7.5 mm Hg at 37.8°C
Henry's law constant at 20°C	5.9x10-5–7.4 atm-m^3/mol[e] (kerosene)	5.9x10-5–7.4 atm-m^3/mol[e] (kerosene)	5.9x10-5–7.4 atm-m^3/mol[e] (kerosene)
Autoignition temperature	229°C[j] (kerosene)	229°C[j] (kerosene)	229°C[j] (kerosene)
Flashpoint (minimum)	60°C[d,i]	38°C[d,i]	38°C[g]
Flammability limits (% volume in air)	0.7–5%[j] (kerosene)	0.7–5%[j] (kerosene)	0.7–5%[j] (kerosene)
Conversion factors	No data	No data	No data
Explosive limits	0.7–5%[l] (kerosene)	0.7–5%[l] (kerosene)	0.7–5%[l] (kerosene)

[a]Values listed are specifications required or general characteristics of each class of jet fuels.
[b]API 2010a
[c]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.
[d]DOD 1992
[e]Air Force 1989b
[f]Army 1988
[g]IARC 1989
[h]Chevron 2006
[i]Air Force 1989a
[j]Coast Guard 1985
[k]OHM/TADS 1985
[l]HSDB 2012

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

5.1 PRODUCTION

No information is available in the TRI database on facilities that manufacture or process JP-5, JP-8, and Jet A fuels because these chemicals are not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005).

As discussed in Chapter 4, most jet fuels are derived from petroleum. During the 1970s and 1980s, shale oil had been used to manufacture jet fuels, but this is no longer economically feasible (Chevron 2006). Figure 4-1 provides a general schematic for the straight-run production of jet fuels from crude oil. Heated crude oil is introduced into an atmospheric pressure distillation unit and the liquefied petroleum gasses (propane and butane) are boiled off from the top of the distillation column and eventually recondensed by a condenser unit. Middle distillates such as kerosene and diesel are drawn off the distillation column and treated by various processes that remove or reduce undesirable components before becoming jet fuels (API 2010b; Chevron 2006). The sweetening process removes corrosive mercaptans from the kerosene fraction by the mercapton oxidation (Merox) process in which mercaptans are converted to disulfides using a catalyst and an alkaline solution. The disulfides are noncorrosive and may be left in the final product or removed by additional treatment to lower the sulfur content of the resultant jet fuel. Hydroprocessing employs hydrogen and an appropriate catalyst to remove olefins, sulfur, and nitrogen-containing compounds from the distilled kerosene. Jet fuel manufactured by a particular refinery may be derived exclusively from straight-run processing or it may be a blend of straight-run, hydroprocessed, and/or hydrocracked product (as depicted in Figure 4-1); however, the finished product must meet all of the performance and regulatory requirements of the specific fuel as discussed in Chapter 4.

Concern that diminishing oil supplies could disrupt production of jet fuels from traditional petroleum sources has prompted research into alternative production methods. The Fischer-Tropsch process has been used to develop synthetic jet fuels from feedstocks other than petroleum (Chevron 2006; FAA 2009). In this process, Syngas (synthesis gas), a mixture of carbon monoxide and hydrogen, is reacted with catalysts to produce a variety of hydrocarbons. These hydrocarbons are then blended to produce a highly paraffinic synthetic jet fuel that contains virtually no sulfur, nitrogen, or aromatic compounds. The benefits and disadvantages of producing jet fuels using the Fischer-Tropsch process and other methods compared to traditional manufacturing methods using petroleum feedstock have been reviewed in a

technical report produced by the Rand Corporation and the Massachusetts Institute of Technology (MIT) (FAA 2009).

Domestic production, import, and export data for kerosene is summarized in Tables 5-1 and 5-2. These data were derived from the EPA Inventory Update Reporting (IUR) system (EPA 2010) and the newly developed Chemical Data Reporting (CDR) database (EPA 2012a). According to the CDR website (http://www.epa.gov/oppt/cdr/), approximately $2.07x10^{11}$ pounds (93,725,241 tonnes) of kerosene was manufactured in 2012; however, several companies claimed this information as confidential business information (CBI) and therefore, the actual production volume is expected to be greater than what is indicated in Table 5-1 (EPA 2012a).

While the demand for kerosene has gradually declined over the previous 4 decades, demand for jet fuels has steadily increased. As a result, many refiners have chosen to produce Jet A-1 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 37,636,000 tonnes (293,560,800 barrels) in 1970 to 56,939,000 tonnes (444,124,200 barrels) in 1985 (IARC 1989). In the countries of the Organisation for Economic Cooperation and Development (OECD), production increased from 57,659,000 tonnes (449,740,200 barrels) to 90,280,000 tonnes (704,184,000 barrels) during the same time period (IARC 1989). According to the Department of Energy, the consumption of jet fuels in the United States in 2010 and 2011 was 1.43 and 1.42 million barrels per day, respectively, for an annual consumption rate of 521,950,000 barrels consumed in 2010 and 518,300,000 barrels consumed in 2011 (EIA 2013c). The consumption rate is projected to increase to 1.52 million barrels per day (554,800,000 barrels annually) by 2020, 1.60 million barrels per day (584,000,000 barrels annually) by 2030, and 1.66 million barrels per day (605,900,000 barrels annually) by 2040 (EIA 2013c).

Data regarding the weekly production of jet fuels by U.S. refineries since 2010 are provided in Tables 5-3 (commercial jet fuels) and 5-4 (military jet fuels) from the U.S. Energy Information Administration (EIA 2014a).

5.2 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

Table 5-1. Domestic Production, Import, and Export Volumes of Kerosene in 2012[a]

Domestic manufacturing (pounds)	Imported (pounds)	Volume used	Volume exported	Parent company name	Parent company city
2,400,000,000		0	0	Sunoco, Inc.	Philadelphia
109,000,000,000		109,000,000,000	0	Sunoco, Inc.	Philadelphia
2,530,000,000		0	0	ConocoPhillips Co.	Linden
3,739,372,000		0	0	Motiva Enterprises LLC	Houston
1,055,839,514		1,055,839,514	0	Equilon Enterprises LLC	Houston
2,946,370,260		2,946,370,260	0	Shell Deer Park Refining Limited Partnership	Deer Park
6,442,919,000		0	0	Motiva Enterprises LLC	Houston
	2,945,948,325	N/A	0	Shell Trading US Co.	Houston
1,185,666,446		1,185,666,446	0	Shell Chemical Company LP	Houston
5,537,432,425		0	0	Motiva Enterprise LLC	Houston
389,977,246		389,977,246	0	Hunt Consolidated, Inc.	Dallas
CBI	CBI	CBI	CBI	CBI	CBI
1,600,000,000		400,000,000	0	Western Refining Southwest, Inc.	El Paso
	490,030,931	N/A	0	Citgo Petroleum Corporation	Houston
	141,484	N/A	0	Equilon Enterprises LLC DBA Shell Oil	Houston
66,697,537		0	0	Calumet Specialty Products Partners LP	Princeton
405,477,132		0	0	Calumet Specialty Products Partners LP	Shreveport
25,920,768		0	0	Calumet Specialty Products Partners LP	Indianapolis
66,000,000		62,000,000	0	Citgo Petroleum Corporation	Lemont
2,691,000,000		2,691,000,000	0	Marathon Oil Corporation	Findlay
620,000,000		0	0	ConocoPhillips Co.	Houston
42,000,000		42,000,000	0	Calumet Specialty Products Partners LP	Indianapolis
857,000,000		0	0	Alon USA LP	Dallas
	105,362	105,362	0	United Refining Co.	Warren
CBI	CBI	CBI	CBI	Lyondell Chemical Co.	Houston
2,213,000,000		1,223,000,000	0	Marathon Oil Corporation	Findlay
126,000,000		126,000,000	0	Murphy Oil USA, Inc.	El Dorado
696,175,997		696,175,997	0	PPB Energy	Parsippany
1,511,255,360		1,511,255,360	0	Total Petrochemicals and Refining USA, Inc.	Houston
CBI		CBI	CBI	Exxon Mobil Corporation	Irving
2,698,292		2,698,292	0	Solvchem, Inc.	Pearland
CBI		CBI	CBI	BASF Corporation	Florham Park
2,830,000,000		2,830,000,000	0	Marathon Oil Corporation	Findlay
97,754,939		97,754,939	0	ConocoPhillips Co.	Anchorage
2,000,000,000		2,000,000,000	0	ConocoPhillips Co.	Ferndale
CBI		CBI	CBI	Koch Industries, Inc.	Wichita

Table 5-1. Domestic Production, Import, and Export Volumes of Kerosene in 2012[a]

Domestic manufacturing (pounds)	Imported (pounds)	Volume used	Volume exported	Parent company name	Parent company city
1,500,000,000		0	0	Tesoro Corporation	Kapolei
CBI		CBI	CBI	Exxon Mobil Corporation	Irving
CBI		CBI	CBI	Chalmette Refining LLC	Chalmette
	200,000,000	N/A	0	Chevron Corporation	Houston
CBI		CBI	CBI	Exxon Mobil Corporation	Irving
2,400,000,000		2,400,000,000	0	Chevron Corporation	San Ramon
71,298,667		0	0	Nustar Energy LP	Brooks City-Base
1,359,000,000		1,359,000,000	0	Marathon Oil Corporation	Findlay
410,000,000		77,000,000	0	Tesoro Corporation	Mandan
1,500,000,000		590,000,000	910,000,000	Petrobras America, Inc.	Pasadena
1,313,155,341		1,313,155,341	0	Valero Services, Inc.	San Antonio
549,000,000		549,000,000	0	Marathon Oil Corporation	Findlay
CBI	CBI	CBI	CBI	Innospec, Inc.	Littleton
	1	N/A	0	ConocoPhillips Co.	Houston
	CBI	N/A	0	Ethyl Corporation	Richmond
940,000,000		0	0	Tesoro Corporation	Wilmington
	330,000,000	N/A	0	Tesoro Corporation	San Antonio
CBI		CBI	0	Exxon Mobil Corporation	Irving
2,809,664,659		2,809,664,659	0	Citgo Petroleum Corporation	Corpus Christi
540,000,000		540,000,000	0	Hollyfrontier Corporation	Dallas
CBI	CBI	CBI	CBI	Valero Energy Corporation	San Antonio
1,600,000,000		1,600,000,000	0	Hollyfrontier Corporation	Dallas
CBI	CBI	CBI	CBI	Valero Energy Corporation	San Antonio
CBI		CBI	0	Alon USA LP	Paramount
CBI	CBI	CBI	CBI	Valero Energy Corporation	Texas City
40,000,000		0	0	Marathon Oil Corporation	Findlay
1,300,000,000		1,300,000,000	0	ConocoPhillips Co.	Houston
CBI	CBI	CBI	CBI	BP Products North America, Inc.	Naperville
1,200,000,000		1,200,000,000	0	Tesoro Corporation	San Antonio
575,862,000		0	72,413,000	Astra West Coast Refining, Inc.	Huntington Beach
1,300,000,000		129,930,445	0	Tesoro Corporation	Kenai
870,000,000		660,000,000	0	Tesoro Corporation	San Antonio
CBI		CBI	CBI	Koch Industries Inc.	Wichita
2,539,212,856		2,539,212,856	0	PBF Energy	Paulsboro
	CBI	N/A	CBI	Dorf Ketal Chemicals LLC	Stafford
1,700,000,000		1,700,000,000	0	ConocoPhillips Co.	Houston
720,000,000		718,496,972	0	Delek Us Holdings Inc.	Brentwood
1,356,000,000		1,356,000,000	0	Husky Energy, Inc.	Wilmington
CBI	CBI	CBI	0	Ocean Investments Corp.	Portsmouth
CBI	CBI	CBI	CBI	Premcor Refining Group	San Antonio

Table 5-1. Domestic Production, Import, and Export Volumes of Kerosene in 2012[a]

Domestic manufacturing (pounds)	Imported (pounds)	Volume used	Volume exported	Parent company name	Parent company city
130,000,000		130,000,000	0	Hollyfrontier Corporation	Dallas
CBI	CBI	CBI	CBI	Valero Services, Inc.	San Antonio
998,799,401		0	0	Suncor Energy USA, Inc.	Commerce City
5,100,000,000		0	0	ConocoPhillips Co.	Houston
500,000,000		500,000,000	0	Countrymark	Indianapolis
220,000,000		0	0	Gary-Williams Energy Corporation	Wynnewood
CBI	CBI	CBI	CBI	Hovensa LLC	Christiansted
	CBI	N/A	0	3M Co.	St. Paul
267,994,032		267,994,032	0	Alon USA LP	Dallas
1,100,000,000		0	0	Hollyfrontier Corporation	Dallas
320,000,000		220,000,000	0	Hollyfrontier Corporation	Dallas
CBI	CBI	CBI	CBI	Casey Co.	Long Beach
770,000,000		9,500,000	0	Tesoro Corporation	Salt Lake City
	45,420,783	N/A	0	Lukoil Pan Americas LLC	New York
CBI	CBI	CBI	CBI	The Premcor Refining Group, Inc.	Memphis
2,464,937,141		2,464,937,141	0	PBF Energy	Oregon
6,332,180,492	1,440,978	6,333,621,470	0	Citgo Petroleum Corporation	Houston
1,925,000,000		1,925,000,000	0	Murphy Oil USA, Inc.	El Dorado
66,000,000		36,000,000	0	Hollyfrontier Corporation	Dallas
930,000,000		930,000,000	0	ConocoPhillips Co.	Houston
19,000,000		18,000,000	0	American Refining Group	Bradford
CBI	CBI	CBI	CBI	Valero Services, Inc.	Corpus Christi
CBI	CBI	CBI	CBI	Sinclair Oil Corporation	Salt Lake City
CBI	CBI	CBI	CBI	CBI	CBI
100,000,000		100,000,000	0	Montana Refining Co.	Great Falls
927,477,168		0	0	Transworld Oil	Lake Charles
CBI	CBI	CBI	CBI	CBI	CBI
3,082,443,279		805,012,637	2,277,430,642	ConocoPhillips Co.	Houston
145,475,223		0	0	CVR Refining, LLC	Coffeyville
390,000,000		390,000,000	0	Western Refining Southwest, Inc.	Gallup
120,000,000		120,000,000	0	WRB Refining LP	Houston
162,100,000		0	162,100,000	Black Elk Refining, LLC	Houston
CBI	CBI	CBI	CBI	Valero Ultramar Holdings, Inc.	Ardmore
841,000,000		841,000,000	0	Northern Tier Energy LLC	Ridgefield
CBI	CBI	CBI	CBI	Valero Energy Corporation	San Antonio
1,600,000,000		1600,000,000	0	National Cooperative Refinery Association	McPherson
CBI		CBI	CBI	Exxon Mobil Corporation	Irving
CBI	CBI	CBI	CBI	CBI	CBI

Table 5-1. Domestic Production, Import, and Export Volumes of Kerosene in 2012[a]

Domestic manufacturing (pounds)	Imported (pounds)	Volume used	Volume exported	Parent company name	Parent company city
CBI	CBI	CBI	CBI	Valero Energy Corporation	San Antonio
480,000,000		240,000,000	0	CHS, Inc.	Inver Grove Heights

[a]Data obtained from the EPA Chemical Data Reporting database (EPA 2012a).

CBI = confidential business information

Table 5-2. Non-confidential 2006 Inventory Update Reporting Records by Chemical, Including Manufacturing, Processing, and Use Information for Kerosene (Petroleum); CAS Registry No. 8008-20-6; Aggregated National Production Volume: ≥1 Billion Pounds

Company and site information						
Company	Site	City	State[a]	Manufacture	Import	Site limited
AGE Refining, Inc.	San Antonio	San Antonio	TX	Yes	No	Yes
Alon USA LP	Big Spring Refinery	Big Spring	TX	Yes	No	Yes
American Refining Group, Inc.	American Refining Group, Inc.	Bradford	PA	Yes	No	No
BP America, Inc.	BP, Prudhoe Bay Crude Oil Topping Plant	Prudhoe Bay	AK	Yes	No	No
BP America, Inc.	Los Angeles (Carson) Refinery	Carson	CA	Yes	No	No
BP America, Inc.	Texas City Refinery	Texas City	TX	Yes	No	No
BP America, Inc.	BP Products North America Inc., IST	Warrenville	IL	No	Yes	N/A
BP America, Inc.	Whiting Refinery	Whiting	IN	Yes	No	No
BP America, Inc.	Toledo Refinery	Oregon	OH	Yes	No	No
Big West Oil, LLC	North Salt Lake Refinery	North Salt Lake	UT			
CHS, Inc.	Laurel Refinery	Laurel	MT	Yes	No	No
CITGO Petroleum Corporation	Corporate Office	Houston	TX	No	Yes	N/A
CITGO Petroleum Corporation	CITGO Refining and Chemicals Company East Plant	Corpus Christi	TX	Yes	No	No
CITGO Petroleum Corporation	PDV Midwest Refining, L.L.C., Lemont Refinery (operated by CITGO Petroleum Corporation)	Lemont	IL	Yes	No	No
CITGO Petroleum Corporation	Port Everglades Terminal	Fort Lauderdale	FL	No	Yes	N/A
CITGO Petroleum Corporation	Tampa Terminal	Tampa	FL	No	Yes	N/A
CITGO Petroleum Corporation	Lake Charles Manufacturing Complex	Lake Charles	LA	Yes	No	Yes
CITGO Petroleum Corporation	Linden Terminal	Linden	NJ	No	Yes	N/A

Table 5-2. Non-confidential 2006 Inventory Update Reporting Records by Chemical, Including Manufacturing, Processing, and Use Information for Kerosene (Petroleum); CAS Registry No. 8008-20-6; Aggregated National Production Volume: ≥1 Billion Pounds

Company and site information						
Company	Site	City	State[a]	Manufacture	Import	Site limited
Calumet Lubricants Co., L.P.	Shreveport Refinery	Shreveport	LA	Yes	No	No
Calumet Lubricants Co., L.P.	Princeton Refinery	Princeton	LA	Yes	No	Yes
Calumet Lubricants Co., L.P.	Cotton Valley Refinery	Cotton Valley	LA	Yes	No	Yes
Chalmette Refining LLC	Chalmette Refining LLC	Chalmette	LA	Yes	No	No
Chevron U.S.A., Inc.	Global Supply and Trading	Houston	TX	No	Yes	N/A
Chevron U.S.A., Inc.	El Segundo	El Segundo	CA	Yes	No	Yes
Coffeyville Resources Refining and Marketing, LLC	Coffeyville Resources Refining and Marketing, LLC	Coffeyville	KS	Yes	No	No
ConocoPhillips Company	Ferndale Refinery	Ferndale	WA	Yes	No	Yes
ConocoPhillips Company	Kaparuk River Unit	Anchorage	AK	Yes	No	No
ConocoPhillips Company	Kaparuk River Unit	Anchorage	AK	Yes	No	Yes
ConocoPhillips Company	Los Angeles Refinery Carson Plant	Carson	CA	Yes	No	No
ConocoPhillips Company	Ponca City Refinery	Ponca City	OK	Yes	No	No
ConocoPhillips Company	Sweeny Refinery	Old Ocean	TX	Yes	No	No
ConocoPhillips Company	Lake Charles Refinery	Westlake	LA	Yes	No	No
ConocoPhillips Company	Ferndale Refinery	Ferndale	WA	Yes	No	No
ConocoPhillips Company	Borger Refinery	Borger	TX	Yes	No	No
ConocoPhillips Company	Bayway Refinery	Linden	NJ	Yes	No	No
ConocoPhillips Company	Alliance Refinery	Belle Chasse	LA	Yes	No	No
Countrymark Cooperative, LLP	Refinery	Mt. Vernon	IN	Yes	No	Yes
Diamond Shamrock Refining Co., L.P.	Valero Three Rivers Refinery	Three Rivers	TX	Yes	No	No

Table 5-2. Non-confidential 2006 Inventory Update Reporting Records by Chemical, Including Manufacturing, Processing, and Use Information for Kerosene (Petroleum); CAS Registry No. 8008-20-6; Aggregated National Production Volume: ≥1 Billion Pounds

Company and site information						
Company	Site	City	State[a]	Manufacture	Import	Site limited
Ethyl Corporation	Houston Plant	Pasadena	TX			
Exxon Mobil Corporation	Baton Rouge Refinery	Baton Rouge	LA	Yes	No	No
Exxon Mobil Corporation	Baytown Refinery	Baytown	TX	Yes	No	No
Exxon Mobil Corporation	Billings Refinery	Billings	MT	Yes	No	Yes
ExxonMobil Oil Corporation	Fairfax	Fairfax	VA	No	Yes	N/A
ExxonMobil Oil Corporation	Torrance Refinery	Torrance	CA	Yes	No	No
ExxonMobil Oil Corporation	Beaumont Refinery	Beaumont	TX	Yes	No	No
ExxonMobil Oil Corporation	Joliet Refinery	Channahon	IL	Yes	No	Yes
Flint Hills Resources, Alaska LLC	North Pole Refinery	North Pole	AK	Yes	No	No
Flint Hills Resources, LP	East Plant	Corpus Christi	TX	Yes	No	No
Flint Hills Resources, LP	West Plant	Corpus Christi	TX	Yes	No	No
Frontier El Dorado Refining Company	Frontier El Dorado Refining Company	El Dorado	KS	Yes	No	No
Giant Refining Company	Ciniza	Jamestown	NM	Yes	No	No
Giant Yorktown, Inc.	Refinery	Grafton	VA	Yes	No	No
Glencore Ltd.	Glencore Ltd.	Stamford	CT			
Holly Refining & Marketing Company	Woods Cross Refinery	Woods Cross	UT	Yes	No	No
Hunt Refining Company	Tuscaloosa Refinery	Tuscaloosa	AL	Yes	No	Yes
Irving Oil, Inc.	Irving Oil Terminals Inc. - PADD 1	Portsmouth	NH			
Marathon Oil Corporation	Catlettsburg Refining, LLC	Catlettsburg	KY	Yes	No	No
Marathon Oil Corporation	Garyville	Garyville	LA	Yes	No	No
Marathon Petroleum Company LLC	Minnesota Refining Division	St. Paul Park	MN	Yes	No	No

Table 5-2. Non-confidential 2006 Inventory Update Reporting Records by Chemical, Including Manufacturing, Processing, and Use Information for Kerosene (Petroleum); CAS Registry No. 8008-20-6; Aggregated National Production Volume: ≥1 Billion Pounds

Company and site information						
Company	Site	City	State[a]	Manufacture	Import	Site limited
Marathon Petroleum Company LLC	Michigan Refining Division	Detroit	MI	Yes	No	Yes
Marathon Petroleum Company LLC	Texas Refining Division	Texas City	TX	Yes	No	No
Midland Asphalt Materials Inc.	Tonawanda	Tonawanda	NY	Yes	No	No
Motiva Enterprises, LLC	Port Arthur Refinery	Port Arthur	TX	Yes	No	No
Motiva Enterprises, LLC	Convent Refinery	Convent	LA	Yes	No	No
Motiva Enterprises, LLC	Norco Refinery	Norco	LA	Yes	No	No
Murphy Oil Corporation	Meraux Refinery	Meraux	LA	Yes	No	No
Murphy Oil USA, Inc.	Superior Refinery	Superior	WI	Yes	No	No
Navajo Refining Company, L.P.	Lovington Refinery	Lovington	NM	Yes	No	No
Navajo Refining Company, L.P.	Artesia Refinery	Artesia	NM	Yes	No	No
Paramount Petroleum Corporation	Paramount	Paramount	CA	Yes	No	No
Paramount Petroleum Corporation	Wilibridge Asphalt Facility	Portland	OR	Yes	No	No
Penreco	Karns City	Karns City	PA	Yes	No	No
Premcor USA Inc.	The Premcor Refining Group Inc. DBA Valero Memphis Refinery	Memphis	TN	Yes	No	No
Premcor USA Inc.	Port Arthur Refinery	Port Arthur	TX	Yes	No	No
Safety-Kleen Systems, Inc.	Safety-Kleen Oil Recovery Co.	East Chicago	IN	Yes	No	No
San Juan Refining Company	Giant Refining, Bloomfield	Bloomfield	NM	Yes	No	No
Shell Chemical LP	Mobile Site	Saraland	AL	Yes	No	No
Shell Chemical LP	St. Rose Site	St. Rose	LA	Yes	No	No
Shell Chemical LP	Yabucoa, Inc.	Yabucoa	PR	Yes	No	No
Shell Deer Park Refining Company	Shell Deer Park Refining Company	Deer Park	TX	Yes	No	No

Table 5-2. Non-confidential 2006 Inventory Update Reporting Records by Chemical, Including Manufacturing, Processing, and Use Information for Kerosene (Petroleum); CAS Registry No. 8008-20-6; Aggregated National Production Volume: ≥1 Billion Pounds

Company and site information						
Company	Site	City	State[a]	Manufacture	Import	Site limited
Shell Oil Products US	Los Angeles Refinery	Los Angeles	CA	Yes	No	No
Shell Oil Products US	Puget Sound Refinery	Anacortes	WA	Yes	No	No
Shell Trading (US) Company	Main office	Houston	TX	No	Yes	N/A
Sigmor Corporation	Diamond Shamrock Refining, L.P., Valero McKee Refinery	Sunray	TX	Yes	No	No
Sinclair Refining Company	Casper Refinery	Casper	WY	Yes	No	Yes
Sinclair Refining Company	Tulsa Refining Company	Tulsa	OK	Yes	No	No
Sinclair Wyoming Refining Company	Sinclair Wyoming Refining Company	Sinclair	WY	Yes	No	No
Suncor Energy (U.S.A.) Inc.	Commerce City Refinery	Commerce City	CO	Yes	No	No
Sunoco, Inc.	Tulsa Refinery	Tulsa	OK	Yes	No	No
Tesoro Corporation	Tesoro Alaska Company - Kenai Refinery	Kenai	AK	Yes	No	No
Tesoro Petroleum Corporation	Hawaii Refinery	Kapolei	HI	Yes	No	No
Tesoro Refining and Marketing Company	Anacortes	Anacortes	WA	Yes	No	No
Tesoro Refining and Marketing Company	Golden Eagle Refinery	Martinez	CA	Yes	No	Yes
Tesoro Refining and Marketing Company	Mandan Refinery	Mandan	ND	Yes	No	No
Tesoro Refining and Marketing Company	Salt Lake City Refinery	Salt Lake City	UT	Yes	No	No
Texaco Downstream LLC	Fuel and Marine Marketing LLC	San Ramon	CA	No	Yes	N/A
The Dow Chemical Company	Headquarters	Midland	MI	No	Yes	N/A
Tremco Incorporated	Beachwood	Beachwood	OH	No	Yes	N/A
U.S. Oil and Refining Co.	Tacoma	Tacoma	WA	Yes	No	No

Table 5-2. Non-confidential 2006 Inventory Update Reporting Records by Chemical, Including Manufacturing, Processing, and Use Information for Kerosene (Petroleum); CAS Registry No. 8008-20-6; Aggregated National Production Volume: ≥1 Billion Pounds

Company and site information						
Company	Site	City	State[a]	Manufacture	Import	Site limited
Valero Energy Corporation	Premcor Refining Group Inc.	Delaware City	DE	Yes	No	Yes
Valero Refining Company	Valero Marketing and Supply Company	San Antonio	TX	No	Yes	N/A
Valero Refining Company	Paulsboro Refinery	Paulsboro	NJ	Yes	No	No
Valero Refining Company	Benicia Refinery and Asphalt Plant	Benicia	CA	Yes	No	Yes
Valero Refining Company	Wilmington	Wilmington	CA	Yes	No	Yes
Valero Refining Company	St. Charles Refinery	Norco	LA	Yes	No	No
Valero Unit Investments, LLC	Houston Refinery	Houston	TX	Yes	No	No
Valero Unit Investments, LLC	Texas City Refinery	Texas City	TX	Yes	No	No
Western Refining Company	Western Refining Company	El Paso	TX	Yes	No	No
Wynnewood Refining Company	Wynnewood Refining Company	Wynnewood	OK	Yes	No	No
Wyoming Refining Company	Newcastle Refinery	Newcastle	WY	Yes	No	Yes

[a]Post Office abbreviations used.

CAS = Chemical Abstracts Service; N/A = not applicable

Source: EPA 2010

Table 5-3. Weekly U.S. Production of Commercial Kerosene-Type Jet Fuel (Thousand Barrels per Day) Since 2010[a]

	Week 1		Week 2		Week 3		Week 4		Week 5	
Year-month	End date	Value	End date	Value	End date	Value	End date	Value	End date	Value
2010-January	01/01	1,335	01/08	1,354	01/15	1,334	01/22	1,264	01/29	1,215
2010-February	02/05	1,157	02/12	1,134	02/19	1,159	02/26	1,141		
2010-March	03/05	1,160	03/12	1,171	03/19	1,147	03/26	1,170		
2010-April	04/02	1,190	04/09	1,209	04/16	1,244	04/23	1,289	04/30	1,319
2010-May	05/07	1,328	05/14	1,342	05/21	1,323	05/28	1,296		
2010-June	06/04	1,290	06/11	1,280	06/18	1,279	06/25	1,291		
2010-July	07/02	1,329	07/09	1,353	07/16	1,381	07/23	1,399	07/30	1,382
2010-August	08/06	1,357	08/13	1,339	08/20	1,308	08/27	1,287		
2010-September	09/03	1,285	09/10	1,281	09/17	1,299	09/24	1,282		
2010-October	10/01	1,269	10/08	1,251	10/15	1,223	10/22	1,219	10/29	1,216
2010-November	11/05	1,199	11/12	1,217	11/19	1,249	11/26	1,248		
2010-December	12/03	1,280	12/10	1,270	12/17	1,266	12/24	1,278	12/31	1,287
2011-January	01/07	1,313	01/14	1,297	01/21	1,288	01/28	1,270		
2011-February	02/04	1,243	02/11	1,215	02/18	1,225	02/25	1,217		
2011-March	03/04	1,223	03/11	1,255	03/18	1,243	03/25	1,262		
2011-April	04/01	1,272	04/08	1,277	04/15	1,293	04/22	1,270	04/29	1,272
2011-May	05/06	1,253	05/13	1,250	05/20	1,278	05/27	1,288		
2011-June	06/03	1,331	06/10	1,347	06/17	1,363	06/24	1,396		
2011-July	07/01	1,381	07/08	1,400	07/15	1,415	07/22	1,394	07/29	1,413
2011-August	08/05	1,389	08/12	1,363	08/19	1,346	08/26	1,362		
2011-September	09/02	1,381	09/09	1,389	09/16	1,415	09/23	1,401	09/30	1,419
2011-October	10/07	1,417	10/14	1,372	10/21	1,342	10/28	1,282		
2011-November	11/04	1,238	11/11	1,228	11/18	1,223	11/25	1,217		
2011-December	12/02	1,250	12/09	1,276	12/16	1,290	12/23	1,309	12/30	1,293
2012-January	01/06	1,310	01/13	1,311	01/20	1,324	01/27	1,319		
2012-February	02/03	1,302	02/10	1,292	02/17	1,296	02/24	1,307		
2012-March	03/02	1,293	03/09	1,279	03/16	1,265	03/23	1,247	03/30	1,257
2012-April	04/06	1,271	04/13	1,263	04/20	1,292	04/27	1,291		
2012-May	05/04	1,280	05/11	1,280	05/18	1,270	05/25	1,280		
2012-June	06/01	1,339	06/08	1,378	06/15	1,425	06/22	1,456	06/29	1,456
2012-July	07/06	1,485	07/13	1,460	07/20	1,447	07/27	1,471		
2012-August	08/03	1,486	08/10	1,502	08/17	1,528	08/24	1,504	08/31	1,448
2012-September	09/07	1,404	09/14	1,367	09/21	1,339	09/28	1,357		
2012-October	10/05	1,358	10/12	1,340	10/19	1,326	10/26	1,313		
2012-November	11/02	1,319	11/09	1,302	11/16	1,297	11/23	1,260	11/30	1,244
2012-December	12/07	1,290	12/14	1,308	12/21	1,339	12/28	1,378		
2013-January	01/04	1,374	01/11	1,381	01/18	1,357	01/25	1,318		
2013-February	02/01	1,299	02/08	1,290	02/15	1,302	02/22	1,305		

Table 5-3. Weekly U.S. Production of Commercial Kerosene-Type Jet Fuel (Thousand Barrels per Day) Since 2010[a]

	Week 1		Week 2		Week 3		Week 4		Week 5	
Year-month	End date	Value	End date	Value	End date	Value	End date	Value	End date	Value
2013-March	03/01	1,312	03/08	1,293	03/15	1,300	03/22	1,347	03/29	1,387
2013-April	04/05	1,423	04/12	1,443	04/19	1,429	04/26	1,389		
2013-May	05/03	1,405	05/10	1,408	05/17	1,373	05/24	1,370	05/31	1,350
2013-June	06/07	1,344	06/14	1,385	06/21	1,416	06/28	1,437		
2013-July	07/05	1,461	07/12	1,460	07/19	1,470	07/26	1,479		
2013-August	08/02	1,482	08/09	1,475	08/16	1,478	08/23	1,475	08/30	1,483
2013-September	09/06	1,516	09/13	1,512	09/20	1,489	09/27	1,451		
2013-October	10/04	1,405	10/11	1,371	10/18	1,364	10/25	1,362		
2013-November	11/01	1,368	11/08	1,380	11/15	1,374	11/22	1,385	11/29	1,401
2013-December	12/06	1,436	12/13	1,475	12/20	1,501	12/27	1,527		
2014-January	01/03	1,543	01/10	1,527	01/17	1,495	01/24	1,444	01/31	1,384
2014-February	02/07	1,375	02/14	1,360	02/21	1,369	02/28	1,384		
2014-March	03/07	1,375	03/14	1,365	03/21	1,362	03/28	1,361		
2014-April	04/04	1,378	04/11	1,395	04/18	1,404	04/25	1,418		
2014-May	05/02	1,416	05/09	1,430	05/16	1,429	05/23	1,413	05/30	1,419
2014-June	06/06	1,417	06/13	1,440	06/20	1,433	06/27	1,419		
2014-July	07/04	1,440	07/11	1,457	07/18	1,510		1,548		

[a]Data obtained from EIA (2014a).

Table 5-4. Weekly U.S. Production of Military Kerosene-Type Jet Fuel (Thousand Barrels per Day) Since 2010[a]

	Week 1		Week 2		Week 3		Week 4		Week 5	
Year-month	End date	Value	End date	Value	End date	Value	End date	Value	End date	Value
2010-January	01/01	128	01/08	105	01/15	109	01/22	134	01/29	148
2010-February	02/05	154	02/12	153	02/19	128	02/26	137		
2010-March	03/05	127	03/12	139	03/19	161	03/26	157		
2010-April	04/02	175	04/09	162	04/16	152	04/23	148	04/30	142
2010-May	05/07	144	05/14	136	05/21	143	05/28	147		
2010-June	06/04	142	06/11	147	06/18	143	06/25	142		
2010-July	07/02	149	07/09	143	07/16	151	07/23	153	07/30	153
2010-August	08/06	153	08/13	138	08/20	140	08/27	141		
2010-September	09/03	147	09/10	161	09/17	144	09/24	132		
2010-October	10/01	124	10/08	108	10/15	105	10/22	118	10/29	109
2010-November	11/05	123	11/12	125	11/19	111	11/26	116		
2010-December	12/03	100	12/10	112	12/17	116	12/24	126	12/31	121
2011-January	01/07	117	01/14	107	01/21	102	01/28	114		
2011-February	02/04	113	02/11	122	02/18	116	02/25	110		
2011-March	03/04	118	03/11	121	03/18	139	03/25	154		
2011-April	04/01	147	04/08	159	04/15	147	04/22	135	04/29	146
2011-May	05/06	144	05/13	140	05/20	138	05/27	131		
2011-June	06/03	126	06/10	137	06/17	142	06/24	135		
2011-July	07/01	148	07/08	143	07/15	149	07/22	160	07/29	137
2011-August	08/05	147	08/12	149	08/19	163	08/26	165		
2011-September	09/02	165	09/09	151	09/16	135	09/23	139	09/30	134
2011-October	10/07	136	10/14	132	10/21	134	10/28	136		
2011-November	11/04	136	11/11	135	11/18	132	11/25	133		
2011-December	12/02	129	12/09	128	12/16	127	12/23	122	12/30	134
2012-January	01/06	130	01/13	129	01/20	125	01/27	118		
2012-February	02/03	110	02/10	110	02/17	103	02/24	98		
2012-March	03/02	103	03/09	106	03/16	102	03/23	118	03/30	129
2012-April	04/06	125	04/13	139	04/20	122	04/27	123		
2012-May	05/04	133	05/11	119	05/18	128	05/25	128		
2012-June	06/01	128	06/08	149	06/15	141	06/22	137	06/29	124
2012-July	07/06	121	07/13	139	07/20	132	07/27	140		
2012-August	08/03	127	08/10	126	08/17	126	08/24	115	08/31	113
2012-September	09/07	110	09/14	120	09/21	130	09/28	131		
2012-October	10/05	131	10/12	132	10/19	142	10/26	142		
2012-November	11/02	134	11/09	135	11/16	117	11/23	117	11/30	134
2012-December	12/07	123	12/14	134	12/21	134	12/28	117		
2013-January	01/04	125	01/11	125	01/18	130	01/25	134		
2013-February	02/01	123	02/08	112	02/15	115	02/22	112		

Table 5-4. Weekly U.S. Production of Military Kerosene-Type Jet Fuel (Thousand Barrels per Day) Since 2010[a]

	Week 1		Week 2		Week 3		Week 4		Week 5	
Year-month	End date	Value	End date	Value	End date	Value	End date	Value	End date	Value
2013-March	03/01	108	03/08	110	03/15	92	03/22	81	03/29	82
2013-April	04/05	86	04/12	87	04/19	93	04/26	112		
2013-May	05/03	113	05/10	118	05/17	139	05/24	136	05/31	134
2013-June	06/07	138	06/14	117	06/21	103	06/28	105		
2013-July	07/05	108	07/12	109	07/19	109	07/26	98		
2013-August	08/02	89	08/09	99	08/16	101	08/23	104	08/30	116
2013-September	09/06	104	09/13	105	09/20	108	09/27	103		
2013-October	10/04	106	10/11	102	10/18	93	10/25	81		
2013-November	11/01	81	11/08	89	11/15	94	11/22	98	11/29	102
2013-December	12/06	98	12/13	96	12/20	98	12/27	93		
2014-January	01/03	89	01/10	89	01/17	91	01/24	99	01/31	97
2014-February	02/07	96	02/14	92	02/21	85	02/28	89		
2014-March	03/07	97	03/14	100	03/21	98	03/28	95		
2014-April	04/04	89	04/11	90	04/18	88	04/25	86		
2014-May	05/02	87	05/09	88	05/16	90	05/23	98	05/30	94
2014-June	06/06	82	06/13	82	06/20	81	06/27	91		
2014-July	07/04	100	07/11	99	07/18	94		99		

[a]Data obtained from EIA (2014b).

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). Table 5-1 shows that approximately 2,399,093 tonnes of kerosene (18,712,925 barrels) were imported into the United States in 2012; however, several companies claimed these data as CBI and did not report any import volumes publically. Table 5-5 shows the weekly import volume of kerosene-type jet fuels since 2000 as reported by the U.S. Energy Information Administration (EIA 2014b).

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%. Table 5-1 shows that approximately 1,609,977 tonnes (12,557,821 barrels) of kerosene were exported from the United States in 2012; however, several companies claimed these data as CBI and did not report any export volumes publically. Table 5-6 provides the U.S. exports of kerosene-type jet fuels since 1981 as reported by EIA (2014c).

5.3 USE

Aviation turbine fuels were not used until the 1930s when the first turbojet engine was developed. 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 by the 1960s. JP-1 was the first U.S. specification for jet fuel (AN-F-32A, 1944). JP-1 was a kerosene fuel with a maximum freeze point of -60°C and a minimum flash point of 43°C established for operability and safety (Air Force 1987). The flash and freeze points establish boundaries on the minimum and maximum size, respectively, of the hydrocarbon molecules in jet fuel. As fuel specifications evolved, trading off producibility and cost versus performance and safety, the U.S. Air Force settled on JP-4 (MIL-F-5624A, a gasoline-kerosene mix) in the 1950s–1970s, the Navy has used JP-5 (a minimum 60°C flash point kerosene also listed in MIL-F-5624) shipboard since the 1950s, and commercial aviation has used Jet A/Jet A-1 (ASTM D1655, minimum 38°C flash point) since its rapid growth in the 1960s (Air Force 1987b; Dukek and Winans 1969; Edwards 2003). Heavier losses in JP-4 fueled aircraft in Vietnam (versus JP-5) caused the U.S. Air Force to convert to JP-8 in 1980s. As discussed in Chapter 4, JP-8 is the military equivalent to Jet A-1, but contains additive packages that may not be required for commercial jet fuels. Recent studies in the United States have indicated that use of Jet A with its -40°C maximum freeze point was an acceptable and cost-effective alternative to JP-8, so the Air Force is scheduled to complete the conversion to F-24 (Jet A + the additive package) in 2014 for use in the continental United States (Air Force 2013). Thus, setting aside the military additive package, jet fuels world-wide consist almost entirely of the very similar

Table 5-5. Weekly U.S. Imports of Kerosene-Type Jet Fuel (Thousand Barrels per Day) Since 2000

	Week 1		Week 2		Week 3		Week 4		Week 5	
Year-month	End date	Value	End date	Value	End date	Value	End date	Value	End date	Value
2000-January	01/07	53	01/14	68	01/21	95	01/28	189		
2000-February	02/04	120	02/11	162	02/18	109	02/25	100		
2000-March	03/03	165	03/10	127	03/17	126	03/24	90	03/31	79
2000-April	04/07	77	04/14	113	04/21	109	04/28	106		
2000-May	05/05	149	05/12	76	05/19	103	05/26	163		
2000-June	06/02	134	06/09	141	06/16	131	06/23	104	06/30	142
2000-July	07/07	118	07/14	115	07/21	152	07/28	76		
2000-August	08/04	177	08/11	121	08/18	174	08/25	52		
2000-September	09/01	125	09/08	122	09/15	76	09/22	140	09/29	190
2000-October	10/06	128	10/13	177	10/20	183	10/27	173		
2000-November	11/03	145	11/10	205	11/17	89	11/24	125		
2000-December	12/01	100	12/08	162	12/15	82	12/22	225	12/29	181
2001-January	01/05	250	01/12	133	01/19	250	01/26	220		
2001-February	02/02	238	02/09	192	02/16	231	02/23	221		
2001-March	03/02	116	03/09	237	03/16	188	03/23	155	03/30	91
2001-April	04/06	148	04/13	156	04/20	148	04/27	165		
2001-May	05/04	175	05/11	318	05/18	97	05/25	167		
2001-June	06/01	144	06/08	151	06/15	137	06/22	94	06/29	147
2001-July	07/06	168	07/13	50	07/20	240	07/27	241		
2001-August	08/03	133	08/10	176	08/17	111	08/24	168	08/31	120
2001-September	09/07	117	09/14	212	09/21	69	09/28	120		
2001-October	10/05	42	10/12	155	10/19	130	10/26	49		
2001-November	11/02	36	11/09	174	11/16	88	11/23	71	11/30	57
2001-December	12/07	85	12/14	104	12/21	131	12/28	68		
2002-January	01/04	88	01/11	105	01/18	39	01/25	193		
2002-February	02/01	113	02/08	77	02/15	146	02/22	76		
2002-March	03/01	105	03/08	28	03/15	48	03/22	135	03/29	116
2002-April	04/05	106	04/12	192	04/19	105	04/26	87		
2002-May	05/03	144	05/10	78	05/17	99	05/24	89	05/31	59
2002-June	06/07	153	06/14	127	06/21	105	06/28	104		
2002-July	07/05	73	07/12	89	07/19	53	07/26	104		
2002-August	08/02	69	08/09	124	08/16	29	08/23	166	08/30	59
2002-September	09/06	145	09/13	93	09/20	166	09/27	86		
2002-October	10/04	156	10/11	143	10/18	160	10/25	243		
2002-November	11/01	192	11/08	86	11/15	123	11/22	101	11/29	218
2002-December	12/06	188	12/13	108	12/20	68	12/27	84		
2003-January	01/03	192	01/10	115	01/17	224	01/24	75	01/31	111
2003-February	02/07	82	02/14	48	02/21	110	02/28	107		

Table 5-5. Weekly U.S. Imports of Kerosene-Type Jet Fuel (Thousand Barrels per Day) Since 2000

	Week 1		Week 2		Week 3		Week 4		Week 5	
Year-month	End date	Value	End date	Value	End date	Value	End date	Value	End date	Value
2003-March	03/07	67	03/14	164	03/21	118	03/28	35		
2003-April	04/04	100	04/11	70	04/18	97	04/25	105		
2003-May	05/02	143	05/09	118	05/16	154	05/23	99	05/30	128
2003-June	06/06	165	06/13	53	06/20	128	06/27	216		
2003-July	07/04	174	07/11	168	07/18	175	07/25	187		
2003-August	08/01	156	08/08	216	08/15	118	08/22	68	08/29	153
2003-September	09/05	122	09/12	122	09/19	149	09/26	48		
2003-October	10/03	108	10/10	298	10/17	49	10/24	90	10/31	91
2003-November	11/07	86	11/14	54	11/21	57	11/28	69		
2003-December	12/05	82	12/12	128	12/19	53	12/26	146		
2004-January	01/02	139	01/09	100	01/16	108	01/23	86	01/30	77
2004-February	02/06	65	02/13	136	02/20	86	02/27	57		
2004-March	03/05	101	03/12	131	03/19	37	03/26	68		
2004-April	04/02	30	04/09	59	04/16	81	04/23	121	04/30	59
2004-May	05/07	102	05/14	173	05/21	159	05/28	166		
2004-June	06/04	172	06/11	211	06/18	80	06/25	234		
2004-July	07/02	160	07/09	86	07/16	81	07/23	67	07/30	136
2004-August	08/06	179	08/13	98	08/20	257	08/27	103		
2004-September	09/03	76	09/10	95	09/17	60	09/24	77		
2004-October	10/01	56	10/08	157	10/15	153	10/22	94	10/29	164
2004-November	11/05	51	11/12	235	11/19	163	11/26	105		
2004-December	12/03	110	12/10	121	12/17	119	12/24	85	12/31	198
2005-January	01/07	30	01/14	107	01/21	134	01/28	76		
2005-February	02/04	57	02/11	143	02/18	66	02/25	127		
2005-March	03/04	63	03/11	77	03/18	88	03/25	145		
2005-April	04/01	200	04/08	51	04/15	111	04/22	49	04/29	75
2005-May	05/06	170	05/13	100	05/20	116	05/27	39		
2005-June	06/03	48	06/10	75	06/17	86	06/24	107		
2005-July	07/01	56	07/08	22	07/15	165	07/22	81	07/29	68
2005-August	08/05	80	08/12	39	08/19	31	08/26	165		
2005-September	09/02	105	09/09	143	09/16	185	09/23	191	09/30	159
2005-October	10/07	179	10/14	221	10/21	319	10/28	301		
2005-November	11/04	444	11/11	249	11/18	139	11/25	183		
2005-December	12/02	183	12/09	400	12/16	138	12/23	258	12/30	167
2006-January	01/06	122	01/13	154	01/20	182	01/27	42		
2006-February	02/03	174	02/10	66	02/17	143	02/24	87		
2006-March	03/03	104	03/10	106	03/17	102	03/24	161	03/31	123
2006-April	04/07	70	04/14	254	04/21	190	04/28	262		

Table 5-5. Weekly U.S. Imports of Kerosene-Type Jet Fuel (Thousand Barrels per Day) Since 2000

	Week 1		Week 2		Week 3		Week 4		Week 5	
Year-month	End date	Value	End date	Value	End date	Value	End date	Value	End date	Value
2006-May	05/05	209	05/12	112	05/19	256	05/26	345		
2006-June	06/02	221	06/09	100	06/16	183	06/23	188	06/30	263
2006-July	07/07	225	07/14	172	07/21	167	07/28	224		
2006-August	08/04	205	08/11	300	08/18	399	08/25	266		
2006-September	09/01	119	09/08	124	09/15	292	09/22	158	09/29	200
2006-October	10/06	215	10/13	399	10/20	182	10/27	201		
2006-November	11/03	186	11/10	78	11/17	127	11/24	96		
2006-December	12/01	141	12/08	247	12/15	107	12/22	163	12/29	249
2007-January	01/05	270	01/12	137	01/19	196	01/26	261		
2007-February	02/02	203	02/09	232	02/16	221	02/23	286		
2007-March	03/02	188	03/09	372	03/16	238	03/23	263	03/30	165
2007-April	04/06	294	04/13	336	04/20	297	04/27	233		
2007-May	05/04	324	05/11	264	05/18	162	05/25	294		
2007-June	06/01	237	06/08	312	06/15	191	06/22	230	06/29	293
2007-July	07/06	305	07/13	194	07/20	189	07/27	265		
2007-August	08/03	247	08/10	231	08/17	283	08/24	203	08/31	224
2007-September	09/07	194	09/14	200	09/21	268	09/28	112		
2007-October	10/05	246	10/12	191	10/19	235	10/26	174		
2007-November	11/02	191	11/09	152	11/16	196	11/23	220	11/30	240
2007-December	12/07	146	12/14	190	12/21	153	12/28	135		
2008-January	01/04	166	01/11	85	01/18	56	01/25	182		
2008-February	02/01	209	02/08	157	02/15	71	02/22	132	02/29	87
2008-March	03/07	258	03/14	298	03/21	41	03/28	111		
2008-April	04/04	203	04/11	318	04/18	178	04/25	114		
2008-May	05/02	131	05/09	300	05/16	161	05/23	116	05/30	162
2008-June	06/06	109	06/13	86	06/20	114	06/27	66		
2008-July	07/04	34	07/11	98	07/18	63	07/25	119		
2008-August	08/01	59	08/08	74	08/15	95	08/22	67	08/29	50
2008-September	09/05	26	09/12	79	09/19	68	09/26	145		
2008-October	10/03	151	10/10	73	10/17	85	10/24	38	10/31	136
2008-November	11/07	36	11/14	88	11/21	77	11/28	45		
2008-December	12/05	26	12/12	45	12/19	111	12/26	54		
2009-January	01/02	56	01/09	10	01/16	69	01/23	101	01/30	16
2009-February	02/06	111	02/13	23	02/20	60	02/27	59		
2009-March	03/06	47	03/13	155	03/20	56	03/27	150		
2009-April	04/03	29	04/10	76	04/17	115	04/24	56		
2009-May	05/01	123	05/08	58	05/15	170	05/22	73	05/29	102
2009-June	06/05	67	06/12	51	06/19	98	06/26	61		

Table 5-5. Weekly U.S. Imports of Kerosene-Type Jet Fuel (Thousand Barrels per Day) Since 2000

	Week 1		Week 2		Week 3		Week 4		Week 5	
Year-month	End date	Value	End date	Value	End date	Value	End date	Value	End date	Value
2009-July	07/03	99	07/10	76	07/17	93	07/24	68	07/31	161
2009-August	08/07	76	08/14	67	08/21	98	08/28	112		
2009-September	09/04	93	09/11	85	09/18	123	09/25	115		
2009-October	10/02	93	10/09	89	10/16	74	10/23	107	10/30	86
2009-November	11/06	35	11/13	82	11/20	102	11/27	63		
2009-December	12/04	96	12/11	57	12/18	77	12/25	65		
2010-January	01/01	102	01/08	87	01/15	108	01/22	140	01/29	116
2010-February	02/05	109	02/12	64	02/19	102	02/26	61		
2010-March	03/05	99	03/12	20	03/19	77	03/26	92		
2010-April	04/02	55	04/09	86	04/16	99	04/23	91	04/30	128
2010-May	05/07	67	05/14	36	05/21	67	05/28	86		
2010-June	06/04	64	06/11	62	06/18	51	06/25	54		
2010-July	07/02	118	07/09	59	07/16	78	07/23	86	07/30	65
2010-August	08/06	70	08/13	77	08/20	93	08/27	69		
2010-September	09/03	94	09/10	136	09/17	98	09/24	120		
2010-October	10/01	28	10/08	64	10/15	80	10/22	37	10/29	74
2010-November	11/05	53	11/12	31	11/19	113	11/26	35		
2010-December	12/03	130	12/10	29	12/17	60	12/24	41	12/31	81
2011-January	01/07	79	01/14	63	01/21	16	01/28	127		
2011-February	02/04	61	02/11	61	02/18	24	02/25	51		
2011-March	03/04	16	03/11	14	03/18	27	03/25	101		
2011-April	04/01	64	04/08	68	04/15	79	04/22	128	04/29	54
2011-May	05/06	72	05/13	102	05/20	73	05/27	63		
2011-June	06/03	98	06/10	86	06/17	72	06/24	53		
2011-July	07/01	53	07/08	73	07/15	114	07/22	80	07/29	108
2011-August	08/05	75	08/12	18	08/19	18	08/26	39		
2011-September	09/02	15	09/09	4	09/16	14	09/23	55	09/30	7
2011-October	10/07	86	10/14	48	10/21	45	10/28	32		
2011-November	11/04	116	11/11	58	11/18	49	11/25	79		
2011-December	12/02	29	12/09	10	12/16	9	12/23	39	12/30	36
2012-January	01/06	7	01/13	1	01/20	4	01/27	7		
2012-February	02/03	5	02/10	87	02/17	28	02/24	52		
2012-March	03/02	34	03/09	4	03/16	3	03/23	7	03/30	55
2012-April	04/06	11	04/13	98	04/20	11	04/27	10		
2012-May	05/04	5	05/11	36	05/18	93	05/25	56		
2012-June	06/01	3	06/08	57	06/15	4	06/22	4	06/29	0
2012-July	07/06	3	07/13	2	07/20	52	07/27	59		
2012-August	08/03	33	08/10	57	08/17	33	08/24	105	08/31	95

Table 5-5. Weekly U.S. Imports of Kerosene-Type Jet Fuel (Thousand Barrels per Day) Since 2000

	Week 1		Week 2		Week 3		Week 4		Week 5	
Year-month	End date	Value	End date	Value	End date	Value	End date	Value	End date	Value
2012-September	09/07	73	09/14	142	09/21	35	09/28	113		
2012-October	10/05	16	10/12	111	10/19	153	10/26	136		
2012-November	11/02	16	11/09	51	11/16	5	11/23	25	11/30	26
2012-December	12/07	53	12/14	25	12/21	0	12/28	0		
2013-January	01/04	63	01/11	0	01/18	2	01/25	96		
2013-February	02/01	54	02/08	47	02/15	45	02/22	77		
2013-March	03/01	23	03/08	34	03/15	44	03/22	4	03/29	0
2013-April	04/05	0	04/12	83	04/19	37	04/26	0		
2013-May	05/03	21	05/10	35	05/17	35	05/24	46	05/31	136
2013-June	06/07	76	06/14	70	06/21	108	06/28	73		
2013-July	07/05	47	07/12	99	07/19	46	07/26	6		
2013-August	08/02	63	08/09	193	08/16	55	08/23	117	08/30	148
2013-September	09/06	85	09/13	67	09/20	96	09/27	73		
2013-October	10/04	45	10/11	50	10/18	52	10/25	80		
2013-November	11/01	53	11/08	55	11/15	77	11/22	123	11/29	18
2013-December	12/06	25	12/13	63	12/20	46	12/27	31		
2014-January	01/03	61	01/10	48	01/17	59	01/24	77	01/31	16
2014-February	02/07	98	02/14	94	02/21	58	02/28	10		
2014-March	03/07	84	03/14	8	03/21	96	03/28	107		
2014-April	04/04	129	04/11	218	04/18	130	04/25	15		
2014-May	05/02	124	05/09	73	05/16	78	05/23	137	05/30	34
2014-June	06/06	92	06/13	28	06/20	196	06/27	154		
2014-July	07/04	103	07/11	71	07/18	122				

[a]Data obtained from EIA (2014b).

Table 5-6. Monthly U.S. Exports of Kerosene-Type Jet Fuel (Thousand Barrels per Month) Since 1981[a]

Year	January	February	March	April	May	June	July	August	September	October	November	December
1981	28	21	10	18	16	12	19	22	20	14	23	222
1982	255	245	80	44	27	38	32	32	41	35	269	692
1983	272	223	27	17	40	21	37	193	270	24	373	458
1984	318	68	21	148	22	191	306	52	27	158	329	738
1985	79	624	182	149	147	102	106	660	133	773	848	559
1986	1,188	429	333	371	428	184	300	138	420	778	668	626
1987	1,404	565	214	121	117	146	139	74	1,029	1,086	1,336	2,287
1988	2,524	974	1,624	392	119	463	107	440	265	54	271	2,470
1989	2,297	566	19	477	36	35	287	467	1,018	849	1,183	1,309
1990	668	1,393	515	331	238	207	302	927	1,349	2,246	4,218	1,854
1991	2,265	4,393	1,197	758	1,047	391	840	326	295	1,342	137	1,273
1992	1,375	1,168	194	368	202	583	1,623	500	333	1,266	1,125	3,439
1993	2,976	451	2,575	1,833	1,460	1,035	1,799	1,017	414	396	765	1,063
1994	561	722	445	71	282	305	340	311	784	541	524	1,002
1995	766	545	528	138	221	311	572	535	587	1,774	387	1,940
1996	3,443	1,929	1,543	333	414	325	837	1,040	1,525	821	1,340	3,418
1997	2,407	635	342	621	275	1,146	1,004	819	471	1,214	1,325	2,429
1998	1,137	710	899	957	702	737	796	225	751	663	722	506
1999	785	225	697	736	997	792	1,073	246	995	800	1,825	1,585
2000	408	503	1,030	1,111	1,095	798	641	583	1,008	1,289	1,902	1,221
2001	839	437	1,262	506	513	544	722	743	620	966	1,917	1,426
2002	264	1,130	62	38	94	29	67	50	424	39	351	447
2003	1,125	519	1,067	1,018	603	200	373	214	588	883	295	549
2004	678	556	1,211	571	916	850	318	1,600	2,314	1,566	1,641	2,579
2005	878	1,875	2,235	2,927	3,575	2,040	1,428	1,706	469	351	1,068	651
2006	742	712	1,105	1,263	1,005	1,005	1,050	1,518	1,789	1,724	1,481	1,477
2007	1,213	870	1,631	1,024	602	754	1,641	826	1,257	1,017	2,750	1,427
2008	1,836	1,956	1,984	959	2,346	2,590	2,899	1,910	860	1,876	1,547	1,627
2009	2,379	1,171	1,899	1,981	2,656	1,270	1,505	1,688	1,901	2,949	2,226	3,605
2010	3,514	1,852	2,173	2,281	2,441	1,701	2,539	2,630	2,426	1,973	3,082	4,141
2011	3,906	2,786	2,715	3,059	1,733	2,221	3,390	2,806	3,089	2,419	3,173	4,027
2012	3,562	3,650	3,090	2,697	3,864	4,562	4,390	3,410	3,920	4,637	4,801	5,874
2013	5,014	3,188	4,093	4,129	4,150	5,407	4,938	6,020	4,217	4,304	6,419	6,262
2014	4,268	4,058	4,322	3,414								

[a]Data obtained from EIA (2014c).

Jet A and Jet A-1, which essentially only differ in freeze point. The composition of these two fuels is very similar, as can be seen in fuel property collections such as the World Fuel Sampling Program (Hadaller and Johnson 2006) and the annual Petroleum Quality Information Service (PQIS) reports by DLA-Energy. For example, in 2012, the PQIS database reported on thousands of samples of Jet A, JP-8, and Jet A-1. The weighted mean freeze points of Jet A/JP-8/Jet A-1 were -49.8, -51.3, and -52.7°C, respectively—much smaller variations than those present within each class of itself. The weighted mean aromatic content of the three fuels were 17.3, 17.1, and 17.6 vol%, respectively—again, much smaller variations than seen within each fuel. Thus, for all intents and purposes, Jet A, JP-8, F-24, and Jet A-1 can be treated as the same fuel in terms of composition and fuel properties, aside from the presence of the military additive package in JP-8 and F-24.

5.4 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 Jet A, 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 (IRPTC 1985). Regulations governing the treatment and disposal of wastes containing JP-5, JP-8, and Jet A fuels are detailed in Chapter 7.

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6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

JP-5, JP-8, and Jet A fuels have not been identified in any of the 1,832 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2015a). However, the number of sites evaluated for JP-5, JP-8, and Jet A fuels is not known.

JP-5, JP-8, and Jet A fuels 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, JP-8, and Jet A fuels 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 1,076,518 employees (including 96,255 females) were exposed to kerosene, a primary component of JP-5, JP-8, and Jet A fuels, 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, JP-8, and Jet A fuels include those involved in jet fuel manufacturing or refueling operations, aircraft and fuel tank

maintenance, or using JP-8 in military vehicles or as fuel heating or lighting sources; populations near an area where Jet A, 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). The general population is unlikely to be exposed to jet fuels, and any exposure that does occur is most likely to be limited to populations living on or near a refinery producing these and other substances, airports, or military installation where these fuels are utilized. Unintentional exposure to JP-5, JP-8, and Jet A fuels may occur as a result of groundwater contamination from accidental spills or contact with soils that have been contaminated with jet fuels. Since kerosene is a substance still used as a fuel for cooking and heating, it is expected that members of the general population who use things such as kerosene heaters or lamps may be exposed through dermal and inhalation routes.

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

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). Jet A and Jet A-1 are used as civilian aviation fuels, and therefore, accidental releases could potentially occur at production (refineries) or storage (e.g., airport) facilities.

Releases of Jet A, 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 2011 TRI (EPA 2005).

6.2.1 Air

There is no information on releases of JP-5, JP-8, and Jet A fuels to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

JP-5, JP-8, and Jet A fuels 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 civilian or military aircraft (Air Force 1981a; NIOSH 1989). Releases into the air may also occur as a result of volatilization of these fuels 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.

6.2.2 Water

There is no information on releases of JP-5, JP-8, and Jet A fuels to the water from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

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 1976–1977 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 fuels including JP-5 (Arthur et al. 1992). Widespread contamination of groundwater at the Diego Garcia Navy Support Facility has been reported after several major releases of JP-5 fuel from 1991 to 1998 (Hansen 1999). From 1996 to 1998, over 70,000 gallons of JP-5 fuel were recovered from contaminated groundwater using a vacuum-enhanced skimming technique that removes fuel floating at the surface of the water table.

On October 16, 1982, a crack in a petroleum pipeline near Ebensburg, Pennsylvania, released an estimated 1,310 barrels of "aviation kerosene" into a stream (Guiney et al. 1987a, 1987b). Kerosene and

other petroleum products were released by accidental spills and discharges into Newark Bay and its major tributaries. From 1986 to 1991, about 306 gallons of kerosene were released to Newark Bay or its tributaries (Crawford et al. 1995).

6.2.3 Soil

There is no information on releases of JP-5, JP-8, and Jet A fuels to the soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

JP-5, JP-8, and Jet A fuels 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 >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).

On November 27, 2001, a pipeline ruptured and released approximately 2,500 barrels of JP-8 into a drainage system that ultimately leads to a nature preserve near Vidor, Texas (Texas Commission of Environmental Quality 2004). The spill resulted in contamination of the Neches River and various managed pasture lands and hardwood forests.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

The transport and dispersion of JP-5, JP-8, and Jet A fuels 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 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, JP-8, and Jet A fuels 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), cycloparaffins (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, 2013). 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, 2013; 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 in Table 6-1 (Coleman et al. 1984).

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,

Table 6-1. Analysis of Water-Soluble Fraction of Kerosene

		Water-soluble fraction[b]	
Kerosene	Whole product[a]	0.5 Hours	17 Hours
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

[a]Estimated weight percent
[b]Estimated weight percent of constituents dissolved in water after 0.5 or 17 hours of incubation

Source: Coleman et al. 1984

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 components 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; 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. 1990). Movement of kerosene through three grades of sand was affected mainly by volatilization of the C9–C13 components; the volatilization of specific kerosene components was generally inversely related to their carbon number (Galin et al. 1990).

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 3 to 4 orders of magnitude greater compared with water (EPA 1984).

Klein and Jenkins (1983) exposed flagfish and rainbow trout to WSF of JP-8 in static acute bioassays and continuous-flow bioassays. 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 of 2.2). Adult flagfish exposed to 2.54 mg/L, for 14 days yielded a BCF of 130 (log value of 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 63–112 (log value of 1.8–2.1) calculated for rainbow trout indicates that the WSF of JP-8 does not concentrate as readily in this species.

6.3.2 Transformation and Degradation

6.3.2.1 Air

No studies on the transformation or degradation of JP-5, JP-8, and Jet A fuels 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 1995, 2007a, 2007b, 2015b). The photooxidation half-life range for a group of representative chemicals of kerosene, JP-5, and JP-8 was reported as 0.2–1.1 days (API 2010a). 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 1981b, 1982b). Reactions of JP-4

produce large amounts of aerosol material (Air Force 1981b), and it should be noted that JP4 has a considerable gasoline component compared to straight kerosene.

6.3.2.2 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/minute for 4 days was inhibited by all concentrations of JP-8 tested (0.01, 0.1, 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 at the concentrations tested, which may severely inhibit microbial activity (Dean-Ross et al. 1992).

Microorganisms readily able to degrade hydrocarbons were isolated from 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 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).

Kerosene achieved 58.6% of its theoretical biochemical oxygen demand (BOD) after 28 days using an activated sludge inoculum obtained from a municipal waste water treatment plant and the manometric respirometry test (OECD 301F). It was classified as not readily biodegradable, but was inherently biodegradable since significant degradation did occur (API 2010a). Two distillate fuels with similar composition to JP-5 and JP-8, a low sulfur diesel fuel and a Nigerian diesel fuel, achieved 60 and 57.5% of their theoretical BOD within 28 days using an activated sludge and the manometric respirometry (OECD 301F) test, and an aviation turbine fuel (Chemical Abstracts Service Registry Number not stated) was degraded up to 46% within 10 days in fresh water amended with nutrient salts (nitrogen and phosphorous) using a study method that appears to be similar to the closed bottle test (OECD 301D) (API 2010a). The degradation rates were 53 and 2% after 10 days using seawater with and without the nutrient amendments, respectively. Over 99% removal of the hydrocarbon fraction of kerosene type aviation fuels (Jet A, Jet A-1, and JP-8) in water-soluble fractions were observed using mixed microbial cultures isolated from aviation fuel contaminated groundwater in a chemostat culture apparatus over a 113-hour incubation period (API 2010a). These study results suggest that many of the components of these mixtures are quickly degraded and are not expected to be persistent in the environment.

6.3.2.3 Sediment and Soil

Ample evidence exists to indicate that many of the components of kerosene, JP-5, JP-8, and Jet A fuels 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 and the degree of branching. 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 (CO2) 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).

The environmental fate of hydrocarbons present in kerosene was studied following a pipeline rupture that contaminated 1.5 hectares of a New Jersey wheat field with kerosene (Dibble and Barth 1979). Hydrocarbon levels were measured in the upper 30 cm of the soil and the 30–45 cm soil core over a 2-year period. After 6 months, the hydrocarbon content began to decrease in the upper 30 cm of soil and at 21 months, the hydrocarbon content was reduced to trace amounts as volatilization and biodegradation removed the hydrocarbons from the soil surface. However, hydrocarbons associated with the kerosene spill were still detected at soil depths of 30–45 cm. The disappearance rate was strongly correlated with the monthly average temperatures. The highest disappearance rates occurred during the warmer summer months but were markedly slower in winter as both volatilization and aerobic biodegradation are attenuated by colder temperatures. 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 species were able to degrade kerosene to a greater extent than were Enterobacter species with stationary phases occurring after 10 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 7 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).

A study was conducted to investigate the loss of JP-8 in soil with the presence of vegetation (Karthikeyan et al. 1999). A biodegradation unit consisting of a sandy soil (82–90% sand, 8–16% silt, 2% clay, and 0.6–1.1 % organic matter) that had previously been contaminated with toluene, phenol, trichloroethylene (TCE), and trichloroethane (TCA) was used to grow alfalfa plants. JP-8 was added to different parts of the biodegradation chamber at depths ranging from 10 to 30 cm and the system was irrigated with water. The overall average level was about 1,700 mg JP-8 per kg of soil at the start of the experiment. Approximately 3 months following the initial application of JP-8 to the system, the total petroleum hydrocarbon (TPH) levels had decreased to about 215 mg/kg (0–10 cm), 1,249 mg/kg (10–20 cm), and 405 mg/kg (20–30 cm) at the front location of the test system. Concentrations at the back location were significantly lower. Experiments conducted on air-dried soils used as sterile controls suggested that volatilization could account for up to about 52% of the losses from these experiments; however, biodegradation was also considered a significant environmental fate process.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to JP-5, JP-8, and Jet A fuels depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of JP-5, JP-8, and Jet A fuels in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on JP-5, JP-8, and Jet A fuel 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, JP-8, and Jet A fuels in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Components of jet fuels can enter the atmosphere through evaporation from spills and leaks, vaporization during fueling operations, fuel jettisoning, and burning in engines. In a "third generation closed aircraft shelter," which has approximately 3 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 <22 mg/m^3 (Air Force 1981a). 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.

6.4.2 Water

No data were located that discussed specific levels of JP-5, JP-8, and Jet A fuels 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).

6.4.3 Sediment 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). Storage and aircraft refueling operations at research facilities such as Scott Base have resulted in jet fuel contamination of soils in the Ross Dependency, Antarctica (Aislabie et al. 1998). TPH levels in contaminated soils of the Ross Dependency ranged from <2 to 17,488 μg/g, with the highest levels observed near leaking pipelines carrying JP-8 and other fuel leak locations near storage and re-fueling areas. The hydrocarbon profile in these contaminated soils consisted of C_9–C_{14} alkanes, C_2–C_4 benzenes, naphthalene, and methyl naphthalene. Quantitative amounts collected from soil samples at Scott Base are shown in Table 6-2.

Concentrations of kerosene-range hydrocarbons in sediment collected one month after an aviation kerosene leaked into a trout stream were reported as "saturated" (Guiney et al. 1987b). Approximately 14 months after the leak, one site still had kerosene-hydrocarbon sediment levels of 18.0±10.8 ppm and a second site had a mean concentration of 9.3±9.0 ppm, while a control site had levels of <2.0 ppm. Kerosene-hydrocarbon sediment levels returned to normal levels in the stream 21 months after the spill.

TPH levels were measured in soil samples located at the Dobbins Air Force Base located in Marietta, Georgia (Reed and Sterner 2002). This facility had a fuel farm that contained eight 50,000-gallon above-ground storage tanks used to store and distribute JP-4, JP-5, and JP-8 from the mid-1950s through 1993. TPH levels at depths of 1–2 feet below the surface ranged from 517 to 2,239 mg/kg in four out of eight grab samples of soil collected in 1997. Xylene levels ranged from 0.026 to 0.70 mg/kg; however, other common constituents of JP-5 and JP-8 such as benzene, toluene, and ethylbenzene were not detected in the 1997 preliminary sampling. Sampling conducted in 2001 at soil depths 1–8.5 feet below the surface had detectable benzene levels of 1.3–31 mg/kg and TPH-gasoline range organics ranged from 1 to 3,400 mg/kg, while TPH-diesel range organics ranged from 7.8 to 9,800 mg/kg (Reed and Sterner 2002). TPH levels in soil samples collected at the site of a Harrier jet fueled by JP-8 that crashed near Wright-Patterson Air Force Base, Ohio ranged from 389 to 11,657 mg/kg and from 3,100 to 8,500 mg/kg for samples collected on two consecutive days and analyzed by two different analytical methods (Merrill 1998). Soil samples collected at Misawa Air Base, Japan in 1998 had TPH levels (total aliphatics and aromatics) ranging from 703 to 11,938 mg/kg at three locations where jet fuels had been stored (Vermulen et al. 1998).

Table 6-2. Hydrocarbon Levels (µg/g) from Jet Fuels in Soil Samples from Scott Base, Antarctica

Hydrocarbon	1	2	3	4	5	6
C9	123	<2	<2	486	1,220	50
C10	383	623	<2	1,740	3,570	163
C11	663	543	263	2,170	4,176	246
C12	446	1,570	554	1,780	3,490	250
C13	240	1,120	653	1,016	1,763	166
C14	<2	900	443	493	920	63
C2-benzenes	772	<2	<2	<2	<2	<2
C3-benzenes	1,338	1,825	<2	360	<2	<2
C4-benzenes	818	2,009	<2	836	<2	<2
Naphthalene	190	773	<2	<2	<2	<2
C1-Napthalene	196	1,076	<2	<2	<2	<2

Source: Aislabie et al. 1998

6.4.4 Other Environmental Media

No data were located that discussed specific levels of JP-5 or JP-8 in other environmental media such as food or 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).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure of the general population to JP-5,JP-8, and Jet A fuels is most likely to be limited to populations living on or near a military installation where JP-5 or JP-8 are utilized or near commercial airports using Jet A fuel. 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. Atmospheric exposure may occur from fuel leakage, spillage, engine cold starts, and high-altitude aircraft fuel jettisoning (Ritchie et al. 2003). Occupational exposure will occur in individuals involved in the production of JP-5, JP-8, or Jet A fuels; fueling and defueling aircraft; cleaning up spills and leaks of jet fuel; and aircraft and fuel tank maintenance. It was reported that over 1 million U.S. military and civilian personnel are occupationally exposed to JP-8, JP-8 + 100, JP-5, or to the civil aviation equivalents, Jet A or Jet A-1 annually (Ritchie et al. 2003). Exposure occurs via four primary scenarios: (1) direct dermal contact with raw fuel and/or aerosols; (2) secondary dermal contact with clothing or other items such as gloves that are contaminated by the fuel; (3) inhalation exposure to fuel or exhaust; or (4) oral exposure to aerosol or to fuel contaminated food or water. In addition to aircraft fueling applications, JP-8 is used for fueling land vehicles and equipment, fueling of heaters and lighting sources, as a coolant in aircraft, combat obscurant, to suppress environmental sand or dust, decontaminate military vehicles and equipment, and as a carrier for herbicide applications (Ritchie et al. 2003).

Because jet fuels such as JP-5, JP-8, and Jet A are complex mixtures of hundreds of aliphatic and aromatic hydrocarbons, exposure to JP-5, JP-8, and Jet A is typically monitored by measuring THCs and certain aromatic components such as benzene, toluene, ethylbenzene, xylenes, and naphthalene in air or expired breath with the knowledge that the levels of these substances may also arise from sources other than jet fuels. Members of the Air National Guard at the Warfield Air National Guard Base in Essex, Maryland were monitored for exposure to JP-8 during normal working hours from August to October

2001 (Tu et al. 2004). Pre-work concentrations of JP-8 constituents in exhaled breath ranged from below the detection limits to 7.6 mg/m^3 and post-work samples ranged from 0.2 to 11.5 mg/m^3; an increase in postwork levels was only found in fuel cell workers and fuel specialists with the greatest change occurring in the fuel cell workers. A control group of 18 nonsmoking, unexposed subjects living in an urban environment had exhaled breath concentrations of 0.30–2.13 mg/m^3 (pre-work) and 0.21–2.28 mg/m^3 (post-work). Merchant-Borna et al. (2012) examined 73 U.S. Air Force personnel at three different bases and monitored their exposure to JP-8 constituents. They categorized the individuals at these bases into low- and high-exposure groups based upon expected exposure scenarios given their job descriptions. The high-exposure group primarily consisted of fuel system workers involved in the removal, repair, inspection, and modification of aircraft fuel systems; the low-exposure group primarily consisted of workers with intermittent or low-no exposure employed in fuel distribution or maintenance, aircraft inspection and maintenance, and administrative/clerical office work. The geometric mean 8-hour time-weighted average (TWA) concentration of JP-8 constituents (THC, benzene, toluene, ethylbenzene, xylene, and naphthalene) in personal air samples were significantly higher in the high-exposure group as compared to the low-exposure group ($p<0.0001$), with the exception of toluene. The geometric mean 8-hour TWAs for THC were 0.52 mg/m^3 (range 0.24–22.01 mg/m^3) and 2.64 mg/m^3 (range 0.24–73.93 mg/m^3) for the low and high exposure groups, respectively (Merchant-Borna et al. 2012; Proctor et al. 2011). The geometric mean 8-hour TWAs for benzene, ethylbenzene, and naphthalene were 0.88 µg/m^3 (range 0.2–250 µg/m^3), 0.72 µg/m^3 (range 0.1–224 µg/m^3), and 0.37µg/m^3 (range 0.2–11 µg/m^3), respectively, in the low-exposure group, and 1.98 µg/m^3 (range 0.2–99 µg/m^3), 5.57 µg/m^3 (range 0.2–390 µg/m^3), and 2.25µg/m^3 (range 0.2–55 µg/m^3), respectively, in the high-exposure group. These results are consistent with the findings of Maule et al. (2013) who examined breathing zone levels of Air Force personnel similarly assigned to high- and low-exposure groups. The geometric mean work-shift THC concentration of high-exposure personnel was reported as 4.4 mg/m^3, while that of the low-exposure group was 0.9 mg/m^3. A study of fuel cell maintenance workers reported geometric mean breathing zone naphthalene levels of 614 mg/m^3 (Chao et al. 2006). The work-shift naphthalene geometric means were 4.8 and 0.7 µg/m^3 for the high- and low-exposure groups, respectively. Egeghy et al. (2003) measured levels of benzene and naphthalene in the air and breath of Air Force personnel exposed to JP-8. Based upon job function, personnel were pre-assigned to high- (fuel maintenance), moderate- (fuel handling, distribution, recovery, and testing), and low- (jobs with minimal jet fuel exposure) exposure groups. Levels of naphthalene in both air and breath samples were highest for personnel assigned to the high-exposure category and there was little overlap in air levels among workers assigned to the high-, moderate-, and low-exposure groups. Benzene levels were also greater in air and breath samples of workers assigned to the high-exposure category; however, there was substantial overlap

in air levels for each category, suggesting that sources other than JP-8 (e.g., smoking or gasoline exhaust) could be accounting for some of the benzene exposure among these personnel (Egeghy et al. 2003). Even so, the authors noted that benzene levels exceeded the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) of 1.6 mg/m^3 in 5 and 15% of the air concentrations of the moderate- and high-exposure groups, respectively. Benzene and naphthalene levels in personal air were also considerably greater in this study (485 µg/m^3 for naphthalene in the high exposure category and 252 µg/m^3 for benzene in the high-exposure category) as compared to the studies of Merchant-Borna et al. (2012) and Maule et al. (2013). The elevated levels in the Egeghy et al. (2003) study may be due to the fact that personnel were actively monitored while working in tanks and the use of fire suppression foam in this study, which increases exposure (Merchant-Borna et al. 2012).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children are expected to be exposed to JP-5, JP-8, and Jet A fuels by the same routes that affect general population adults; however, barring an accidental spill near their residence, it is unlikely that children will be exposed to significant levels of these fuels as they are primarily used in the aviation industry and the highest exposure levels are expected to occur for workers and military personnel involved in aviation fueling procedures or the production of kerosene-based fuels. Children residing on or near military bases where JP-8 and JP-5 are used may experience a slightly higher level of exposure than children of the general population.

As mentioned in Section 3.7, Children's Susceptibility, exposure to kerosene via ingestion is one of the most common forms of acute childhood poisoning in many developing countries, since kerosene is used for cooking, heating, and lightning and is usually stored in containers and places easily accessible to children.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Military or civilian workers involved in fueling and defueling operations may be exposed to higher levels of JP-5, JP-8, and Jet A fuels than members of the general population (Air Force 1981a; Merchant-Borna et al. 2012; Tu et al. 2004). Maintenance workers who monitor jet fuel storage tanks may be exposed to components of these fuels 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 (Chao et al. 2005; NIOSH 1989). The military also uses JP-8 in ground vehicles, generators, cooking stoves, and tent heater; workers involved in fueling and maintaining this equipment may also be exposed to higher levels. 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.

6.8 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, JP-8, and Jet A fuels is available. Where adequate information is not available, ATSDR, in conjunction with 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, JP-8, and Jet A fuels.

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.

6.8.1 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. Additional information on the identification of the compounds used as additives would be useful in assessing the environmental fate of jet fuels. 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 1995, 2007a, 2007b, 2015b).

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 substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2011, became available in November of 2013. This database is 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). Production, consumption, import, and export volumes are available for kerosene and jet fuels (EIA 2013c; EPA 2012a). Further information on the production volumes for each specific 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, JP-8, and Jet A fuels 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, JP-8, and Jet A fuels 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, JP-8, and Jet A fuels (e.g., benzene, toluene, xylene, and PAHs) are presented in the ATSDR toxicological profiles for these chemicals (ATSDR 1995, 2007a, 2007b, 2015b). Information on light- and chemical-mediated reactions of jet fuel components would aid in determining the fate of JP-5, JP-8, and Jet A fuels in soil and water. More information on the fate of individual components of these fuels under varying environmental conditions, including the interaction of JP-5, JP-8, and Jet A fuels 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, JP-8, and Jet A fuels 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 1995, 2007a, 2007b, 2015b). 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, JP-8, and Jet A fuels 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 1995, 2007a, 2007b, 2015b). 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, JP-8, and Jet A fuels in contaminated media at hazardous waste sites are needed so that the information obtained on levels of JP-5, JP-8, and Jet A fuels in the environment can be used in combination with the known body burden of JP-5, JP-8, and Jet A fuels 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 1981a). Very little information is available for JP-5, JP-8, and Jet A fuels 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, JP-8, and Jet A fuels in contaminated media at hazardous waste sites are needed so that the information obtained on levels of these fuels in the environment can be used in combination with the known body burdens of JP-5, JP-8, and Jet A fuels 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, JP-8, and Jet A fuels 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 military 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). Although there are studies assessing the exposure levels of these groups (Maule et al. 2013; Merchant-Borna et al. 2012; Tu et al. 2004), further information is needed to assess the continuing levels of exposure for these populations. This information is necessary for assessing the need to conduct health studies on these populations.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Unless an accidental spill occurs near their residence, it is unlikely that children will be exposed to JP-5, JP-8, and Jet A fuels since they are primarily used in the aviation industry and the highest exposure levels are expected to occur for workers and military personnel involved in aviation fueling procedures. Children residing on military bases where JP-8 and JP-5 are used may experience a slightly higher level of exposure than children of the general population.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for JP-5, JP-8, and Jet A fuels were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries 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.

6.8.2 Ongoing Studies

No ongoing environmental fate studies for JP-5, JP-8, and Jet A fuels were identified using the National Institutes of Health (NIH) RePORTER version 6.1.0 (NIH Research Portfolio Online Reporting Tools) or the Defense Technical Information Center (DTIC) online database.

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7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring Jet A, JP-5, and JP-8, their metabolites, and other biomarkers of exposure and effect to Jet A, 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.

7.1 BIOLOGICAL MATERIALS

No analytical methods were located for detecting JP-5, JP-8, and Jet A fuels in biological materials. However, analytical methods for detection in biological samples do exist for kerosene, which has a similar chemical composition as jet fuels (Air Force 1989a; Army 1988; DOD 1992). See Table 7-1 for a summary of the analytical methods most commonly used to measure kerosene in biological samples. Analytical methods are available for a number of the components of jet fuels; the analytical methods for some of the individual hydrocarbon components of JP-5, JP-8, and Jet A fuels (e.g., benzene, toluene, xylenes, and PAHs) are discussed in the toxicological profile for the component (ATSDR 1995, 2007a, 2007b, 2015b). The toxicological profile for total petroleum hydrocarbons (ATSDR 1999) provides additional information on analytical methods.

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, 1991). 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).

Table 7-1. Analytical Methods for Determining Kerosene in Biological Materials

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	Not reported	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)	Not reported	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 detection; GC = gas chromatography; MS = mass spectrometry

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 (FID). This method determined levels of *m*- and *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).

B'Hymer et al. (2005, 2012b) discussed an analytical method to detect 2-methoxyethoxy acetic acid (MEAA) in urine samples using GC with a MS detector (detection limit 0.1 μg/mL). MEAA is a metabolite of 2-(2-methoxyethoxy) ethanol, a glycol ether that is used as an anti-icing agent in JP-8. In a study of Air Force personnel exposed to JP-8, mean post-shift urinary MEAA levels in personnel assigned to a high exposure group (aircraft fuel system maintenance workers) were approximately 10 times greater than personnel assigned to a low exposure group, and the frequency of detection (n>the limit of detection) of MEAA in post-shift urine samples was 94% for the high exposure group and only 3% for the low exposure group (B'Hymer et al. 2012b).

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

7.2 ENVIRONMENTAL SAMPLES

Because JP-5, JP-8, and Jet A fuels 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 GC/FID and GC/MS. See Table 7-2 for a summary of the analytical methods used to determine hydrocarbon components in environmental samples. Environmental levels of JP-5, JP-8, and Jet A fuels are often characterized by measuring the total hydrocarbons and other important constituents typically found in the jet fuels (benzene, toluene, ethylbenzene, xylene, and naphthalene) and reporting these levels. NIOSH method 1550 provides a general description of an analytical procedure for characterizing various types of hydrocarbon mixtures (NIOSH 1994). 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 1995, 2007a, 2007b, 2015b). The toxicological profile for total petroleum hydrocarbons (ATSDR 1999) provides additional information on analytical methods for environmental samples.

Table 7-2. Analytical Methods for Determining Kerosene and Hydrocarbons in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery[a]	Reference
Air	Samples are collected by drawing a known volume of air through glass sampling tubes containing coconut shell charcoal; samples are extracted with 99:1 carbon disulfide (CS_2):N,N-dimethyl-formamide (DMF)	GC/FID	0.1 mg/5–10 mL sample	96–106	NIOSH 1994 (Method 1550)
Air	Adsorb to Florisil filter; elute with CS_2; evaporate under vacuum	GC	Not reported	Not reported	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	Not reported	Dell'Acqua and Bush 1973
Water (purgeable aromatics)	Purge sample with inert gas; adsorb vapor in trap; heat trap; backflush to gas chromatograph	GC/FID	0.2 µg/L	92–96	EPA 1991b (Method 602 and 610)
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 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	Not reported	Not reported	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)	Not reported	EPA 1991b (Method 602 and 610)

Table 7-2. Analytical Methods for Determining Kerosene and Hydrocarbons in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery[a]	Reference
Seawater	Extract aqueous phase of sample with pentane; evaporate; inject to gas chromatograph	GC/MS	Not reported	Not reported	Boylan and Tripp 1971
Soil (other solid materials)	Extract sample with CCl_4; inject extract	GLC	Not reported	Not reported	Midkiff and Washington 1972
Solid waste matrices	Solvent extraction followed by purge-and-trap or direct injection	GC/MS	0.01–0.50 µg/L	84–109	EPA 2006 (Method 8260 C)
Soil	Extract sample with CCl_4; centrifuge; remove water and humic materials with NA_2SO_4 and Al_2O_3; inject extract	GC/FID	Not reported	Not reported	Galin et al. 1990
Soil	Purge at elevated temperatures; heat trap to desorb material into gas chromatograph column	GC	Not reported	Not reported	Chang and Lopez. 1992
Soil	Sample extracted using water and cyclohexane	Synchronous scanning fluorescence spectroscopy	Not reported	Not reported	Phaff et al. 1992
Sediment	Sample dried, ground, and extracted with *n*-pentane	GC/FID	Not reported	Not reported	Guiney et al. 1987b
Fish tissue	Extract with KOH in methanol; partition into *n*-pentane; concentrate; analyze using gas chromatograph	GC/FID	Not reported	95	Guiney et al. 1987b

[a]The sample detection limit and percent recovery will vary for each of the components of these mixtures. The reported values in these tables are for the specific components analyzed in each method.

Al_2O_3 = aluminum oxide; CCl_4 = carbon tetrachloride; CH_2Cl_2 = dichloromethane (methylene chloride); FID = flame ionization detection; GC = gas chromatography; GLC = gas liquid chromatography; KOH = potassium hydroxide; MS = mass spectrometry; Na_2SO_4 = sodium sulfate

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 1994). 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 SD = 0.052) using the charcoal tubes (NIOSH 1994); 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 (Coleman et al. 1984; Dell'Acqua and Bush 1973), and groundwater (Thomas and Delfino 1991). Purge-and-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.

EPA Method 8260C is a GC/MS method that is used to quantify volatile organic compounds in various solid waste matrices and is applicable for the components of JP-5, JP-8, and Jet A fuels. This method is appropriate for nearly all types of environmental sample matrices, regardless of water content. Sample types that can be analyzed include air sampling trapping media, groundwater, surface water, aqueous sludges, caustic liquors, acid liquors, waste solvents, oily wastes, mousses, tars, fibrous wastes, polymeric emulsions, filter cakes, spent carbons, spent catalysts, soils, and sediments (EPA 2006).

Distinctions between WSFs of mixed hydrocarbons may be made by using solvent extraction of the water-soluble 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 15-mL 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 2 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. 1990), 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. 1987b). Carbon tetrachloride is the recommended solvent because it causes less interference with the chromatographic peaks of the jet fuels (Galin et al. 1990; 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 C18 columns that offer these advantages: rapid separation (approximately 15 minutes for a run); good recovery of hydrocarbons (85% for the C18 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.

Tissues 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 >95% recovery.

7.3 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, JP-8, and Jet A fuels is available. Where adequate information is not available, ATSDR, in conjunction with 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, JP-8, and Jet A fuels.

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.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. While standard procedures exist for identifying or quantifying exposure to volatile compounds based on hydrocarbon components in blood, urine, and stomach contents (Hara 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, JP-8, and Jet A fuels and to other types of hydrocarbon mixtures. Egeghy et al. (2003) noted a correlation to the levels of naphthalene in air and breath of Air Force personnel who were highly exposed to JP-8, but noted that benzene levels in breath could not be correlated solely to exposure from JP-8. In a similar study, Serder et al. (2003) concluded that naphthalene and napthols (1- and 2-hydroxynaphthalene) may

be useful urinary biomarkers of exposure to populations routinely exposed to JP-8, such as aircraft maintenance workers. Smith et al. (2012) also concluded that elevated urinary naphthol levels could be used as a surrogate for short-term occupational exposure to JP-8. The sum concentration of nonane, decane, undecane, and dodecane was used as a composite fingerprint of JP-8 short term exposure for Air Force personnel regularly exposed to this fuel (Air Force 2001).

MEAA was shown to be a urinary metabolite for exposure to 2-(2-methoxyethoxy)ethanol, which is an additive to JP-8 (B'Hymer et al. 2005, 2012a). Because this substance has limited industrial uses, its addition to jet fuels makes its metabolite a possible biomarker for exposure to these fuels.

Effect. No specific biomarkers of effect were identified for JP-5, JP-8, and Jet A fuels 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 specific 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, JP-8, and Jet A fuels in air (Andrasko 1983; Baldwin 1977; NIOSH 1994), 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. 1990; Midkiff and Washington 1972), and biological media (Guiney et al. 1987b). The most commonly used methods are GC/FID 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.

7.3.2 Ongoing Studies

No ongoing studies for JP-5, JP-8, and Jet A fuels were identified using the NIH RePORTER version 6.1.0 or the DTIC online database. Analytical methods are continuously being developed and updated for individual constituents that may be contained in JP-5, JP-8, and Jet A fuels. For additional information,

see toxicological profiles for substances such as benzene, toluene, xylenes, and PAHs (ATSDR 1995, 2007a, 2007b, 2015b).

8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

ATSDR has derived an intermediate-duration inhalation MRL of 2 mg/m^3 for JP-5 vapor. The MRL is based on minimal LOAEL of 150 mg/m^3 for liver effects in mice continuously exposed to JP-5 vapor for 90 days (Gaworski et al. 1984). The minimal LOAEL was multiplied by the default human to mouse blood:gas partition coefficient ratio of 1 to calculate the human equivalent concentration ($LOAEL_{HEC}$). The minimal $LOAEL_{HEC}$ of 150 mg/m^3 was divided by a total uncertainty factor of 90 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustment, and 10 for human variability).

ATSDR has derived an intermediate-duration inhalation MRL of 3 mg/m^3 for JP-8 vapor. The MRL is based on NOAEL of 500 mg/m^3 and LOAEL of 1,000 mg/m^3 for neurobehavioral effects in rats exposed to JP-8 vapor 6 hours/day, 5 days/week for 90 days (Ritchie et al. 2001). The NOAEL was adjusted for intermittent exposure and multiplied by the default human to mouse blood:gas partition coefficient ratio of 1 to calculate the human equivalent concentration ($LOAEL_{HEC}$). The $NOAEL_{HEC}$ of 89 mg/m^3 was divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment, and 10 for human variability).

ATSDR has derived an acute-duration oral MRL of 3 mg/kg/day for JP-8. The MRL is based on NOAEL of 250 mg/kg/day and LOAEL of 500 mg/kg/day for immunological effects in mice administered via gavage JP-8 in olive oil for 14 days (Keil et al. 2004). The NOAEL of 250 mg/kg/day was divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ATSDR has derived an intermediate-duration oral MRL of 0.3 mg/kg/day for JP-8. The MRL is based on a LOAEL of 325 mg/kg/day for neurodevelopmental effects in the offspring of rats administered via gavage JP-8 for 90 days prior to cohabitation and during gestation and lactation (Mattie et al. 2001). The LOAEL of 325 mg/kg/day was divided by a total uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

EPA has not derived inhalation reference concentrations (RfCs) or oral reference doses (RfDs) for JP-5, JP-8, or Jet A fuels (IRIS 2015).

The international and national regulations, advisories, and guidelines regarding JP-5, JP-8, and Jet A in air, water, and other media are summarized in Table 8-1.

Table 8-1. Regulations and Guidelines Applicable to Jet Fuels

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification (jet fuel)	Group 3[a]	IARC 2013
WHO	Air quality guidelines	No data	WHO 2010
	Drinking water quality guidelines	No data	WHO 2011
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV-TWA[b,c] (kerosene/jet fuels)	200 mg/m^3	ACGIH 2013
AIHA	ERPGs	No data	AIHA 2013
DOE	PAC-1[d] (JP-5 and JP-8)	290 mg/m^3	DOE 2012
	PAC-2 (JP-5 and JP-8)	1,100 mg/m^3	
	PAC-3 (JP-5 and JP-8)	1,100 mg/m^3	
EPA	AEGL-1 (JP-5 and JP-8)		EPA 2013c
	10 minutes	290 mg/m^3	
	30 minutes	290 mg/m^3	
	60 minutes	290 mg/m^3	
	4 hours	290 mg/m^3	
	8 hours	290 mg/m^3	
	AEGL-2 (JP-5 and JP-8)		
	10 minutes	1,100 mg/m^3	
	30 minutes	1,100 mg/m^3	
	60 minutes	1,100 mg/m^3	
	4 hours	1,100 mg/m^3	
	8 hours	1,100 mg/m^3	
	AEGL-3 (JP-5 and JP-8)		
	10 minutes	NR[e]	
	30 minutes	NR[e]	
	60 minutes	NR[e]	
	4 hours	NR[e]	
	8 hours	NR[e]	
	Hazardous air pollutant	No data	EPA 2014a
	NAAQS	No data	EPA 2014d
NIOSH	REL (kerosene)	100 mg/m^3	NIOSH 2014
	IDLH	No data	
OSHA	PEL (8-hour TWA) for general industry	No data	OSHA 2013b 29 CFR 1910.1000, Table Z-1
	Highly hazardous chemicals	No data	OSHA 2013a 29 CFR 1910.119, Appendix A

Table 8-1. Regulations and Guidelines Applicable to Jet Fuels

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	No data	EPA 2013d 40 CFR 116.4
	Drinking water contaminant candidate list	No data	EPA 2009a 74 FR 51850
	Drinking water standards and health advisories	No data	EPA 2012b
	National primary drinking water standards	No data	EPA 2009b
	National recommended water quality criteria	No data	EPA 2014e
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	No data	EPA 2013f 40 CFR 117.3
c. Food			
FDA	EAFUS[f]	No data	FDA 2014
d. Other			
ACGIH	Carcinogenicity classification (kerosene/jet fuels)	A3[g]	ACGIH 2013
EPA	Carcinogenicity classification	No data	IRIS 2015
	RfC	No data	
	RfD	No data	
	Identification and listing of hazardous waste	No data	EPA 2013e 40 CFR 261, Appendix VIII
	Inert pesticide ingredients applied to animals exemptions from the requirement of a tolerance	Yes	EPA 2014b
	Master Testing List	No data	EPA 2014c
	RCRA waste minimization PBT priority chemical list	No data	EPA 1998 63 FR 60332
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list	No data	EPA 2013g 40 CFR 264, Appendix IX
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance and reportable quantity	No data	EPA 2013h 40 CFR 302.4
	Superfund, emergency planning, and community right-to-know		
	Effective date of toxic chemical release reporting	No data	EPA 2013j 40 CFR 372.65

Table 8-1. Regulations and Guidelines Applicable to Jet Fuels

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Extremely hazardous substances and its threshold planning quantity	No data	EPA 2013i 40 CFR 355, Appendix A
	TSCA chemical lists and reporting periods	No data	EPA 2013a 40 CFR 712.30
	TSCA health and safety data reporting	No data	EPA 2013b 40 CFR 716.120
NTP	Carcinogenicity classification	No data	NTP 2011

[a]Group 3: Not classifiable as to its carcinogenicity to humans.
[b]As total hydrocarbon vapor for kerosene/jet fuels. Application restricted to conditions in which there are negligible aerosol exposures.
[c]Skin designation: refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, by contact with vapors, liquids, and solids (ACGIH 2013).
[d]PAC-1: mild, transient health effects; PAC-2: irreversible or other serious health effects that could impair the ability to take protective action; PAC-3: life-threatening health effects (DOE 2012).
[e]Not recommended due to insufficient data.
[f]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[g]A3: confirmed animal carcinogen with unknown relevance to humans.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; FR = Federal Register; GRAS = generally recognized as safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NAAQS = National Ambient Air Quality Standards; NIOSH = National Institute for Occupational Safety and Health; NR = not recommended; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PBT = persistent, bioaccumulative, and toxic; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

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

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

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 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.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

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.

Biomarkers—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.

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.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

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.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

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.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

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 occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (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.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

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

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

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

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

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

***In Vivo*—**Occurring within the living organism.

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

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that 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 exposure level 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.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

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

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

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

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a 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.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a

variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

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 no-observed-adverse-effect level (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 the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 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.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

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)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

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

Toxic Dose$_{(50)}$ (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.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) 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 lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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. 99–499], 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.

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 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide 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 and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: JP-5 vapor
CAS Number: 8008-20-6
Date: March 2017
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 23
Species: Mouse

Minimal Risk Level: 2 [ ] mg/kg/day [X] mg/m^3

Reference: Gaworski CL, MacEwen JD, Vernot EH, et al. 1984. Comparison of the subchronic inhalation toxicity of petroleum and oil shale JP-5 jet fuels. In: MacFarland HN, Holdsworth CE, MacGregor JA, et al., eds. Advances in modern environmental toxicology. Volume VI: Applied toxicology of petroleum hydrocarbons. Princeton, NJ: Princeton Scientific Publishers, 33-47.

Experimental design: Groups of approximately 35 female C57BL/6 mice were exposed by inhalation to petroleum-based JP-5 vapor at 0, 150, or 750 mg/m^3 continuously for 90 days. End points evaluated included: clinical signs, body weight (measured monthly), 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).

Effect 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 incidences were 8/37 (22%), 29/33 (88%), and 23/34 (68%) in the 0, 150, and 750 mg/m^3 groups, respectively.

Dose and end point used for MRL derivation:

[ ] NOAEL [X] minimal LOAEL

150 mg/m^3; hepatocellular fatty changes and vacuolization.

Uncertainty Factors used in MRL derivation:

- [x] 3 for use of a minimal LOAEL
- [x] 3 for extrapolation from animals to humans with dosimetric adjustments
- [x] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: A human equivalent concentration (HEC) of 150 mg/m^3 was calculated by multiplying the mouse LOAEL by the ratio of the blood:gas partition coefficients in humans and animals. Because blood:gas partition

coefficients are not measurable for a complex mixture such as JP-5, the default ratio of 1 was used (EPA 1994).

$$150 \text{ mg/m}^3 \text{ x } 1 = 150 \text{ mg/m}^3$$

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: The intermediate-duration toxicity of inhaled JP-5 has been investigated in rats, mice, and dogs. In male rats, the most sensitive effect is an increase in the occurrence of hyaline droplets in the proximal renal tubules, which was observed in rats continuously exposed to ≥150 mg/m^3 JP-5 vapor (Gaworski et al. 1984). This effect, which is only observed in male rats, is due to an accumulation of alpha$_{2u}$-globulin in hyaline droplets and is not considered relevant to humans (EPA 1991a; Flamm and Lehman-McKeeman 1991; Hard et al. 1993; Swenberg 1993). No adverse effects were observed in female rats exposed to ≤750 mg/m^3 JP-5 vapor (Gaworski et al. 1984). Similar to mice, the liver appears to be the most sensitive target of toxicity in dogs; diffuse hepatocellular swelling was observed in male and female dogs continuously exposed to ≥150 mg/m^3 JP-5 vapor (Gaworski et al. 1984). The nervous system was the only other target examined in intermediate JP-5 studies. An evaluation of neurobehavioral performance in rats found increased forelimb grip strength in rats similarly exposed to 1,200 mg/m^3 JP-5 vapor (Rossi et al. 2001); no alterations in other neurobehavioral tests were found.

Studies with JP-8 have also identified the immune system as a sensitive target of toxicity; based on the similarity between JP-5 and JP-8, it is likely that the immune system will also be a relevant target of JP-5. The lowest reliable LOAEL for immunotoxicity following acute-duration inhalation exposure to JP-8 was 1,000 mg/m^3 identified in rats exposed to JP-8 vapor and aerosol 1 hour/day for 7 days (Hilgaertner et al. 2011).

Agency Contacts (Chemical Managers): John Risher and Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: JP-8 vapor
CAS Number: 8008-20-6
Date: March 2017
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 31
Species: Rat

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

Reference: Ritchie GD, Rossi J, Nordholm AF, et al. 2001. Effects of repeated exposure to JP-8 jet fuel vapor on learning of simple and difficult operant tasks by rats. J Toxicol Environ Health, Part A 64: 385-415.

Experimental design: Groups of male Sprague-Dawley rats (16/group) were exposed whole-body to 0, 500, or 1,000 mg/m^3 JP-8 fuel vapors 6 hours/day, 5 days/week for 6 weeks. Sixty-five days after exposure termination, the rats underwent simple and difficult operant tasks (lever acquisition, fixed ratio, lever spatial reversal, stimulus reversal, and incremental repeated acquisition in order of increasing difficulty). After the neurobehavioral testing, 4 rats/group were killed and the brains were dissected and processed for determination of neurotransmitters and their metabolites.

Effect noted in study and corresponding doses: Exposure to 1,000 mg/m^3 JP-8 fuel vapors induced significant deficits in acquisition or performance of the two most difficult tasks, but not in the simple learning tasks compared to rats in the low-exposure group. Learning/performance of complex tasks in the low-exposure group generally exceeded performance of control rats, while learning by high-exposure rats was almost always inferior to control rats, suggesting possible neurobehavioral hormesis. Neurochemical analyses showed significantly increased levels of dopamine in the cerebral cortex and DOPAC (major dopamine metabolite) in the brainstem for as long as 180 days post-exposure in both exposed groups relative to controls. This could have resulted from solvent-induced reductions in cyclic guanosine monophosphate (GMP) that is involved in signal transduction in specific brain regions.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL

The MRL is based on a NOAEL of 500 mg/m^3 and LOAEL of 1,000 mg/m^3 for neurotoxicity.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustments
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: A $NOAEL_{HEC}$ of 89 mg/m^3 was calculated by multiplying the $NOAEL_{ADJ}$ by the ratio of the blood:gas partition coefficients in humans and animals. Because blood:gas partition coefficients are not measurable for a complex mixture such as JP-8, the default ratio of 1 was used (EPA 1994).

$$89 \text{ mg/m}^3 \times 1 = 89 \text{ mg/m}^3$$

Was a conversion used from intermittent to continuous exposure? The NOAEL of 500 mg/m^3 was adjusted for intermittent exposure:

$$NOAEL_{ADJ} = 500 \text{ mg/m}^3 \times 6 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days} = 89 \text{ mg/m}^3$$

Other additional studies or pertinent information that lend support to this MRL: Two studies have examined the systemic toxicity of JP-8 following intermediate-duration inhalation exposure. Mattie et al. (1991) reported an increase in hyaline nephropathy in male rats continuously exposed to ≥500 mg/m^3 JP-8 vapor for 90 days. No other effects were observed in the male rats and no effects were observed in the female rats; the highest concentration tested was 1,000 mg/m^3. In contrast, Hanas et al. (2010) reported a number of adverse effects in male rats exposed to JP-8 vapor 6 hours/day for 91 days. At 250 mg/m^3 proximal tubular damage was observed in the kidneys; enlarged alveolar capillaries, myocardial scarring, reduction in fat cells/globules in bone marrow, and dilated sinusoids and fatty hepatocytes were observed at 500 mg/m^3. Interpretation of the results of the Hanas et al. (2010) study is limited by the small number of animals tested (3/group). The renal effects observed in the Mattie et al. (1991) and Hanas et al. (2010) studies are characteristic of $alpha_{2u}$-globulin nephropathy, which is not considered a relevant effect in humans (EPA 1991a; Flamm and Lehman-McKeeman 1991; Hard et al. 1993; Swenberg 1993).

A 6-week study conducted by Rossi et al. (2001) also evaluated the neurotoxicity of JP-8 in rats exposed for 6 weeks. An alteration in a novel appetitive stimulus test was observed in rats exposed to 1,000 mg/m^3 JP-8 vapor; the investigators suggested that this test quantified dopamine system sensitization in the rat. No other alterations in neurobehavioral tests were found. Studies by Fechter et al. (2012) and Guthrie et al. (2014, 2015) evaluated the potential of JP-8 to damage the auditory system. No significant alterations in auditory function was observed in rats exposed to 1,500 mg/m^3 JP-8 vapor for 4 weeks (Fechter et al. 2012); however, if the rats were also exposed to non-damaging noise, there was damage to the auditory function. Central auditory processing dysfunction was observed in rats exposed to 1,000 mg/m^3 JP-8 vapor for 4 weeks; however, no damage to peripheral auditory function, including damage to cochlear hair cells, was observed (Guthrie et al. 2014, 2015).

In addition to these studies, three University of Arizona studies have reported edema and inflammation of the terminal bronchioles in rats exposed 1 hour/day for 28 or 56 days to JP-8 aerosols and vapors (Hays et al. 1995; Pfaff et al. 1995, 1996). Hays et al. (1995) also found increased lung epithelial permeability and alveolar permeability. None of the three studies measured the vapor component of the test atmosphere (see Section 3.2.1 for a discussion of these studies).

Agency Contacts (Chemical Managers): John Risher and Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: JP-8
CAS Number: 8008-20-6
Date: March 2017
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 11
Species: Mouse

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

Reference: Keil D, Dudley A, EuDaly JG, et al. 2004. Immunological and hematological effects observed in B6C3F1 mice exposed to JP-8 jet fuel for 14 days. J Toxicol Environ Health Part A 67:1109-1129.

Experimental design: The study examined the effects of JP-8 fuel on humoral and cell-mediated and hematological parameters in female B6C3F1 mice. Groups of mice (4–6/group) were administered doses of JP-8 fuel ranging from 250 to 2,000 mg/kg/day by gavage in olive oil for 14 days. End points monitored included body weight; weight of the liver, kidneys, spleen, and thymus; spleen and thymus cellularity; lymphocyte proliferation; natural killer (NK) cell activity; antibody plaque-forming cells assay; splenic and thymic CD4/CD8 subpopulations; and bone marrow cellularity and colony-forming units.

Effect noted in study and corresponding doses: There were no clinical signs during the study. There was a trend for increase in body weight gain, but there was no statistical significance. Relative kidney weight was not affected, but liver weight was significantly increased at ≥1,000 mg/kg/day (23%). Significant hematological alterations included decreases in hemoglobin levels, hematocrit levels, and red blood cell counts and increases in mean corpuscular volume at 2,500 mg/kg/day; mean corpuscular volume was also increased at 1,500 and 2,000 mg/kg/day. All of these changes were ≤7% relative to controls and probably of no toxicological significance. There were no significant changes in peripheral blood differential count. An increase in colony forming units was observed in the bone marrow of mice administered 2,000 mg/kg/day, but there were no alterations in bone marrow cellularity. A significant decrease in cellularity was observed in the thymus at 2,000 mg/kg/day; no alterations were observed in the spleen. No significant alterations in mitogen-induced T or B cell proliferation or alterations in NK activity were observed. In response to sheep red blood cells (SRBCs), there were significant suppression of IgM antibody production (when assessed using antibody plague-forming cell response) at doses ≥500 mg/kg/day. However, there were no significant alterations in serum levels of anti-SRBC IgM when measured by ELISA or hemagglutination. In the spleen, there were no alterations in the percentage of individual T-cell phenotypes or the ratio of CD4+ to CD8+ cells; however, decreases in $CD4^-/CD8^-$ cells were observed at 1,000 and 2,000 mg/kg/day. In contrast, there were significant decreases in the absolute values of $CD8^+$, $CD4^+$, and $CD4^+/CD8^+$ T-cell subpopulations in the thymus in mice administered 2,000 mg/kg/day.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL

The MRL is based on a NOAEL of 250 mg/kg/day and LOAEL of 500 mg/kg/day for an impaired response to SRBCs.

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: The available data on the acute-toxicity of JP-8 primarily focused on immunotoxicity. Altered immune function (response to SRBCs) was observed in mice administered 1,000 mg/kg/day JP-8 for 7 days (Dudley et al. 2001) or 500 mg/kg/day for 14 days (Keil et al. 2004; Peden-Adams et al. 2001). At higher doses, decreases in thymus weight and cellularity were observed (Dudley et al. 2001). Impaired immune response was also observed in the offspring of mice administered 1,000 mg/kg/day on GDs 6–15 (Keil et al. 2003). In another developmental toxicity study (Cooper and Mattie 1996), a decrease in fetal body weight was observed at a dose (1,000 mg/kg/day) that also resulted in decreased maternal weight gain and mortality.

Although the acute-duration studies did not examine the potential for systemic toxicity, intermediate-duration JP-8 oral studies suggest that systemic effects such as liver toxicity would occur at higher doses than the LOAEL for immunotoxicity (Mattie et al. 1995, 2000).

Agency Contacts (Chemical Managers): John Risher and Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: JP-8
CAS Number: 8008-20-6
Date: March 2017
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 28
Species: Rat

Minimal Risk Level: 0.3 [X] mg/kg/day [ ] mg/m^3

Reference: Mattie DR, Cooper JR, Sterner TR, et al. 2001. Developmental neurobehavioral effects on JP-8 jet fuel on pups from female Sprague-Dawley rats exposed by oral gavage. Wright-Patterson, AFB: OH: Air Force Research Laboratory. 22. ARFL-HE-WP-TR-2001-0186. ADA428272.

Experimental design: The study examined neurobehavioral parameters in pups from rats exposed to JP-8 fuel for a total of 21 weeks (90 days followed by cohabitation, gestation, delivery, and lactation). Groups of rats (35/groups) were administered 0, 325, 750, or 1,500 mg/kg neat JP-8 fuel by gavage. Litters were standardized to four male and four female pups on PND 4. Pup weights were recorded on PNDs 1, 4, 14, 21, and 90. Male pups were checked for descent of testes on PND 21 or 22. Female pups were checked for vaginal opening on PND 30. The following neurobehavioral tests were conducted: surface righting (beginning PND 4), negative geotaxis (beginning PND 5), swimming development (PNDs 6–20), and water maze (PNDs 70 and 77)

Effect noted in study and corresponding doses: The results showed a significant alteration in the total score for the swimming development test at ≥325 mg/kg/day on PND 8 and at 750 and 1,500 mg/kg/day on PND 14; however, no significant alterations in total score were observed on PNDs 10, 12, 16, 18, or 20. The alterations in the total scores were primarily due to swimming direction scores; significant decreases in direction scores were observed on PND 6 (750 and 1,500 mg/kg/day), PND 8 (≥325 mg/kg/day), and PND 14 (750 and 1,500 mg/kg/day); no alterations in angle of head or limb usage scores were observed at any time point. No significant alterations in surface righting (tested on PND 4), negative geotaxis (tested on PND 5), or water maze performance (tested on PNDs 70 and 77) were observed. The investigators suggested that the results in the swimming development test were indicative of a possible developmental delay in motor coordination; however, the delay did not affect motor ability at later ages.

Dose and end point used for MRL derivation:

[ ] NOAEL [X] LOAEL

The MRL is based on a LOAEL of 325 mg/kg/day for neurodevelopmental effects.

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Two studies have evaluated the intermediate-duration oral toxicity of JP-8 (Mattie et al. 1995, 2000). Administration of 750 mg/kg/day resulted in increases in serum ALT and AST activities in male rats, stomach hyperplasia in male and female rats, hypoglycemia in male rats, perianal dermatitis in male rats, and hyaline droplet formation in the kidneys of male rats; perianal dermatitis was also observed in female rats at 1,500 mg/kg/day. The third study in the intermediate-duration database was the Mattie et al. (2001) developmental study, which was the basis of the MRL.

Acute-duration oral studies suggest that the immune system is also a sensitive target of JP-8 toxicity; however, this end point has not been investigated following intermediate-duration exposure. The lowest LOAEL for immune effects identified in oral exposure studies was 500 mg/kg/day for an impaired response to SRBCs (Keil et al. 2004). Since the LOAEL for neurodevelopmental is similar to this LOAEL, the intermediate MRL should be protective for potential immune effects.

Agency Contacts (Chemical Managers): John Risher and Obaid Faroon

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

Relevance to Public Health

This chapter 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 chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and 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 chapter.

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 Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived 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.

MRLs 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. MRLs 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, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "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 that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point 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 end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (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 levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures 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, 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 NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(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. Typically when sufficient data exist, 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 Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(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 in LSE tables and figures include death, systemic, immunological and lymphoreticular, 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 two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "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 regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 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, one systemic effect (respiratory) was investigated.

(8) NOAEL. A 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 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 end point 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 9 of the profile.

(11) CEL. A 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 that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

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 acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same 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/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. 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 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL 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

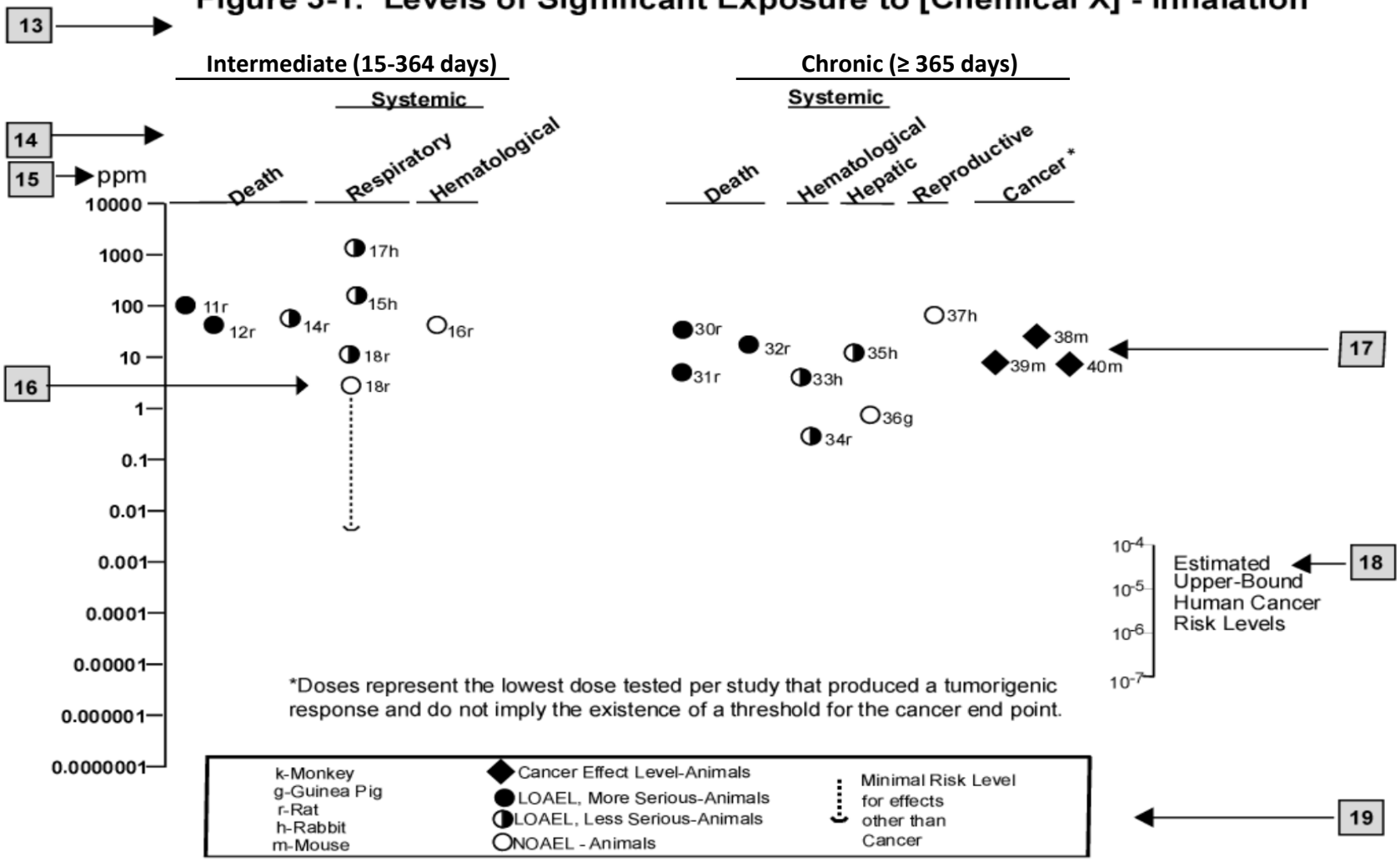
Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation

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

[a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor

DOT	Department of Transportation
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
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_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie

MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result