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/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
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/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	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/m^3)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m^3)	Serious (mg/m^3)		
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)

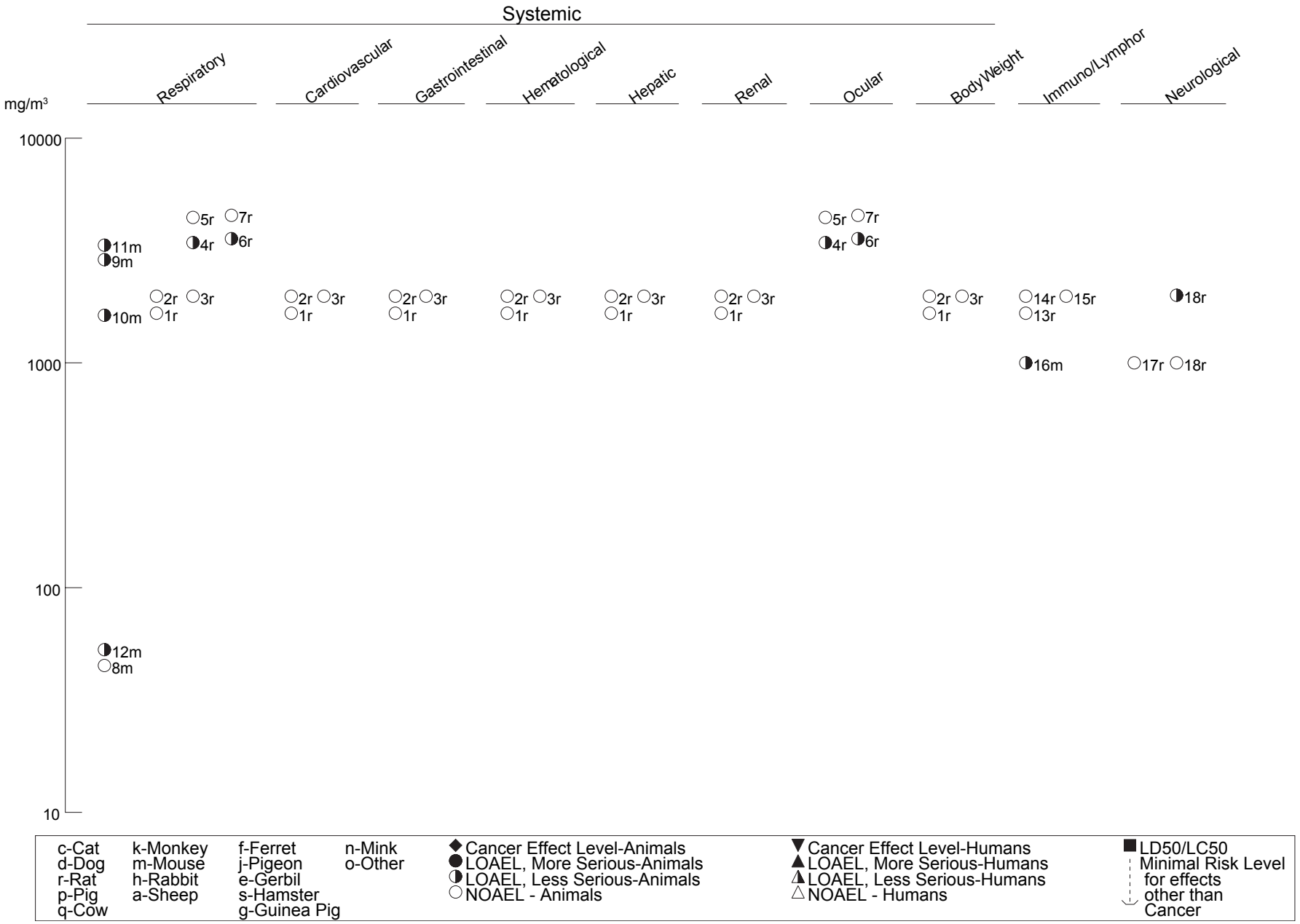


Figure 3-1 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Inhalation *(Continued)*

Intermediate (15-364 days)

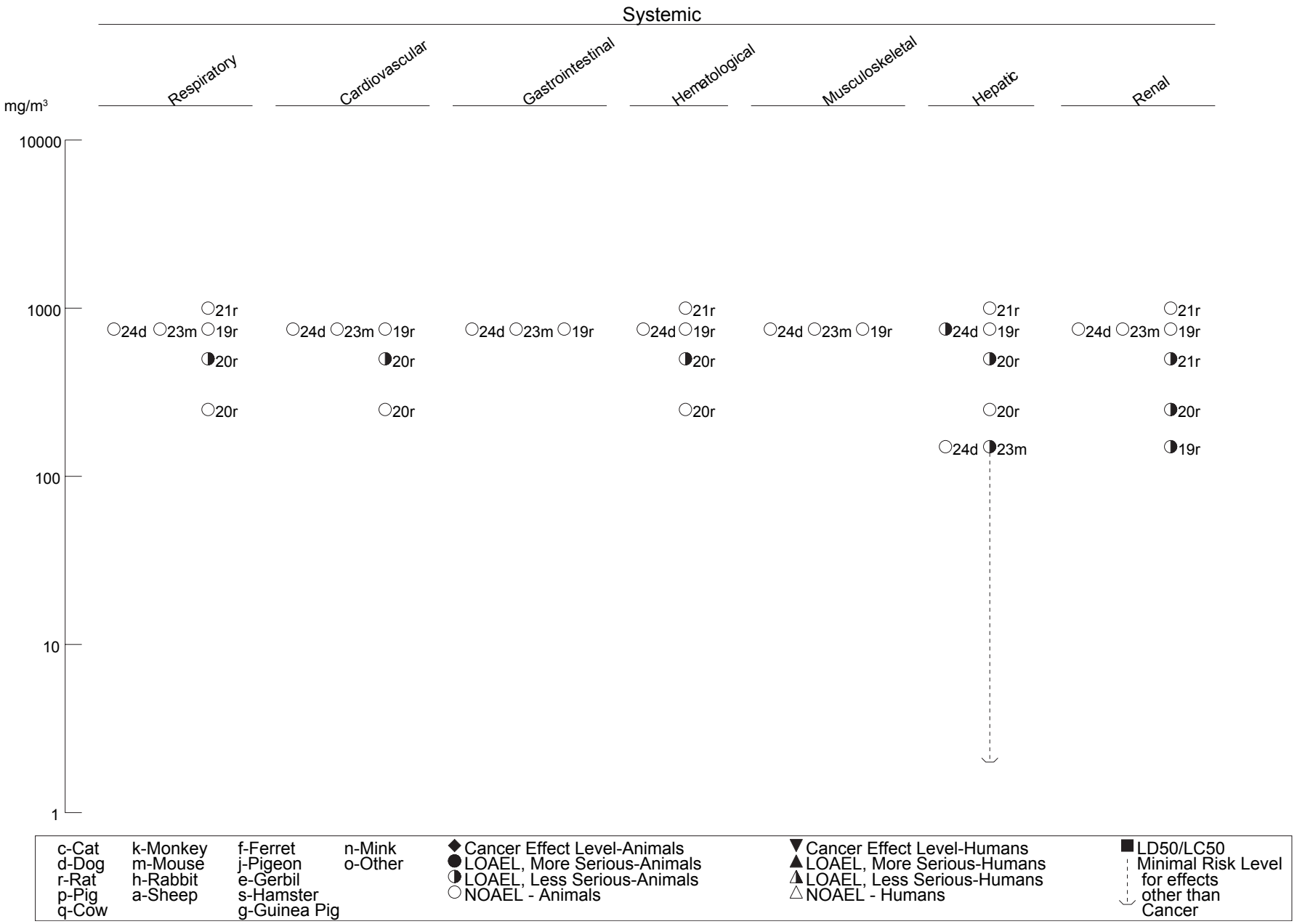


Figure 3-1 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Inhalation *(Continued)*

Intermediate (15-364 days)

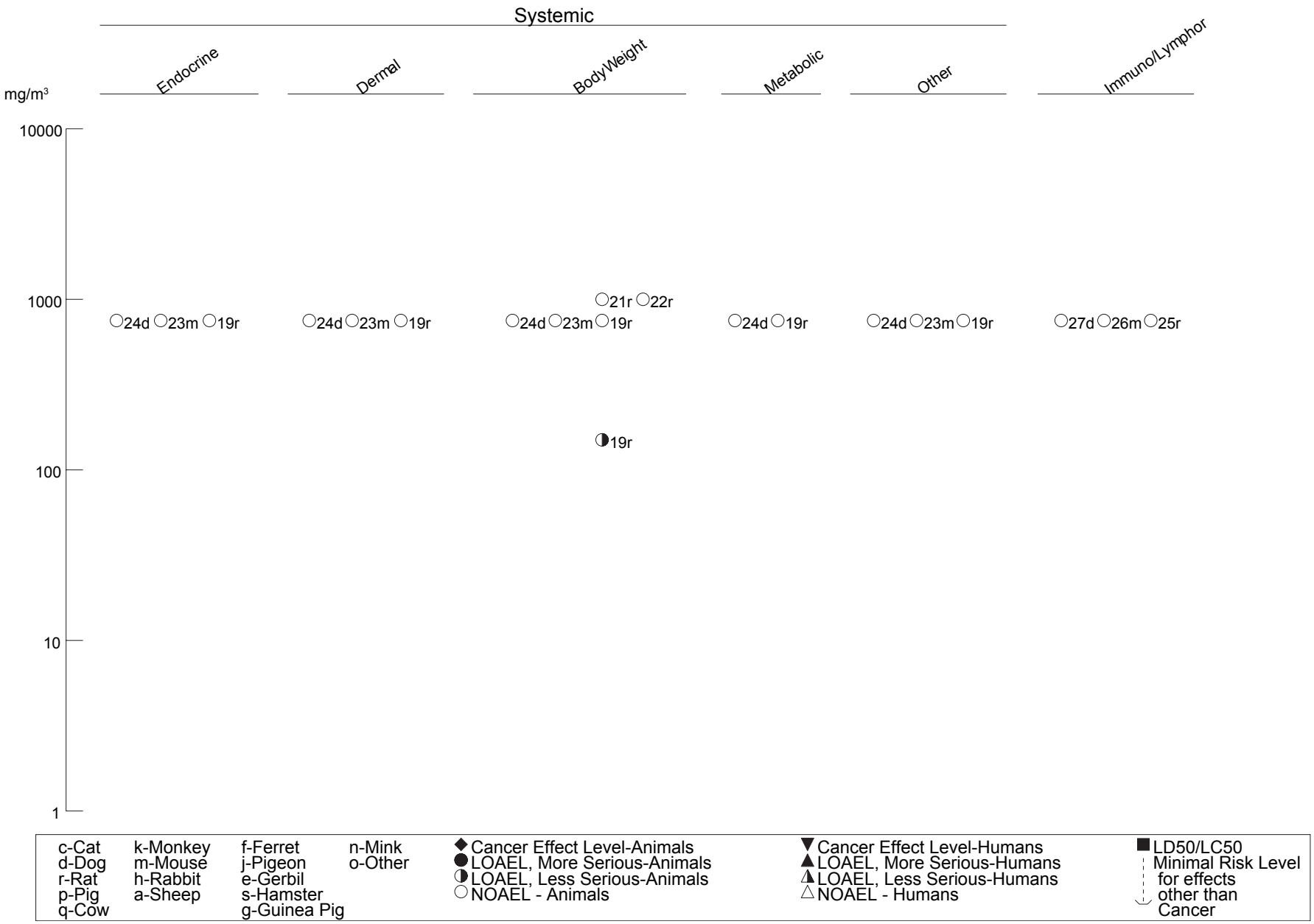
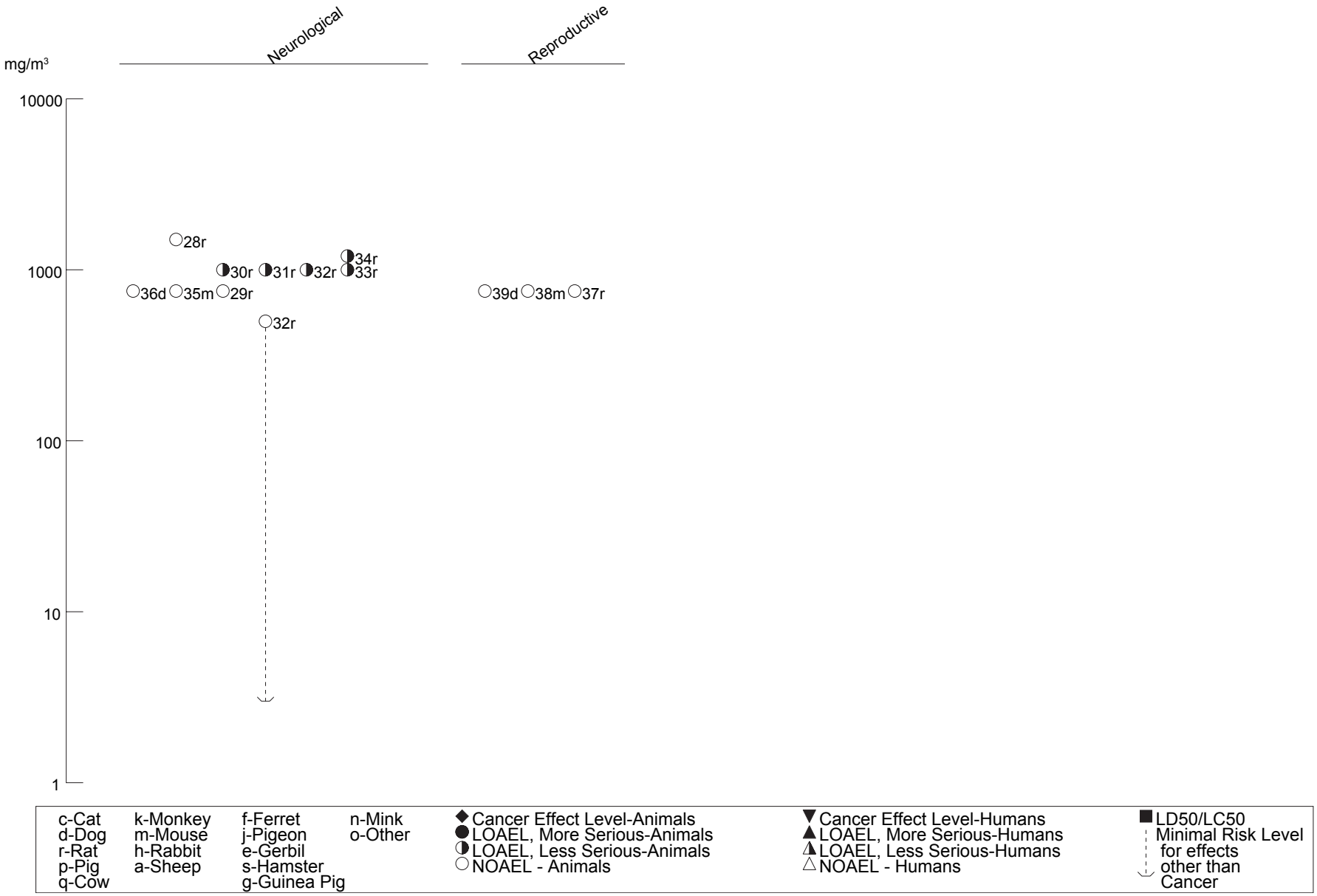


Figure 3-1 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Inhalation *(Continued)*

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)

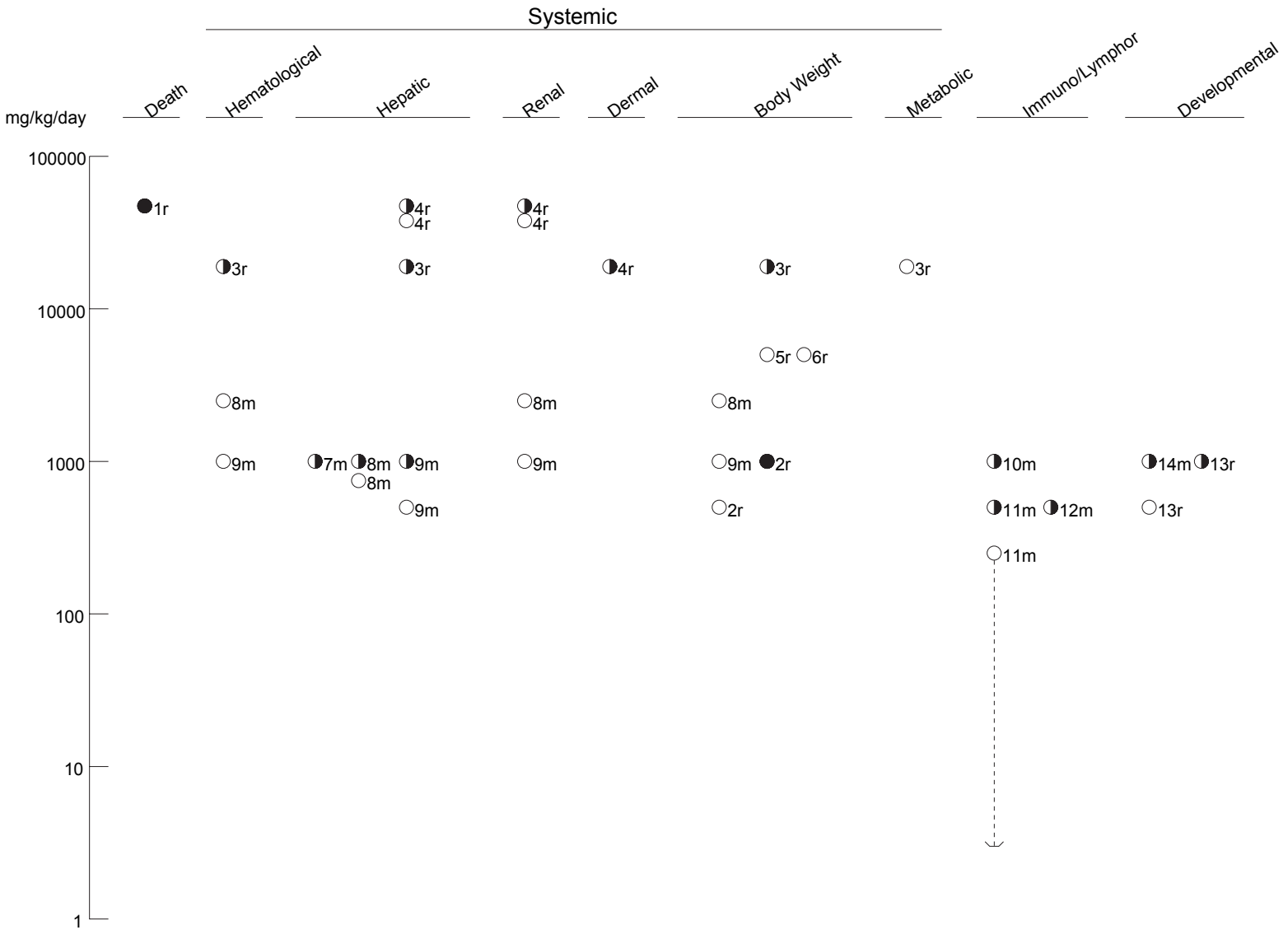


Figure 3-2 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Oral *(Continued)*

Intermediate (15-364 days)

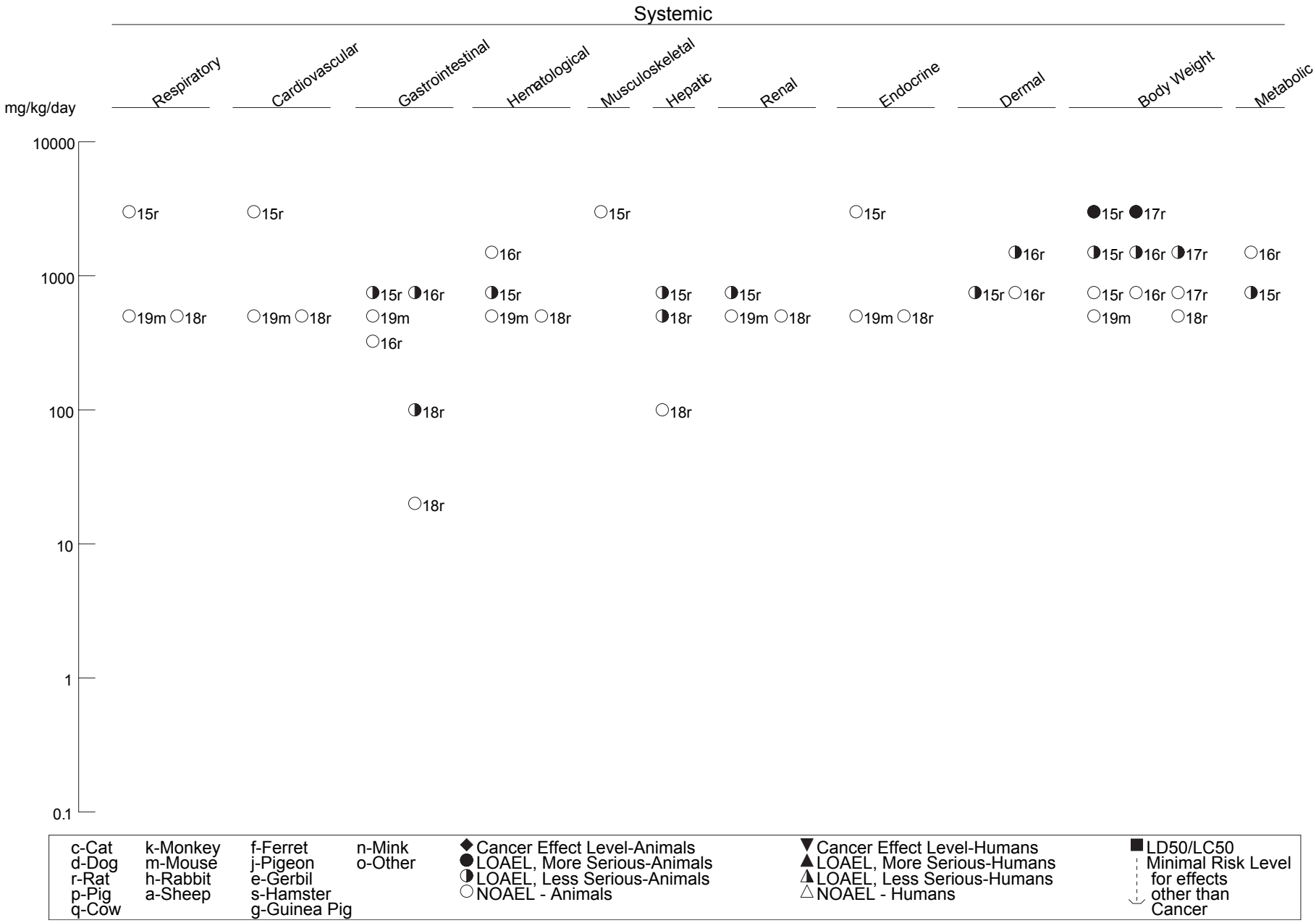
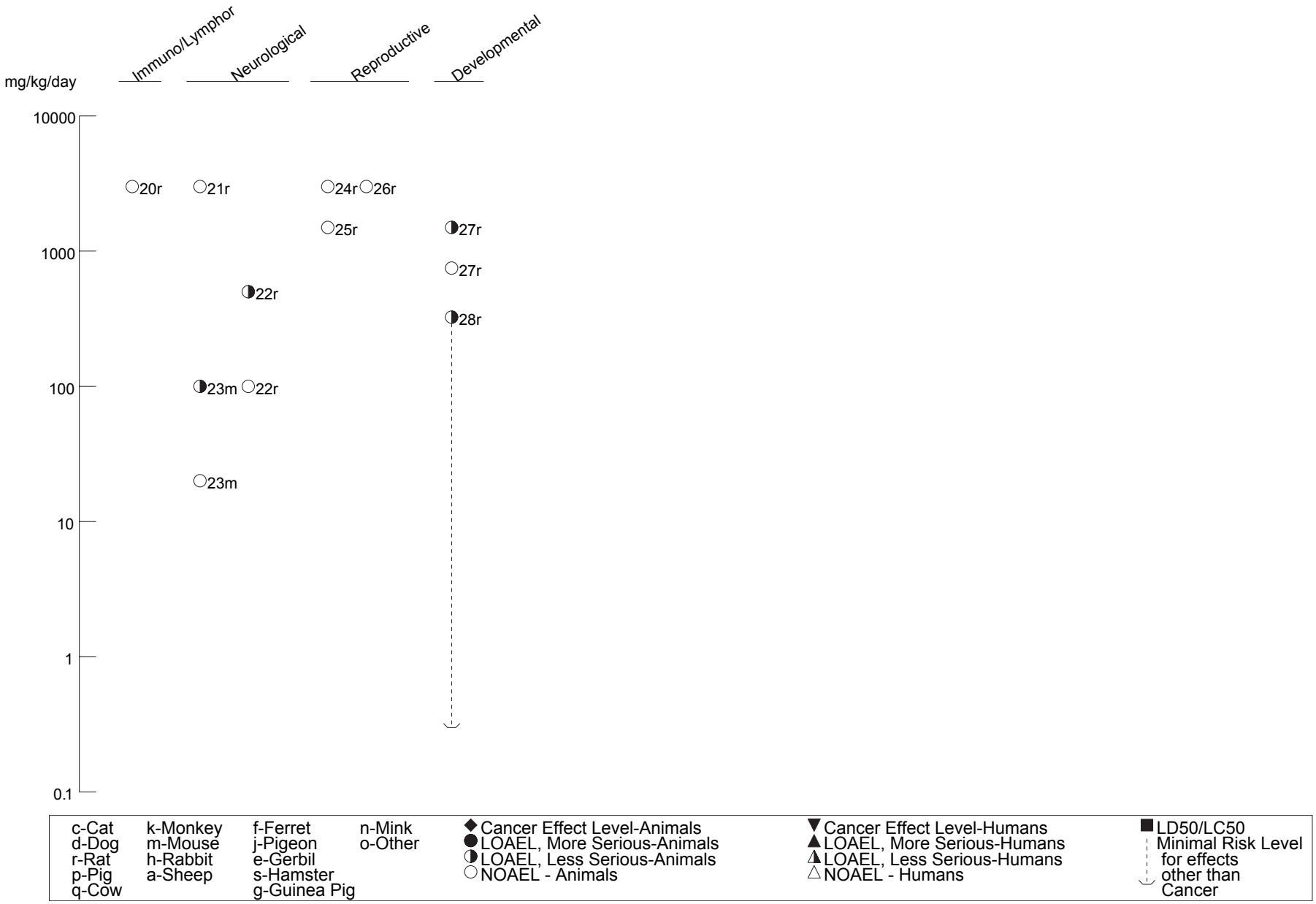


Figure 3-2 Levels of Significant Exposure to JP-5, JP-8, And Jet A Fuels - Oral *(Continued)*

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 Less Serious	LOAEL Serious	Reference Chemical Form	Comments
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 Less Serious	LOAEL Serious	Reference Chemical Form	Comments
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		Reference
		With activation	Without activation	
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.

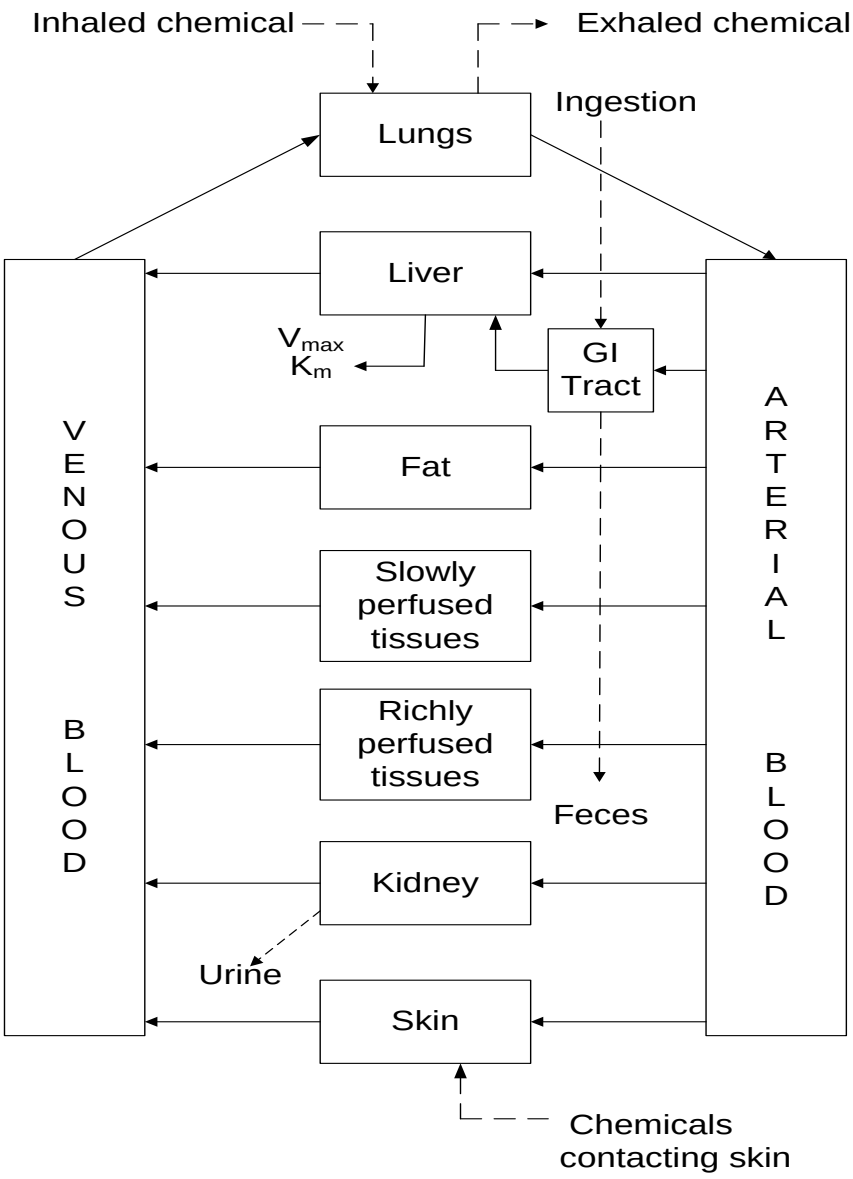
PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in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

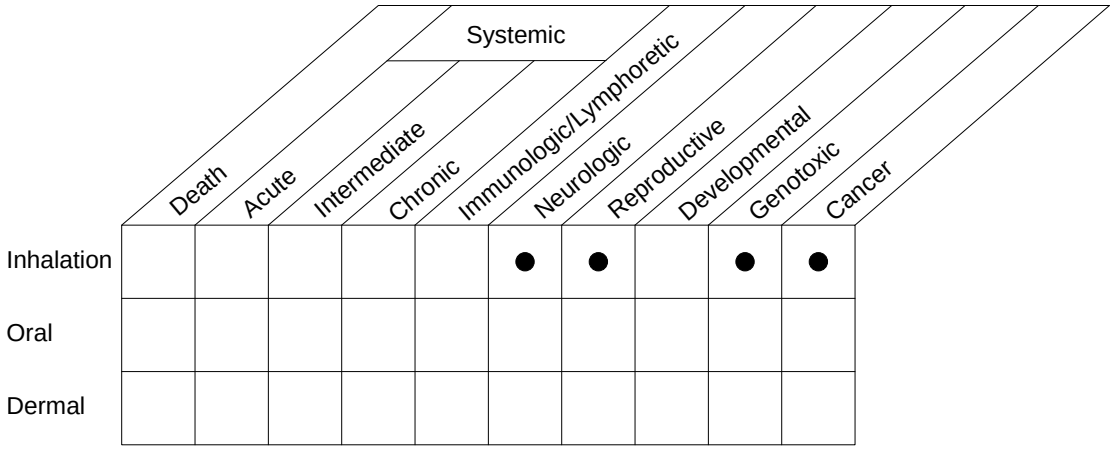
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean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

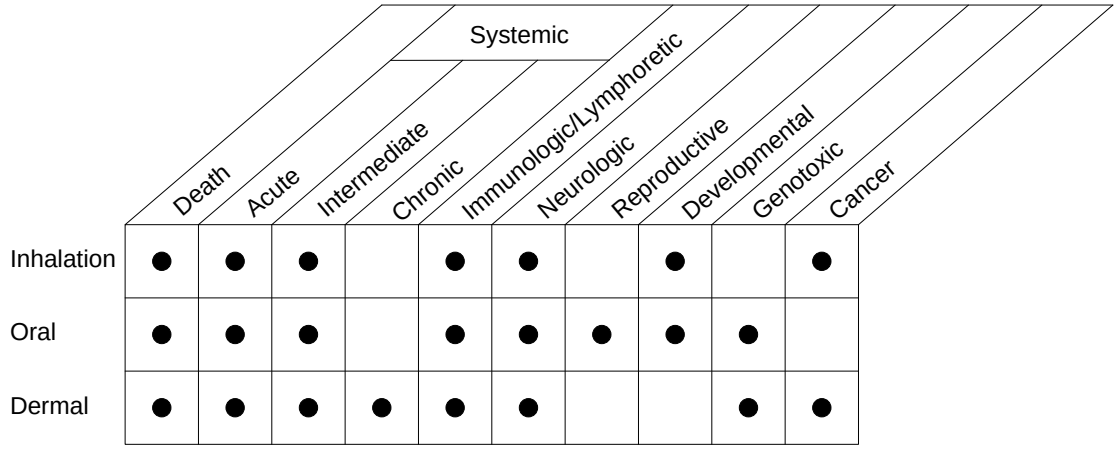
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to JP-5, JP-8, and Jet A fuels are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of JP-5, JP-8, and Jet A fuels. Each dot in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