2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health.officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of jet fuels JP-4 and JP-7 and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for JP-4 and JP-7 based on toxicological studies and epidemiological investigations.

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

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals 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, developmental, reproductive, 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. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine 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 tables and figures may differ depending on the user’s perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with “serious” effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste

sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

The jet fuels JP-4 and JP-7 are liquid military aviation turbine fuels whose composition varies slightly with the nature of the crude petroleum from which they were derived (Dukek 1978). Jet fuels derived from crude oil, the common name for liquid petroleum, are referred to as petroleum-derived jet fuels. Jet fuels derived from an organic material found in shale that can be converted by heat to shale oil are called shale-derived jet fuels. JP-4 is a wide-cut fuel; this is a refinery term indicating that it is distilled from crude oil using a broad temperature range and consists of hydrocarbons in a wide range of chain-lengths (4 to 16 carbons long) (Air Force 1989b; CONCAWE 1985). It was developed by the U.S. Air Force in order to ensure fuel availability in times of war (Dukek 1978; ITC 1985). JP-7 is a kerosene with a high flash point and is used in advanced supersonic aircraft. The jet fuels are blends of various hydrocarbons, including alkanes (paraffins) and cycloalkanes (naphthenes), aromatics, and olefins, as well as small amounts of compounds such as benzene, n-hexane, and polycyclic aromatic hydrocarbons.

The purpose of this chapter is to consider the toxicological effects of exposure to the mixture JP-4 or JP-7. Exposure to jet fuel components, exhaust, or combustion products will not be discussed. 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 for benzene (ATSDR 1991a), toluene (ATSDR 1990), total xylenes (ATSDR 1991c), and polycyclic aromatic hydrocarbons (ATSDR 1991b). In addition, because of the variable composition of the jet fuels, the molecular weights are unknown (Kinkead et al. 1974).

2.2.1 Inhalation Exposure

2.2.1 .I Death

No studies were located regarding death in humans after inhalation exposure to JP-4 or JP-7.

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Exposure of Sprague-Dawley rats to concentrations as high as 5,000 mg/m^3 shale- or petroleum derived JP-4 for 4 hours did not result in any mortality or apparent toxic signs during the 2-week post exposure holding period (Clark et al. 1989).

Intermediate-duration exposure of rats and mice to concentrations of JP-4 as high as 5,000 mg/m^3 resulted in death in 1 of 40 exposed mice and 1 of 50 exposed rats, between 4 and 6 months after the exposure was begun (Air Force 1974). It was concluded that exposure to the test substance was probably not responsible for the deaths of these animals since two unexposed mice and one unexposed rat also died and because there were no abnormal histological findings in the rat. No deaths occurred when dogs or monkeys were exposed to similar JP-4 concentrations for 8 or 6 months, respectively (Air Force 1974).

No increase in mortality was seen in chronic studies in which mice and rats were exposed intermittently (6 hours/day, 5 days/week) to as much as 5,000 mg/m^3 JP-4 (Air Force 1981i; Bruner et al. 1993) or in studies where rats were exposed to 750 mg/m^3 JP-7 (Air Force 19828, 1983e, 1991). Additionally, no increase in mortality was observed in rats or mice 12 months after chronic intermittent exposure (6 hours/day, 5 days/week) to 5,000 mg/m^3 JP-4 (Bruner et al. 1993).

2.2.1.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, musculoskeletal, dermal or ocular effects in humans or animals after inhalation exposure to JP-7. No studies were located regarding gastrointestinal, musculoskeletal, dermal or ocular effects in humans after inhalation exposure to JP-4. No studies were located regarding musculoskeletal or dermal effects in animals after inhalation exposure to JP-4.

The highest NOAEL values and all reliable LOAEL values for systemic effects for each study and end point are recorded in Table 2-l and plotted in Figure 2-l.

Respiratory Effects. No studies were located regarding respiratory effects in humans after inhalation exposure to JP-7.

TABLE 2-1. Levels of Significant Exposure to Jet Fuels/ JP-4 and JP-7 - Inhalation

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
INTERMEDIATE EXPOSURE							
Systemic							
1	Monkey (Rhesus)	6 mo 5 d/wk 6 hr/d	Hemato	5000			Air Force 1974 JP-4
			Hepatic	5000			
			Bd Wt	5000			
2	Rat (Fischer 344)	90 d 7 d/wk 24 hr/d	Hemato	1000			Air Force 1980 JP-4 (PET)
			Hepatic	1000 F	500 M (9% decreased liver weight)		
			Renal	500 M	1000 M (22% increased kidney weight)		
				1000 F			
			Bd Wt	500			
3	Rat (Fischer 344)	90 d 7 d/wk 24 hr/d	Resp	1000			Air Force 1984b JP-4 (PET)
			Hemato	1000			
			Hepatic	1000			
			Renal	1000 F	500 M (hyaline degeneration of renal tubular epithelium, renal tubular casts related to alpha-2μ-globulin nephropathy)		
			Bd Wt		500 (unspecified decreased body weight)		

TABLE 2-1. Levels of Significant Exposure to Jet Fuels/ JP-4 and JP-7 - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
4	Rat (Fischer 344)	90 d 7 d/wk 24 hr/d	Hemato	1000			Air Force 1984c JP-4 (SH)
			Hepatic	500 F	1000 F (5% increased liver weight) 500 M (11% increased liver weight)		
			Renal	1000 F	500 M (19% increased kidney weight, 26% decreased urine osmolality)		
			Bd Wt	1000			
5	Rat (Fischer 344)	90 d 7 d/wk 24 hr/d	Resp	1000 M			Newton et al. 1991 JP-4 (SH)
6	Mouse (C57BL/6)	90 d 7 d/wk 24 hr/d	Resp	1000 F			Air Force 1984b JP-4 (PET)
			Hepatic		500[b] F (fatty degeneration)		
			Renal	1000 F			
7	Dog (Beagle)	8 mo 5 d/wk 6 hr/d	Resp	5000			Air Force 1974 JP-4
			Gastro	2500	5000 (emesis)		
			Hemato	5000 M 2500 F	5000 F (unspecified increased red blood cell fragility)		
			Bd Wt	5000			
8	Dog (Beagle)	90 d 7 d/wk 24 hr/d	Resp	1000			Air Force 1984b JP-4 (PET)
			Cardio	1000			
			Renal	1000			
			Other	1000			

TABLE 2-1. Levels of Significant Exposure to Jet Fuels/ JP-4 and JP-7 - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL			Reference Chemical Form
					Less serious (mg/m3)		Serious (mg/m3)	
	Neurological							
9	Monkey (Rhesus)	6 mo 5 d/wk 6 hr/d			2500	(unspecified depressed activity)		Air Force 1974 JP-4
10	Dog (Beagle)	8 mo 5 d/wk 6 hr/d			2500	(unspecified depressed activity)		Air Force 1974 JP-4
	Reproductive							
11	Rat (F-344, S-D, Wistar, O-M)	90 d 7 d/wk 24 hr/d			1000 M	(at day 90: 3% increased testis weight for Fischer 344 rats)		Air Force 1984d JP-4 (SH)

TABLE 2-1. Levels of Significant Exposure to Jet Fuels/ JP-4 and JP-7 - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
CHRONIC EXPOSURE							
Systemic							
12	Rat (Fischer 344)	1 yr 5 d/wk 6 hr/d	Resp	750			Air Force 1991 JP-7
			Hemato	750 F	150 M (16% decreased WBC count)		
			Hepatic		150[c] (21and 29% increased alkaline phosphatase in males and females respectively, 9% increased absolute liver weight in females)		
			Renal	750 F	150 M (hyaline droplet formation, hydronephrosis,tubular mineralization and 13% increased BUN)		
			Ocular	750			
			Bd Wt		150 (unspecified decrease "throughout the study period")		
13	Rat (Fischer 344)	12 mo 5 d/wk 6 hr/d	Resp	5000			Bruner et al. 1993 JP-4
			Hemato		1000 (23 and 24% reduced mean WBC in females and males, respectively)		
			Hepatic	5000			
			Renal	1000 M	5000 M (mild progressive nephropathies, medullary mineral deposits)		
				5000 F			
			Bd Wt	5000			

TABLE 2-1. Levels of Significant Exposure to Jet Fuels/ JP-4 and JP-7 - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
14	Rat (Fischer 344)	12 mo 5 d/wk 6 hr/d	Resp	5000			Bruner et al. 1993 JP-4
			Hepatic	5000 F	1000 M (11% decreased liver weight - 12 months post-exposure)		
			Renal		1000 (4 and 10%decreased kidney weight in males and females respectively, increased medullary mineral deposits in 14% of males - 12 months post-exposure)		
			Bd Wt	1000			
15	Mouse (C57BL/6)	1 yr 5 d/wk 6 hr/d	Hepatic	750 M	150 F (inflammation after 12-month post-exposure period)		Air Force 1991 JP-7
16	Mouse (C57BL/6)	1 yr 5 d/wk 6 hr/d	Endocr	750 M	150 F (43% increased incidence of adrenal capsular cell hyperplasia)		Air Force 1991 JP-7
17	Mouse (C57BL6)	12 mo 5 d/wk 6 hr/d	Resp		1000 (M: 38% increased nasolacrimal duct hyperplasia. F: 27% increased mild pulmonary inflammation)		Bruner et al. 1993 JP-4
			Hepatic	5000 M 1000 F	5000 F (37% increased lymphocytic inflammatory infiltrates)		
			Renal	5000			
			Bd Wt	5000			

TABLE 2-1. Levels of Significant Exposure to Jet Fuels/ JP-4 and JP-7 - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
18	Mouse (C57BL6)	12 mo 5 d/wk 6 hr/d	Resp	5000			Bruner et al. 1993 JP-4
			Hepatic	5000			
			Renal	5000			
			Bd Wt	5000			
Immuno./Lymphor							
19	Rat (Fischer 344)	12 mo 5 d/wk 6 hr/d		5000 M	1000 F (24% increased spleen weight)		Bruner et al. 1993 JP-4
Reproductive							
20	Rat (Fischer 344)	12 mo 5 d/wk 6 hr/d			5000 (increased cystic degeneration of the prostate in 52% of males; increased cystic hyperplasia of the mammary glands in 35% of females - 12 months post-exposure)		Bruner et al. 1993 JP-4
21	Mouse (C57BL6)	12 mo 5 d/wk 6 hr/d		5000			Bruner et al. 1993 JP-4

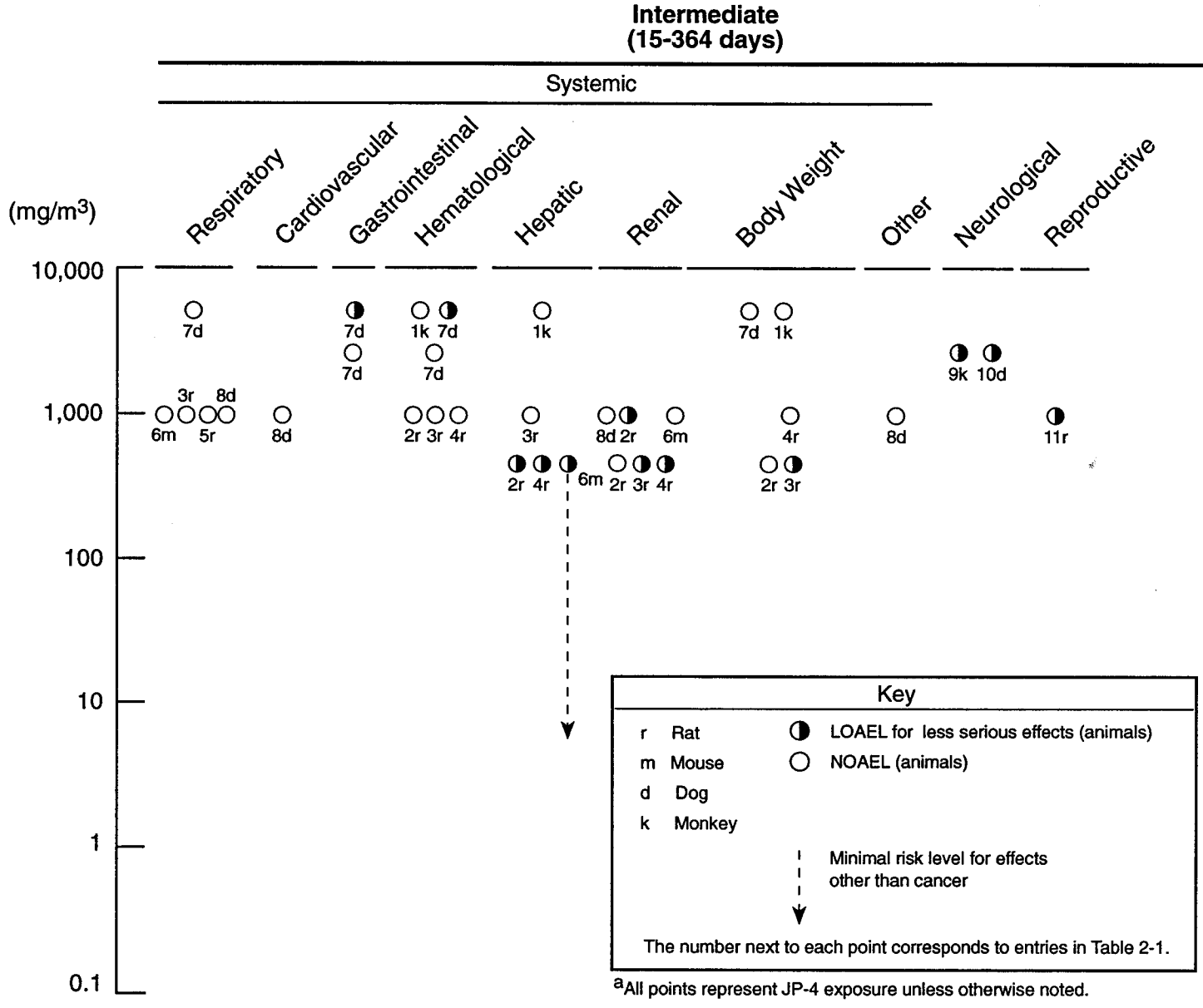
TABLE 2-1. Levels of Significant Exposure to Jet Fuels/ JP-4 and JP-7 - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL			Reference Chemical Form
					Less serious (mg/m3)		Serious (mg/m3)	
22	Mouse (C57BL6)	12 mo 5 d/wk 6 hr/d		5000 F	1000 M	(increased testicular atrophy in 47% of males - 12 months post-exposure)		Bruner et al. 1993 JP-4

[a]The number corresponds to entries in Figure 2-1.
[b]Used to derive an intermediate inhalation minimal risk level (MRL) of 9 mg/m^3, concentration divided by an uncertainty factor of 300 (10 for use of a LOAEL, 3 for interspecies extrapolation, and 10 for human variability) and multiplied by a factor of 5.7 for converting from animal to human exposure.
[c]Used to derive a chronic inhalation MRL of 0.3 mg/m^3, concentration adjusted from intermittent to continuous dosing (150 mg/m^3 x 5 d/7 d x 6 hr/24 hr); adjusted concentration divided by an uncertainty factor of 300 (10 for use of a LOAEL, 3 for interspecies extrapolation, and 10 for human variability) and multiplied by a factor of 3.3 for converting from animal to human exposure.

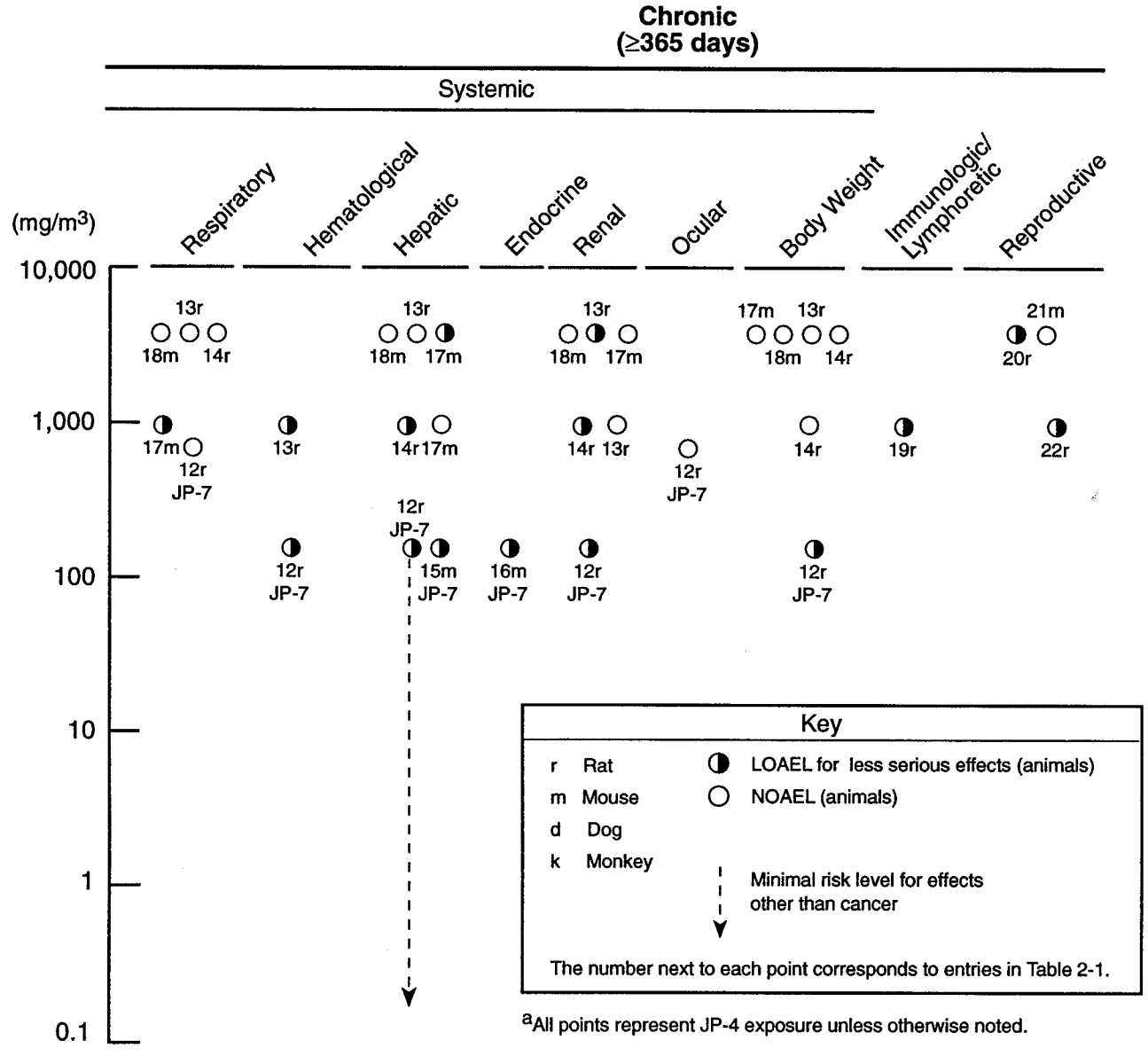
Bd Wt = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); F = female; F-344 = Fischer 344; Gastro = gastrointestinal; HCT = hematocrit; Hemato = hematological; HGB = hemoglobin; hr = hour(s); Immuno./Lymphor = immunological/lymphoreticular; JP-4 = jet propellant-4; JP-7 = jet propellant-7; LOAEL = lowest-observable-adverse-effect level; LT50 = time to 50% kill; O-M = Osborne-Mendel; M = male; MCH = mean corpuscular hemoglobin; mo = month(s); NOAEL = no-observable-adverse-effect level; PET = petroleum-derived; Resp = respiratory; SH = shale-derived; S-D = Sprague-Dawley; WBC = white blood cell; wk = week(s).

Figure 2-1. Levels of Significant Exposure to Jet Fuels[a] – Inhalation



[a]All points represent JP-4 exposure unless otherwise noted.

Figure 2-1. Levels of Significant Exposure to Jet Fuels[a] – Inhalation (continued)



[a]All points represent JP-4 exposure unless otherwise noted.

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A pilot who was exposed to high levels of JP-4 vapor had symptoms of intoxication, but pulmonary function appeared normal upon clinical examination. Lungs were clear to percussion and auscultation, and respirations were normal (Davies 1964). The authors estimated that the exposure levels were between 3,000 and 7,000 ppm, based on the degree of the pilot's neurological impairment.

Intermediate-duration studies in rats revealed normal pulmonary mechanics (lung volume, pressurevolume relationships), pulmonary dynamics (airway resistance, lung compliance), and gas distribution and transfer in anesthetized rats exposed to 1,000 mg/m3 shale-derived JP-4 (Air Force 1985c; Newton et al. 1991). The effects of intermittent exposure to 1,000 or 5,000 mg/m^3 JP-4 were determined in dogs, rats, and mice with up to a 12-month postexposure period (Air Force 1974, 1976, 1984b) indicated that JP-4 did not cause adverse respiratory clinical signs or lung histopathology.

Chronic exposure (12 months) to 1,000 or 5,000 mg/m^3 JP-4 did not cause respiratory tract irritation or pulmonary lesions in rats at the end of the exposure period or 12 months postexposure (Bruner et al. 1993). Differing effects were observed in mice exposed to JP-4 under an identical study design (Bruner et al. 1993). At the end of the 12-month exposure period, mild pulmonary inflammation was seen only in treated females, and hyperplasia of the nasolacrimal duct epithelium was detected only in treated males. However, those effects had disappeared by the end of the 12-month postexposure period.

Cardiovascular Effects. A pilot who was exposed to estimated concentrations of 3,000-7,000 ppm JP-4 did not show any adverse effects on blood pressure or heart sounds (Davies 1964).

Dogs exposed for 90 days to 1,000 mg/m3 JP-4 did not experience cardiac histopathological changes (Air Force 1984b).

Gastrointestinal Effects. Exposure to 5,000 mg/m^3 JP-4 for 8 months caused emesis in male and female dogs (Air Force 1974), but no emesis was seen at 2,500 mg/m^3 JP-4.

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Hematological Effects. No studies were located regarding hematological effects in humans after inhalation exposure to JP-7.

Accidental exposure of a pilot to a high concentration of JP-4 during a leak in the jet's fuel system did not result in any abnormalities in hematological or clinical chemistry tests during a physical examination performed after an unspecified period of time had passed since the exposure (Davies 1964).

Hematological parameters have been measured on a routine basis during exposure of animals to JP-4 and JP-7 in intermediate- and chronic-duration studies. Such measurements have included red and white blood cell counts, methemoglobin concentration, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, hematocrit, and hemoglobin concentration. Exposure for 90 days to 1,000 mg/m^3 JP-4 caused increased white blood cell counts and increased the mean corpuscular hemoglobin in Fischer 344 rats (Air Force 1984d). In the same study, increased white blood cell counts and decreased hematocrit and hemoglobin concentrations were observed in Osborne-Mendel rats. In contrast, continuous exposure (24 hours/day) of rats to 1,000 mg/m^3 JP-4 vapor for 90 days did not affect white blood cell and red blood cell counts in males or females (Air Force 1980).

Treatment for 12 months, 5 days/week, 6 hours/day with 0, 1,000, or 5,000 mg/m^3 JP-4 revealed a treatment-related decrease in white blood cell count and blood glucose levels in exposed male and female rats at the conclusion of the exposure period (Bruner et al. 1993). Histopathological evaluation of various tissues in the exposed rats did not reveal a definitive cause for the decreases in white blood cells. However, bone marrow cytopenia was reported to be of borderline statistical significance (significance level not specified) in the treated animals. The incidence in males of this finding was 0%, 1%, and 4% for the control, low, and high concentrations, respectively. Incidence in females was 0%, 0%, and 2%, respectively. These findings may have contributed to the decreases in white blood cell count. The LOAEL for this effect was 1,000 mg/m^3.

The results of hematological tests conducted in monkeys and dogs following intermediate-duration (Air Force 1974, 1984c) or chronic-duration exposures (Air Force 1981i) revealed no significant effects that were dose dependent or out of the range of normal biological variation.

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Intermediate-duration exposure of animals to 2,500 or 5,000 mg/m^3 JP-4 was tested in combination with 12.5 or 25 ppm benzene, respectively (Air Force 1974). Benzene was administered in combination with the jet fuel because benzene is sometimes a contaminant of jet fuels and exposure to benzene is associated with hematological effects. Both air-exposed controls and a positive control group were used for comparison. Three species of animals were exposed to 25 ppm benzene so that the level would not exceed that equivalent to a 6-hour time-weighted average concentration of 10 ppm (Air Force 1974, 1976). For further information on the hematological effects of benzene, refer to the ATSDR toxicological profile for benzene (ATSDR 1991a). In this study, the myeloid/erythroid ratio in rats and the hematocrit, hemoglobin, and red blood cell counts in monkeys were not different from those of the air-exposed control group after 6 months of exposure to JP-4 (Air Force 1974). However, between weeks 12 and 24 of this study, red blood cell fragility was abnormally high in female dogs exposed to 5,000 mg/m^3 JP-4 (Air Force 1974). This effect was transient, since red blood cell fragility was normal at the end of the exposure. No concomitant hemolytic changes occurred in these animals, and the mechanisms and significance, if any, of these findings are unclear. In a 90-day continuous exposure (24 hours/day) of male and female dogs (3 per group) to 500 or 1,000 mg/m^3, there was no increase in red blood cell fragility (Air Force 1980).

Rats chronically exposed to 750 mg/m^3 JP-4 did not exhibit any abnormal hematology, but alkaline phosphatase and blood urea nitrogen were elevated at 150 mg/m^3 (Air Force 1991).

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to JP-4 or JP-7.

Hepatocellular fatty change occurred in the livers of 88-89% of JP-4-exposed C57BL/6 mice (50 females/group) after 90 days of continuous exposure (24 hours/day) to 500 or 1,000 mg/m^3 (Air Force 1984b). The lesions in mice were described as multiple, discrete vacuoles of varying sizes within the hepatocytes. They occurred primarily in the centrilobular region of the liver and were regarded as reversible degenerative processes. The incidence of these lesions immediately after the exposure period was 3/49 for controls, 42/48 (87%) for 500 mg/m^3, and 40145 (88%) for 1,000 mg/m^3 JP-4. A LOAEL of 500 mg/m^3 was identified for fatty changes in the liver. The incidence of sinusoidal hematopoiesis also increased with increasing exposure concentration; however, statistical significance was only achieved in the 1,000-mg/m^3 group. Rats and dogs, also included in that study, did not develop histopathological liver changes. In contrast, intermediate exposure to 500 or 1,000 mg/m^3

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JP-4 has been shown to increase (Air Force 1980, 1984c, 1984d) male rat liver weight, but doses as high as 1,000 mg/m^3 JP-4 apparently have no effect on female rat liver weight (Air Force 1980, 1984c).

Chronic (12 months), intermittent exposure (5 days/week, 6 hours/day) to 1,000 or 5,000 mg/m^3 JP-4 caused no liver toxicity in rats that were examined at the end of the 12-month exposure period (Bruner et al. 1993). However, in a subset of the exposed animals examined 12 months after the end of the exposure period, the same doses caused non-dose-related decreases in male, but not female, rat liver weight (Bruner et al. 1993). In mice exposed to JP-4 under an identical study design, there was an increase in lymphocytic inflammatory infiltrates in the livers of high-dose female mice, but not males, at the end of the 12-month exposure period (Bruner et al. 1993). However, that effect was no longer evident 12 months after the end of the exposure period.

Chronic exposure of C57BW6 mice to 0 (control), 150, or 750 mg/m^3 JP-7 resulted in an increased incidence of hepatic inflammation in female mice exposed to 750 mg/^{3} after a l-year postexposure period (Air Force 1991). One year after the end of the exposure period, hepatic inflammation was discovered in females from both the 150 and 750 mg/m^3 groups. Hepatic inflammation was not observed in the exposed males. A LOAEL of 150 mg/m^3 was identified for hepatic inflammation in female mice.

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to JP-4 or JP-7.

Blood urea nitrogen was elevated, but considered to be within normal limits, in Fischer 344 rats exposed continuously (24 hours/day) for 90 days to 500 or 1,000 mg/m^3 shale- or petroleum-derived JP-4 (Air Force 1980, 1984c). In a subsequent l-year study using an intermittent exposure protocol (6 hours/day, 5 days/week) and a higher concentration of JP-4 (5,000 mg/m^3), blood urea nitrogen was increased only in female rats (Air Force 1981i). Thus, no consistent effect was seen in this parameter with JP-4 exposure.

The effects of intermediate (24 hours/day for 90 days) exposure to 500 or 1,000 mg/m^3 shale-derived JP-4 was determined in rats (Air Force 1984c). Increased kidney weight was observed in male rats at 500 mg/m^3, but no effect on kidney weight was seen in females at either dose of JP-4. Urinalysis

conducted in the male rats revealed a 50-70% decrease in osmolality at termination of exposure and 2 weeks postexposure. Urine pH was not affected. The decreased osmolality was also found when comparing the renal effects in four strains of male rats (Fischer 344, Sprague-Dawley, Wistar, and Osborne-Mendel) after 90 days of continuous exposure (24 hours/day) to 1,000 mg/m^3 JP-4 (Air Force 1984d). In this study, rats from all four strains were killed midway through the exposure period (45 days) and at the end of the exposure period. No effect on urine osmolality was observed at the 45-day interim kill. But after 90 days, urine osmolality.was statistically decreased in all except the Wistar strain of rats. Urine osmolality was decreased in the Wistar rats, but the variability in the treated group prevented statistical significance from being reached. Blood urea nitrogen was transiently elevated in the Fischer 344 and Sprague-Dawley strains at 45 days of exposure. That effect was not detected in any strain at the end of the dosing period. Similarly, blood creatinine levels were elevated after 45 days of exposure in the Fischer 344 and Wistar rats, but that effect was also transient as no differences were found in blood creatinine in any strain after 90 days of exposure. Kidney weight was increased in all strains at the end of the 90-day exposure period. The methods section in the report states that additional animals were allowed to live for 6 or 12 months postexposure, but there is no mention of those animals in any other section of the report. Consequently, it is not known if the renal effects persisted after dosing had concluded.

Absolute kidney weight was increased in male Fischer 344 rats exposed continuously (24 hours/day) for 90 days (Air Force 1980) to 500 or 1,000 mg/kg JP-4 and Sprague-Dawley rats exposed intermittently (6 hours/day, 5 days/week) for 8 months (Air Force 1976) to 5,000 mg/m^3 JP-4. Chronic (12 months) intermittent exposure to 1,000 or 5,000 mg/m^3 JP-4 decreased kidney weight in male and female rats 12 months after the end of the exposure period (Bruner et al. 1993).

Histopathological changes have also been observed following intermediate- and chronic-duration exposure to JP-4 treatment (Air Force 1984b; Bruner et al. 1993) or chronic JP-7 treatment (Air Force 1991). Microscopic examination of the kidneys revealed hyaline droplet formation in renal proximal tubular epithelium in both dose groups; this effect was more severe in high dose animals, indicating a dose-response relationship in male rats exposed to 1,000 or 5,000 mg/m^3 JP-4 (Air Force 1984b). In addition, there were intratubular casts of necrotic debris in the outer renal medulla. Mild progressive kidney neuropathies and medullary mineral deposits were observed in male, but not female, rats exposed to 5,000 mg/m^3 JP-4 for 12 months, 6 hours/day, 5 days/week (Bruner et al. 1993). Twelve months after the conclusion of the exposure period, medullary mineral deposits were still present in the

5,000 mg/m^3 group. Moreover, those changes were also seen in the kidneys of rats exposed to 1,000 mg/m^3 JP-4 (Bruner et al. 1993). Similar effects were observed in rats after 1 year of intermittent exposure to 150 or 750 mg/m^3 JP-7 (Air Force 1991). No nephrotoxicity was observed in mice following chronic (12 months), intermittent exposure to 1,000 or 5,000 mg/m^3 JP-4 (Bruner et al.1993).

The histopathological changes described above are characteristic of a syndrome of nephropathy unique to male rats following intermediate- or chronic-duration inhalation exposure to hydrocarbons (Bruner et al. 1993). These changes have also been found to increase with age (Air Force 1991). This syndrome was not induced in female rats (Air Force 1976, 1984b, 1991; Bruner et al. 1993), mice of either sex (Air Force 1976, 1980, 1984b; Bruner et al. 1993), or dogs of either sex (Air Force 1984b) when exposed to JP-4 or JP-7. This type of nephropathy appears to be unique to male rats and is most likely not relevant to humans (EPA 1991) (see Section 2.4); therefore, this end point was not used for MRL derivation.

Endocrine Effects. Chronic (12 months) intermittent exposure to 5,000 mg/m^3 JP-4 in rats caused an increase in cystic degeneration of the prostate 12 months postexposure (Bruner et al. 1993). No effects were observed in female rats, or in mice of both sexes, under identical exposure conditions (Bruner et al. 1993).

Ocular Effects. Chronic (1 year, 5 days/week) exposure to 750 mg/m^3 did not cause any histopathological changes in the eyes of male or female rats (Air Force 1991).

Body Weight Effects. The effects of intermediate exposure to between 500 and 1,000 mg/m^3 JP-4 on body weight has not been consistent. Intermediate-duration exposure of rats to JP-4 decreased the body weight of male (Air Force 1980, 1984b) and female (Air Force 1980, 1984b, 1984c) rats. However, similar doses and dosing models produced no effect on rat body weight (Air Force 1984d). Additionally, doses of JP-4 as high as 5,000 mg/m^3 did not affect the body weight of dogs (Air Force 1974) or monkeys (Air Force 1974).

Chronic (1 year, 5 days/week, 6 hours/day) exposure to 750 mg/m^3 JP-4 had no effect on rat body weight (Air Force 1991). Similarly, chronic exposure to 1,000 or 5,000 mg/m^3 JP-4 did not adversely affect body weight in rats immediately after a 12-month exposure period (Bruner et al. 1993).

However, 1,000 mglm^3 caused minor body weight reductions (3-4%) in both female and male rats 12 months postexposure (Bruner et al. 1993). This statistically significant decrease in body weight is not considered to be biologically significant. Mice exposed to 1,000 or 5,000 mg/m^3 JP-4 for 1 year did not exhibit adverse body weight effects either at the end of the exposure period or 12 months postexposure (Bruner et al. 1993).

Other Systemic Effects. Histological exammation of rat lymph nodes after the intermediate exposure to 1,000 mg/m^3 JP-4 did not reveal any abnormalities (Air Force 1984b). Chronic exposure to 5,000 mg/m^3 JP-4 in rats increased the incidence of cystic hyperplasia of the mammary glands 12 months after a l-year intermittent exposure period (Bruner et al. 1993).

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans after inhalation exposure to JP-4 or JP-7. Additionally, no studies were found regarding immunological and lymphoreticular effects in animals after inhalation exposure to JP-7.

Chronic (12 months) intermittent exposure to 1,000 mg/m^3 JP-4 was found to increase spleen weight in female rats at the end of the dosing period (Bruner et al. 1993). However, no effect on spleen weight was observed at the higher dose of 5,000 mg/m^3 or at either dose 12 months after the end of the exposure period.

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals after inhalation exposure to JP-7.

Acute exposure to a high level of JP-4 (3,000-7,000 ppm) from a fuel leak on a routine flight produced a groggy, weak, intoxicated state in the pilot (Davies 1964). Neurological examination revealed that the mild intoxication was accompanied by normal cardiovascular and respiratory function. The pilot had a staggering gait, mild muscular weakness, decreased sensitivity to painful stimuli, slight slurring of speech, and a positive Romberg; these effects were no longer evident 36 hours postexposure.

2. HEALTH EFFECTS

Animals acutely exposed by inhalation to very high concentrations of JP-4 (38,000 mg/m^3) exhibited neurotoxic effects including poor coordination and convulsions (Air Force 1974). Dogs (4 males, 2 females/exposure level), monkeys (1 male, 3 females/exposure level), rats (50 males/exposure level), and mice (40 females/exposure level) were exposed to 0, 2,500, or 5,000 mg/m^3 JP-4, 6 hours/day, 5 days/week for 6 months (rats, mice, and monkeys) or 8 months (dogs) (Air Force 1974). During the initial 3 weeks of exposure, dogs were reported to have decreased activity compared to control animals. When the animals were not sleeping, they were reported to be "quiescent and prostrate" during exposure periods. Monkeys in both JP-4 groups also demonstrated decreased activity, but to a lesser extent than the dogs. Rats and mice did not exhibit neurological signs at either dose of JP-4.

No long-term epidemiological studies were located regarding exposure to JP-4.

No NOAEL values for neurological effects of JP-4 were recorded in Table 2-l or plotted in Figure 2-l. The case study (Davies 1964) has inadequately characterized exposure conditions and the intermediate animal exposure studies lacked presentation of important experimental details.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to JP-4 or JP-7. Additionally, no studies were found regarding reproductive effects in animals after inhalation exposure to JP-7.

Chronic (12 months) exposure to 1,000 or 5,000 mg/m^3 of JP-4 did not adversely affect the testis in rats, but did cause testicular atrophy in mice 12 months after the end of exposure period (Bruner et al. 1993).

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to JP-4 or JP-7.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after *in vivo* inhalation exposure to JP-4 or JP-7. Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding carcinogenic effects in humans after inhalation exposure to JP-4 or JP-7.

Long-term animal studies were conducted to investigate the potential of JP-4 or JP-7 to induce cancer in laboratory animals. Groups of 50 male Sprague-Dawley rats and 40 female CF-1 mice were exposed to JP-4 intermittently (6 hours/day, 5 days/week) for 8 months. Interim sacrifices were performed immediately after exposure and at 12 months postexposure (Air Force 1976). No increase in the incidence of tumors was seen in any group following gross and histopathologic examination of tissues from either rats or mice.

Fischer-344 rats exposed chronically to JP-4 for 12 months at 5,000 mg/m^3 had an increased incidence of interstitial cell tumors in the testis 12 months after the termination of the exposure period (Bruner et al. 1993). Under an identical exposure regimen, no effect on the incidence of neoplastic lesions was seen in mice (Bruner et al. 1993). A l-year JP-7 exposure produced no toxicologically significant treatment-related neoplastic lesions in mice or rats except for a small increase in the incidence of C-cell adenomas and kidney adenomas in male rats exposed to 750 mg/m^3 of JP-7 (Air Force 1991).

The exposure period in the above carcinogenicity studies was only 1 year compared to the 2 years (lifetime) of exposure normally included in standard carcinogenicity assays. This less-than-lifetime exposure was chosen because the authors believed it is more typical of military occupational exposure to jet fuels. Nevertheless, the results from the above studies suggest that jet fuels JP-4 and JP-7 are not carcinogenic to humans.

2. HEALTH EFFECTS

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to JP-4 or JP-7, or in animals after oral exposure to JP-7.

The acute oral administration of 5,000 mg/kg (Clark et al. 1989) or 8,000 mg/kg (Air Force 1974) shale-derived JP-4 to rats did not result in treatment-related mortality. Two of three mice died after administration of 500 mg/kg JP-4; one of three mice died after administration of 1,000 mg/kg (Air Force 1974). However, no histopathology was performed on these animals and the numbers of mice dosed in this study were so small that the reported deaths are not necessarily relevant.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, or body weight effects in humans or animals after oral exposure to JP-4 or JP-7.

No studies were located regarding the following health effects in humans or animals after oral exposure to JP-4 or JP-7:

2.2.2.3 Immunological and Lymphoreticular Effects

2.2.2.4 Neurological Effects

2.2.2.5 Reproductive Effects

2.2.2.6 Developmental Effects

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to JP-4 or JP-7, or in animals after oral exposure to JP-7.

Two dominant lethal studies were found in the literature where mice or rats were orally exposed to JP-4. Ten random-bred, male CD-l mice received the compound in their food for 5 consecutive days at concentrations of 7.6, 22.8, and 68.4 mg/kg (0.01, 0.03, and 0.09 mL/kg, respectively). Two days after the last treatment, each male was caged with two untreated virgin females for 7 days. At the end of 1 week, the females were replaced with two new untreated females; this process was repeated for 7 weeks. The females were killed 14 days after the midweek of mating, and their uteri were examined for live, dead, and total implantation. When the negative controls were compared to the treated females, no significant differences were noted for dominant lethal effects. This finding suggests that JP-4 was not clastogenic in the germinal cells of male mice (Air Force 1978a). However, the results cannot be considered conclusive because of the small number of pregnant females used in the study. The interpretation of the results is further confounded by the fact that the highest dose used in the study was probably too low to cause significant cellular toxicity.

Ten random-bred male rats were exposed to JP-4 by gavage for 5 consecutive days (Air Force 1978a). The concentrations tested were 68.4, 228, and 684 mg/kg (0.09, 0.3, and 0.9 mL/kg, respectively). The mating protocol was the same as that used in the mouse dominant lethal experiment. The administration of JP-4 did not decrease the average number of implantations per litter except after the fourth week of mating, when a transient decrease of 31-50% was noted for the low through high doses of JP-4, respectively. Individually significant reductions in the number of implants per litter were detected only for the 0.3 mL/kg group at that time. There was no increase in the average number of resorptions per litter or in the average number of late fetal deaths. Thus, the effects appeared to be confined to the pre-implantation phase. Except for the effects noted for week 4, indices of reproductive function were comparable to controls. Since there were no significant dominant lethal effects corresponding to the pre-implantation effects, the researchers considered the results to be negative (Air Force 1978a). As in the mouse study, the sample size of pregnant female rats per group was small, which renders the study inconclusive.

Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans or animals after oral exposure to JP-4 or JP-7.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to JP-4 or JP-7, or in animals after dermal exposure to JP-7.

Acute (24 hours) dermal application of 2,000 mg/kg shale-derived JP-4 (Clark et al. 1989; Dennis 1982a) or petroleum-derived JP-4 (Clark et al. 1989) to rabbits did not result in mortality after a 24-hour or 14-day time period, respectively. No rabbits died after dermal application of 0.5 mL undiluted JP-7 to the skin (Air Force 1984a).

Application of shale-derived JP-4 to the skin of C3H mice on a chronic basis resulted in a greater survival rate compared to those treated with petroleum-derived JP-4 (Clark et al. 1988). At week 52 of a 105-week study in which animals were treated with shale-derived JP-4, the survival rate was ≈90% compared to ≈72% in animals treated with petroleum-derived JP-4. By the end of the 2-year study, both groups had similar survival rates (≈15%). However, petroleum-derived JP-4 appeared to have greater toxicity than shale-derived JP-4 by virtue of the higher mortality that occurred in the first year of exposure, and both groups had a lower survival rate than controls (≈50%). More information regarding the differences between shale- and petroleum-derived jet fuels is provided in the introduction to Chapter 4. Both groups appeared to have a higher mortality than did control animals, although no statistics were shown. Mortality resulted from inflammatory lesions at the site of the test material application and subsequent septicemia. The mortality data from those studies were not included in Table 2-2 because of the lack of statistical testing.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, or musculoskeletal effects in humans or animals after dermal exposure to JP-4 or JP-7. The highest NOAEL values and all reliable LOAEL values for systemic effects for each study and end point are recorded in Table 2-2.

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to JP-4 or JP-7 or in animals after dermal exposure to JP-7.

Application of 2,000 mg/kg shale-derived JP-4 to the skin of rabbits for 24 hours did not result in hepatic lesions after a 14-day postexposure period (Dennis 1982a).

Renal Effects. No studies were located regarding renal effects in humans after dermal exposure to JP-4 or JP-7 or in animals after dermal exposure to JP-7.

Dermal application of 2,000 mg/kg shale-derived JP-4 in five male and five female rabbits for 24 hours did not result in pathological renal effects related to the test material after a 14-day postexposure period (Dennis 1982a). In one animal, a pathological lesion was noted on one kidney but was not believed to be related to the test material.

Dermal Effects. No studies were located regarding dermal effects in humans after dermal exposure to JP-4 or JP-7.

Experiments in rabbits show that acute exposure to JP-4 or JP-7 is irritating to the skin. Application of 0.5 mL undiluted JP-4 (both shale- and petroleum-derived) produced severe irritation that was characterized by edema and erythema 24 hours post-application (Air Force 1984a; Clark et al. 1989; Dennis 1982b; Walter 1982c), whereas the application of the same amount of JP-7 was shown to produce slightly greater irritation that persisted for a longer period of time (Air Force 1984a). Chronic application of 25 mg undiluted petroleum- or shale-derived (from hydrotreated crude shale) JP-4 to the skin of mice resulted in initial dermal irritation that progressed to necrosis and visible separation and sloughing of skin (Clark et al. 1988).

TABLE 2-2. Levels of Significant Exposure to Jet Fuels/ JP-4 and JP-7 - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference Chemical Form
				Less Serious	Serious	
ACUTE EXPOSURE						
Systemic						
Rabbit (New Zealand)	24 hr	Dermal		0.5 mL	(no skin irritation at 24 hours but moderate erythema at 72 hours)	Air Force 1984a JP-4 (PET)
Rabbit (New Zealand)	24 hr	Dermal		0.5 mL	(severe primary dermal irritation; moderate erythema, mild edema at 72 hours)	Air Force 1984a JP-4 (SH)
Rabbit (New Zealand)	24 hr	Dermal		0.5 mL	(severe primary irritation, slight edema, moderate erythema at 72 hours)	Air Force 1984a JP-7
Rabbit (New Zealand)	once	Ocular	0.1 mL			Air Force 1984a JP-4 (PET)
Rabbit (New Zealand)	once	Ocular	0.1 mL			Air Force 1984a JP-4 (SH)
Rabbit (New Zealand)	24 hr	Hepatic	2000 mg			Dennis 1982a JP-4 (SH)
		Renal	2000 mg			
		Dermal		2000 mg	(mild inflammation discoloration of skin)	
Rabbit (New Zealand)	24 hr	Dermal		0.5 mL	(severe dermal irritation)	Dennis 1982b JP-4 (SH)

TABLE 2-2. Levels of Significant Exposure to Jet Fuels/ JP-4 and JP-7 - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form
Gn pig (Hartley)	4 x	Dermal	0.1 mL					Air Force 1984a JP-4 (PET)
Gn pig (Hartley)	4 x	Dermal		0.1 mL	(weak to mild dermal sensitization potential)			Air Force 1984a JP-7
Gn pig (Hartley)	2 d	Dermal		0.1 mL	(mild to moderate dermal sensitization)			Air Force 1984a JP-4 (SH)
Gn pig (HLA Hartley)	3 wk 1 x/wk 6 hr	Dermal	0.25 M mL					Clark et al. 1989 JP-4 (PET)
Gn pig (HLA Hartley)	3 wk 1 x/wk 6 hr	Dermal	0.25 M mL					Clark et al. 1989 JP-4 (SH)
INTERMEDIATE EXPOSURE								
Systemic								
Gn pig (Hartley)	3 wks 1 x/wk 6 hr/day	Dermal	0.25 M mL					Walter 1982c JP-4 (PET)
CHRONIC EXPOSURE								
Cancer								
Mouse (C3H/Hen)	105 wk 3 x/wk					25 mg	(24 and 17% increased incidence of squamous cell carcinoma and fibrosarcoma, respectively)	Clark et al. 1988 JP-4 (SH)

TABLE 2-2. Levels of Significant Exposure to Jet Fuels/ JP-4 and JP-7 - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL			Reference Chemical Form
				Less Serious	Serious		
Mouse (C3H/Hen)	105 wk 3 x/wk				25 mg	(increased incidence of squamous cell carcinoma and fibrosarcoma)	Clark et al. 1988 JP-4 (PET)

d = day(s); Derm = dermal; Gn Pig = guinea pig; hr = hour(s); JP-4 = jet propellant-4; JP-7 = jet propellant-7; LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level; NS = sex not specified; PET = petroleum-derived; SH = shale-derived; wk = week(s); x = times.

2. HEALTH EFFECTS

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to JP-4 or JP-7.

There was no evidence of primary ocular irritation after application of undiluted shale-derived JP-4, undiluted petroleum-derived JP-4, or JP-7 to the eyes of rabbits (Air Force 1984a; Clark et al. 1989; Dennis 1982c; Walter 1982a). Some studies (Walter 1982a) noted that when shale-derived JP-4 was applied and not rinsed from the rabbits' eyes, minimal irritation (0.3 out of a maximum 2.0 score) resulted 24 hours after instillation of test material. The irritation cleared by the 7th day postexposure.

2.2.3.3 Immunological and Lymphoreticular Effects

No information is available on the immunological effects of JP-4 or JP-7 in humans or animals following dermal exposure.

JP-4 (shale-derived or petroleum-derived) did not cause dermal sensitization in guinea pigs when applied to the skin in a 50% dilution in mineral oil (Clark et al. 1989; Walter 1982c). However, JP-7 and shale-derived JP-4 have sensitization potential (Air Force 1984a). Data regarding the immunological effects of JP-4 are limited to the dermal sensitization tests conducted in guinea pigs (Air Force 1984a; Clark et al. 1989; Walter 1982c). In these studies petroleum-derived JP-4 was not found to be a dermal sensitizer. However, JP-7 and shale-derived JP-4 have weak-to-mild and mildto-moderate sensitization potential, respectively (Air Force 1984a).

No studies were located regarding the following health effects in humans or animals after dermal exposure to JP-4 or JP-7:

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects after dermal exposure to JP-4 or JP-7 in humans, or in animals after dermal exposure to JP-7.

The effects of intermittent (3 times/week) dermal administration of 25 mg of shale- or petroleumderived JP-4 to the skin of mice for 105 weeks on the incidence of neoplasms was studied (Clark et al. 1988). Squamous cell carcinoma and fibrosarcoma formation was increased in the mice exposed to shale-derived (50% incidence) and petroleum-derived JP-4 (26% incidence) compared to the appropriate control groups (2% and 0%, respectively). In general, shale-derived JP-4 (derived from hydrotreated crude shale oil) had greater irritant and carcinogenic potency than did petroleum-derived JP-4. The positive control substances, crude shale-derived and petroleum-derived oils (not hydrotreated), had skin cancer incidences of 54% and 84%, respectively. Other histopathological diagnoses were judged by the authors to be secondary to the long-term irritation at the test site. The most noteworthy of these diagnoses was reactive hyperplasia of the spleen and bone marrow that probably resulted from septicemia that developed from the attendant inflammation, necrosis, and infection at the application site. The incidence of these findings was not reported.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located that examined the absorption of JP-4 or JP-7 in humans or animals after inhalation exposure. However, indirect evidence from the case report of a pilot exposed to a JP-4 fuel leak indicates that JP-4 can be absorbed following inhalation exposure in humans (Davies 1964). Animals exposed to JP-4 on an acute, intermediate, or chronic basis, or exposed chronically to JP-7,

also exhibited effects that provide evidence for inhalation absorption in animals (Air Force 1974, 1976, 1980, 1983, 1984b, 1985b, 1991; Bruner et al. 1993).

2.3.1.2 Oral Exposure

There is no quantitative information on the absorption of JP-4 or JP-7 following oral exposure in humans or animals.

2.3.1.3 Dermal Exposure

There is no quantitative information on the absorption of JP-4 or JP-7 following dermal exposure in humans or animals. Animal studies have shown that both JP-4 and JP-7 are irritating to the skin (Air Force 1984b; Clark et al. 1988, 1989; Dennis 1982b; Walter 1982a, 1982c), and long-term studies have demonstrated the carcinogenic potential of JP-4 at the site of application (Clark et al. 1988). However, no effects have been reported in these studies in organs or tissues distant from the site of application of the test material.

2.3.2 Distribution

There is no quantitative information on the distribution of JP-4 or JP-7 following inhalation, oral, or dermal exposure in humans or animals. However, liver effects after treatment of mice with JP-4 suggest distribution to that organ (Air Force 1984b; Bruner et al. 1991).

2.3.3 Metabolism

There is no quantitative information on the metabolism of JP-4 or JP-7 following inhalation, oral, or dermal exposure in humans or animals.

2.3.4 Excretion

There is no quantitative information on the excretion of JP-4 or JP-7 following inhalation, oral, or dermal exposure in humans or animals.

2.3.5 Mechanisms of Action

It is apparent from animal studies described in the earlier sections that exposure to JP-4 or JP-7 causes toxicity, but data have been descriptive (e.g., decreased liver weight) instead of mechanistic (e.g., slows nerve conduction). Additionally, the absorption and distribution of the jet fuels is not understood. Thus, insufficient data exist for postulating a mechanism of action. Moreover, since both fuels are complex mixtures, it seems likely that elucidating a mechanism of action would be difficult.

2.4 RELEVANCE TO PUBLIC HEALTH

Exposure to JP-4 and JP-7 may occur via the inhalation, oral, or dermal routes, but exposure by inhalation is most likely because of the high volatility of many of the jet fuel components. Military personnel and those involved in the manufacture of the jet fuels are at the greatest risk for exposure because the fuels are produced only for military use. Thus, apart from those individuals involved in the manufacturing process, persons living or working near or on a military base would constitute the greatest population at risk for JP-4 and JP-7 exposure. Additionally, military personnel stationed on aircraft carriers or submarines would also be at increased risk.

JP-4 and JP-7 are also found in waste sites, so exposure of the general public to the fuels in those areas is possible, but not likely. Moreover, because the jet fuels are complex mixtures of components with differing volatilities, solubilities, and biodegradation potentials, it is probable that people will be exposed to only a subset of the components from the original mixture. However, because of the large number of components in JP-4 and JP-7, it is impractical, if not impossible, to predict what components of the original mixture will be present at a waste site. Therefore, the inhalation exposure MRLs described below are based on the concentration of the original complex mixture. Additionally, the concentrations of JP-4 or JP-7 reported in the studies used to derive the MRLs are based on the concentration of total hydrocarbons present in the vapors after the original mixture was heated to 50 °C.

2. HEALTH EFFECTS

Minimal Risk Levels for Jet Fuels JP-4 and JP-7.

Inhalation MRLs.

Only one controlled acute-duration inhalation exposure study for JP-4 was found (Clark et al. 1989), and it was limited by a low number of animals per group. No acute-duration exposure studies were located for JP-7. Thus, no acute inhalation MRLs'"were calculated for JP-4 and JP-7. However, sufficient information exists for the calculation of intermediate and chronic exposure MRLs for JP-4 and JP-7, respectively. The MRLs are based on hepatic toxicity because the liver appears to be a target organ for JP-4- and JP-7-related toxicity (Air Force 1974, 1984b, 1984c, 1991; Bruner et al. 1993).

- An MRL of 9 mg/m^3 has been derived for intermediate-duration inhalation exposure (15-364 days) to JP-4.

The intermediate inhalation exposure MRL of 9 mg/m^3 was based on an increase in hepatic toxicity observed in mice at 500 mg/m^3 (Air Force 1984b). In that study, female C57BL/6 mice (150/group) were exposed to 0, 500, or 1,000 mg/m^3 of petroleum-derived JP-4 continuously for 90 days. The variation in the day-to-day concentration of JP-4 was reported to be less that 1%. Hepatocellular fatty changes were seen in both dose groups. The changes were described as multiple, discrete vacuoles of varying sizes within the cytoplasm of hepatocytes, especially in the centrilobular region of the liver. The incidence of the hepatic fatty degenerative changes was 6%, 15%, and 25% in the control, 500 mg/m^3, and 1,000 mg/m^3 groups, respectively. Renal tubular dilatation was also increased at 500 mg/m^3, but not at 1,000 mg/m^3. This was thought to be an incidental finding resulting from mild glomerulonephritis, common in aging mice. Inflammation and lymphocytic inflammatory infiltrate was found in females exposed to 500 mg/m^3 and was frequently accompanied by hyaline degeneration. These findings are common in older C57BW6 mice, and because the effects were not dose-dependent, they were not considered to be treatment-related. Based on the increased incidence of hepatic toxicity at 500 mg/m^3 JP-4 and an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for interspecies extrapolation, and 10 for human variability) and a human equivalent dose conversion factor of 5.7, an MRL of 9 mg/m^3 was calculated. However, this MRL may be overly conservative for intermittent exposure and should probably used for screening purposes.

2. HEALTH EFFECTS

- An MRL of 0.3 mg/m^3 has been derived for chronic-duration inhalation exposure (365 days or more) to JP-7.

The chronic inhalation exposure MRL of 0.3 mg/m^3 was based on an increase in hepatic toxicity observed in rats at 150 mg/m^3 (Air Force 1991). The average variability of chamber JP-7 concentrations during the experiment was 5%. In that study, the tumorigenic effect of JP-7 was studied in a year-long exposure (6 hours/day, 5 days/week) of Fischer 344 rats (100/sex/group) to 0 (air), 150, or 750 mg/m^3 JP-7. Following the exposure period, 10 animals/sex/group were killed and examined while the remaining animals were killed after a l-year postexposure period. Liver, kidney, and spleen weights were determined at sacrifice, and portal blood samples were taken for clinical chemistry and hematologic determinations. Additionally, gross and microscopic histopathological examination of the collected tissues was performed. One year after the end of the exposure period, hepatic inflammation was discovered in females from both the 150 and 750 mg/m^3 groups. Hepatic inflammation was not observed in the exposed males. A LOAEL of 150 mg/m^3 was identified for hepatic inflammation in female mice. Exposure to JP-7 did not result in any change in mortality when exposed rats were compared to controls. Based on the increased incidence of hepatic toxicity at 150 mg/m^3 JP-7, an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for interspecies extrapolation, and 10 for human variability), a human equivalency dose factor of 3.3 (0.36 m3/day/0.38 kg x 70 kg/20 m^3/day), and a continuous exposure adjustment of 0.18 (6 hours/24 hours x 5 days/7 days), an MRL of 0.3 mg/m^3 was calculated.

Oral MRLs.

No MRLs for acute-, intermediate-, or chronic-duration exposure to JP-4 or JP-7 were calculated because insufficient toxicological data exist for those fuels. The data on the potential toxicity of orally administered JP-4 were limited to acute exposure studies (Air Force 1974; Clark et al. 1989). No studies designed to determine the toxic effects of oral exposure to JP-7 were found.

No acute-, intermediate-, or chronic-duration dermal MRLs were derived for JP-4 or JP-7 because of the lack of an appropriate methodology for the development of dermal MRLs.

2. HEALTH EFFECTS

Death. No studies were located that reported human deaths resulting from JP-4 or JP-7 exposure by any route. The LD_{50} has not been determined in laboratory animals. However, data indicate that the lethal inhalation concentration for JP-4 in monkeys, dogs, rats, and mice exceeds 5,000 mg/m^3 (Air Force 1974, 1976, 1980, 1984b, 1985b; Clark et al. 1989; Newton et al. 1991). Inhalation exposure of rats or mice to up to 750 mg/m^3 JP-7 did not result in any deaths (Air Force 1982f, 1991). Oral administration of up to 8,000 mg/kg JP-4 in rats was not lethal. Some mortality was found in mice given 500 or 1,000 mg/kg JP-4 (Air Force 1974), but the small number of animals used in the study makes interpretation of the results difficult. No studies were located that reported death from oral JP-7 exposure. Death did not occur after acute dermal application of up to 2,000 mg (Dennis 1982a) or chronic application of 25 mg of JP-4 to the skin of animals (Clark et al 1988). In rabbits, the acute-duration dermal exposure to 0.5 mL JP-7 did not result in any deaths (Air Force 1984a). Although environmental data are limited, based on the high doses of JP-4 and JP-7 that are necessary to cause death, it is unlikely that JP-4 or JP-7 levels near hazardous waste sites are sufficient to cause death in exposed populations.

Systemic Effects.

Respiratory Effects. It is uncertain whether exposure to JP-4 causes respiratory effects in humans. In fact, there are no reports of chronic human occupational exposure to JP-4. No respiratory effects were reported after an acute accidental inhalation exposure to high levels of JP-4 (Davies 1964). In animal studies, inhalation exposure to up to 5,000 mg/m^3 JP-4 (Air Force 1974, 1976, 1984b; Bruner et al. 1993) or up to 750 mg/m^3 JP-7 (Air Force 1982g, 1983e) did not result in any reported alterations in respiratory clinical signs. Pulmonary mechanics and function did not change after intermediate-duration inhalation exposure to 1,000 mg/m^3 JP-4 (Air Force 1985c; Newton et al. 1991). The data regarding respiratory effects of JP-4 and JP-7 are insufficient to draw conclusions about the effects that may be seen in the workplace or near waste disposal sites.

Hematological Effects. No information is available on the hematological effects of JP-4 or JP-7 exposure in humans. In animals, routine hematological testing revealed occasional differences in various hematological tests; however, the values were within the normal range of biological variation (Air Force 1974, 1980, 1982f, 1984b, 1985b, 1991; Bruner et al. 1993). Additionally, the hematological effects were not dose-dependent or found in both sexes. Thus, they were not regarded as physiologically significant.

2. HEALTH EFFECTS

Hepatic Effects The effect of JP-4 or JP-7 on the human liver is unknown. Female mice exposed to 500 mg/m^3 JP-4 continuously for 90 days had degenerative fatty changes in liver cells (Air Force 1984b) that were likely reversible (Bruner et al. 1993). The fatty changes were not seen in a 12-month intermittent (6 hours/day, 5 days/week) exposure. Inflammation of the liver occurred in female mice exposed intermittently for 12 months to 150 mg/m^3 JP-7. In general, there were no changes in blood chemistry that would indicate abnormal liver function in animals exposed by inhalation. It is unknown if liver effects would occur in humans exposed to JP-4 or JP-7 at hazardous waste sites. There are no data regarding liver effects after oral or dermal administration of JP-4 or JP-7 in animals.

Renal Effects. There are no data regarding the effect of JP-4 or JP-7 on renal function in humans. In animal experiments, male rat nephropathy is a common finding after inhalation exposure to either JP-4 or JP-7 (Air Force 1976, 1984b, 1991; Bruner et al. 1993). However, the evidence is overwhelming that the male rat nephropathy is unique to male rats, and is related to the binding of xenobiotic compounds to $\alpha_{2\mu}$-globulin, a low molecular weight serum protein synthesized in the liver of male rats. Subsequent accumulation of this complex is thought to trigger pathological responses within the kidney (Bruner et al. 1993). This syndrome is characterized by the following progression of lesions (Alden 1986; Bruner 1984; Bruner et al. 1993; EPA 1991; Short et al. 1987):

- Excessive accumulation of hyaline droplets in the P2 segment of the proximal tubule region of the kidney. This accumulation is evident after 1 or 2 days of exposure and is reversible within 3 days to 2 weeks after termination of exposure. The hyaline droplets are associated with the protein $\alpha_{2\mu}$-globulin.

- .Evidence of single cell necrosis in the P2 segment epithelium and exfoliation of these degenerated cells and cell fragments filled with crystalloid phagolysosomes into the tubule lumen after 5 days of continuous exposure. This can also be seen with longer exposure.

- Sustained regenerative tubule cell proliferation with continued exposure. After the initial cytotoxic injury, evidence of regeneration of the tubular epithelium can be seen as an increase in cell proliferation within the P2 segment in response to cell damage and loss. The cell proliferation can be seen following 3 weeks of continuous exposure and is also

obvious after 48 weeks of exposure. Tubular dilation and tubular epithelial necrosis are often associated with the regenerative changes.

- Accumulation of granular casts, formed from the cellular debris and subsequent tubule dilation, is seen at the junction of the P3 segment and the thin loop of Henle. This can be seen as early as 2-3 weeks after exposure begins. These casts are not always seen in male rat nephropathy and may reflect a more severe response.

- Linear mineralization of the renal papillar tubules with hyperplasia of the renal pelvic urothelium. These lesions are thought to be the result of mineralized remnants of debris from disintegrating granular casts that lodge in the prebend segments of Henle's loop.

Several mechanisms have been proposed to account for this unique sequence of events in male rats following exposure to certain hydrocarbons, including the jet fuels. Currently, the most likely mechanism is that a metabolite of jet fuel or one of its constituents (especially isoparaffinic hydrocarbons) binds to $\alpha_{2\mu}$globulin. The complex is then reabsorbed in the proximal tubule and phagocytized by lysosomes within the tubule cells. This protein complex is difficult to catabolize and accumulates in the lysosomes. Eventually, the lysosomes burst, and digestive enzymes contained within the lysosomes induce cytotoxicity and cell death, which in turn leads to the accumulation of casts and the hyperplastic events described above (Swenberg et al. 1989).

The available data indicate that the nephrotoxic syndrome is induced by hydrocarbons such as jet fuels and is unique to male rats. The hepatic synthesis of $\alpha_{2\mu}$-globulin protein is under androgenic control and is found at concentrations 100-300 times higher in male rat urine than in female rat urine (Shapiro and Sachchidananda 1982; Van Doren et al. 1983). Human urine contains only 1% of the total concentration of this protein present in mature male rat urine (Olson et al. 1990). $\alpha_{2\mu}$-Globulin and associated hyaline droplet accumulation and the associated constellation of nephrotoxic effects that are observed in male rats have not been observed in female rats, or in mice or monkeys of either sex (Air Force 1976, 1980, 1984b, 1991; Brnner et al. 1993). In addition, this syndrome could not be induced in male NCI-Black-Reiter rats, an inbred strain of rats that does not synthesize $\alpha_{2\mu}$-globulin (Dietrich and Swenberg 1991). In light of this evidence, EPA's Risk Assessment Forum in its document entitled *Alpha-$_{2\mu}$p-Globulin: Association with Chemically-Induced Renal Toxicity and Neoplasia in the Male Rat* (EPA 1991), made the following conclusions:

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> "If a compound induces $\alpha_{2\mu}$g accumulation in hyaline droplets, the associated nephropathy in male rats is not used as an endpoint to determine noncancer (systemic) effects potentially occurring in humans. Likewise, quantitative estimates of noncancer risk (e.g., reference doses and margin-of-exposure determinations) are based on other endpoints wherever possible."
>
> "...If the sequence of lesions characteristic-of the $\alpha_{2\mu}$g syndrome are present, the associated nephropathy in the male rat does not contribute to determinations of noncarcinogenic hazard of risk."

Thus, it does not appear that the nephrotoxicity observed in male rats after exposure to JP-4 or JP-7 is relevant to humans exposed to JP-4 or JP-7 in the workplace or at hazardous waste sites.

Dermal Effects. There is no information regarding the dermal effects of JP-4 or JP-7 in humans after acute, intermediate, or chronic exposure to JP-4 or JP-7. Experiments in rabbits show that acute application of JP-4 or JP-7 is irritating to the skin. Application of 0.5 mL undiluted JP-4 (both shaleand petroleum-derived) produced severe irritation that was characterized by edema and erythema 24 hours post-application (Air Force 1984a; Clark et al. 1989; Dennis 1982b; Walter 1982c), whereas the application of the same amount of JP-7 was shown to produce slightly greater irritation that persisted for a longer period of time (Air Force 1984a). Skin sensitization assays in guinea pigs have shown that petroleum-derived JP-4 is not a dermal sensitizer (Clark et al. 1989; Walter 1982c). However, JP-7 and shale-derived JP-4 appear to have weak-to-mild and mild-to-moderate sensitization potential, respectively (Air Force 1984a).

Ocular Effects. There is no information regarding the ocular effects of JP-4 or JP-7 in humans after acute, intermediate, or chronic exposure to JP-4 or JP-7. Petroleum-derived JP-4, shale-derived JP-4, and JP-7 caused no irritation when applied to the eyes of rabbits (Air Force 1984a; Clark et al. 1989; Dennis 1982c; Walter 1982a).

Body Weight Effects. Decreases in body weight were observed in some, but not all, rats exposed to JP-4 in intermediate- or chronic-duration experiments (Air Force 1980, 1981i, 1985b; Bruner et al. 1993). The decrease in weight gain was found to occur primarily in male rats and may be related to altered protein metabolism in male rats, which was related to the synthesis, excretion, and conservation

of $\alpha 2\mu$,-globulin by the kidney (Bruner et al. 1993). The significance of body weight depression for humans cannot be determined from these findings.

Immunological and Lymphoreticular Effects. Data regarding the immunological effects of JP-4 are limited to the dermal sensitization tests conducted in guinea pigs (Air Force 1984a; Clark et al. 1989; Walter 1982c). In these studies petroleum-derived JP-4 was not found to be a dermal sensitizer. However, JP-7 and shale-derived JP-4 have weak-to-mild and mild-to-moderate sensitization potential, respectively (Air Force 1984a). No studies were located regarding the immunological effects in humans after inhalation, oral, or dermal exposure to JP-7. It is not possible to determine the likelihood of immunological effects occurring in humans because of the paucity of data.

Neurological Effects. The only information found regarding human exposure to JP-4 is a case study in which a pilot was accidentally exposed to a very high level of the jet fuel from a fuel leak (Davies 1964). The exposure concentration was estimated to be approximately 3,000-7,000 ppm. In this case report, the overwhelming finding was neurological impairment, specifically described as "intoxication." Other cardiovascular and respiratory functions appeared normal on physical exam. Therefore, it is likely that under very high exposure conditions, the nervous system is the target organ for JP-4 toxicity. Supportive evidence is found in an acute exposure of rats (number unspecified) to a very high concentration of JP-4 (38,000 mg/m^3) that resulted in poor coordination and convulsions (Air Force 1974). Those studies are both flawed by poor characterization of exposure concentrations. No studies were located regarding neurological effects in animals or humans after oral or dermal exposure to JP-4. There is no information regarding the neurological effect of JP-7 exposure in humans or animals after inhalation, oral, or dermal exposure.

Reproductive Effects. No studies were located regarding reproductive effects in humans or animals after inhalation, oral, or dermal exposure to JP-4 or JP-7. Since no information is available, the likelihood of reproductive effects occurring in humans cannot be determined.

Developmental Effects. No studies were located regarding developmental effects in humans or animals after inhalation, oral, or dermal exposure to JP-4 or JP-7. Since no information is available, the likelihood of developmental effects occurring in humans cannot be determined.

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Genotoxic Effects. No studies involving human exposure to jet fuels were located, and only two animal in viva studies were found. Male mice and rats were exposed to JP-4 and then allowed to mate with unexposed females in dominant lethal experiments. Statistically significant dominant lethal effects were not observed for either mice or rats (Air Force 1978a). However, because of the small sample size of pregnant females, the results cannot be considered conclusive. Refer to Table 2-3 for a further summary of these results.

Most of the genotoxicity data concerning jet fuels comes from *in vitro* studies. Human diploid WI-38 cells (cells derived from embryonic lung) were treated with JP-4 and examined for unscheduled deoxyribonucleic acid (DNA) synthesis (Air Force 1978a). Unscheduled DNA synthesis (UDS) is a repair process that occurs when DNA has been damaged. Therefore, UDS activity is an indirect measurement of DNA damage. The cells were treated with 0.1, 0.5, 1.0, and 5.0 µL/mL (in water) in both activation and nonactivation systems. A dose-dependent increase in UDS activity was observed, indicating that JP-4 can produce repairable damage in the DNA of human WI-38 cells. The cells that were cultured in the presence of metabolic activators exhibited greater UDS activity suggesting that toxic metabolites may be involved. The remaining *in vitro* investigations were negative for chromosome aberrations in Chinese hamster ovary cells (EPA 1982a, 1982b; Galloway 1982a, 1982b), gene mutations in mouse L5178Y lymphoma cells (Air Force 1978a; Cifone 1982a, 1982b; EPA 1982a, 1982b), and gene mutations in *Saccharomyces cerevisiae* (Air Force 1978a) and *Salmonella typhimurium* (Air Force 1978a; EPA 1982a, 1982b; Jagannath 1982; Rabenold 1982). Refer to Table 2-4 for a further summary of these results. One of the series of studies compared the effects of two types of JP-4: shale-derived JP-4 (Cifone 1982b; EPA 1982b; Galloway 1982b; Rabenold 1982) and petroleum-derived JP-4 (Cifone 1982a; EPA 1982a; Galloway 1982a; Jagannath 1982). The difference in origin did not produce a difference in effect; the results were negative in all tests for both types of JP-4.

The only positive response to JP-4 was observed in human WI-38 cells tested for UDS; but the nature of the DNA damage was not necessarily mutagenic (Air Force 1978a). The negative data for gene mutations and chromosome aberrations suggest that JP-4 is not a mutagenic or clastogenic mixture. The negative results observed in the dominant lethal experiments and the micronuclei study may not be reliable because of low sample size and poor experimental protocol. Results from Ames testing indicated that JP-4 was not mutagenic. Additionally, the solubility and volatility of hydrocarbon mixtures such as JP-4 or JP-7 is a confounding factor in experiments involving exposure of cultured

TABLE 2-3. Genotoxicity of JP-4[a] *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells:			
Mouse (germinal cells)	Dominant lethal mutation	+/–	Air Force 1978a
Rat (germinal cells)	Dominant lethal mutation	+/–	Air Force 1978a

[a]No information regarding the genotoxicity of JP-7 was located.

+/– = inconclusive result; JP-4 = jet propellant-4; JP-7 = jet propellant-7

Table 2-4. Genotoxicity of JP-4[a] *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms				
Salmonella typhimurium (TA1535, TA1537, TA1538, TA98, TA100)	Gene mutation	–	–	Air Force 1978a
S. typhimurium (TA1535, TA1537, TA1538, TA98, TA100)	Gene mutation	–	–	Galloway 1982b; Dennis 1982b[b]
S. typhimurium (TA1535, TA1537, TA1538, TA98, TA100)	Gene mutation	–	–	Cifone 1982b
Eukaryotic organisms:				
Fungi:				
Saccharomyces cerevisiae (D_4)	Gene mutation	–	–	Air Force 1978a
Mammalian cells:				
Mouse L5178Y lymphoma cells (TK +/– locus)	Gene mutation	–	–	Air Force 1978a
Mouse L5178Y lymphoma cells (TK +/– locus)	Gene mutation	–	–	Cifone 1982a; Dennis 1982b[b]
Mouse L5178Y lymphoma cells (TK +/– locus)	Gene mutation	–	–	EPA 1982a
Chinese hamster (ovary cells)	Chromosome aberrations	–	–	Jagannath 1982; Dennis 1982b[b]
Chinese hamster (ovary cells)	Chromosome aberrations	–	–	Rabenold 1982
Dog (peripheral lymphocytes)	Micronuclei induction	No data	–[c]	Air Force 1979b
Human (WI-38 cells)	Unscheduled DNA synthesis	+	+[d]	Air Force 1978a

[a]No information regarding the genotoxicity of JP-7 was located.
[b]Petroleum derived JP-4 tested
[c]Result is not meaningful because of unquantifiable testing protocol.
[d]Metabolic activation produced results of greater magnitude.

– = negative result; + = positive result; DNA = deoxyribonucleic acid; JP-4 = jet propellant-4; JP-7 = jet propellant-7; TK = thymidine kinase; WI-38 cells derived from human embryonic lung

cells to mixtures of such hydrocarbons. Negative data may, therefore, be misinterpreted in such a system. No genotoxicity data were obtained for JP-7.

Cancer. No studies were located regarding cancer in humans after inhalation, oral, or dermal exposure to JP-4 or JP-7. In inhalation animal studies, there does not appear to be any carcinogenic potential of chronic JP-7 exposure (Air Force 1991). A l-year JP-4 exposure in rats and mice resulted in increased alveolar/bronchiolar tumors in female rats and mice (Bruner et al. 1993). Renal tumor increases that were seen in male rats were attributable to $\alpha 2\mu$-globulin nephropathy syndrome (see the discussion of renal effects above) and are not likely to be relevant to other animals or to humans. Finally, an increased hepatocellular tumor incidence occurred in treated female mice (9/80) versus controls (2/83). In males, this trend was reversed (l/38 treated versus 14/71 controls). There are currently widely divergent views regarding the validity of mouse liver tumors as an indication of human carcinogenicity for a compound (EPA 1986b). Squamous cell carcinoma and fibrosarcoma formation was increased in the mice exposed to shale-derived (50% incidence) and petroleum-derived JP-4 (26% incidence) compared to the appropriate control groups (2% and 0%, respectively) (Clark et al. 1988). The current animal data regarding the carcinogenicity of JP-4 are equivocal, and the evidence is insufficient to draw conclusions regarding the carcinogenic potential of JP-4 or JP-7 in humans exposed at hazardous waste sites.

2.5 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 or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the

properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic 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-4 and JP-7 are discussed in Section 2.5.1.

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 often not 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-4 and JP-7 are discussed in Section 2.5.2.

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, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, Populations That Are Unusually Susceptible.

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Jet Fuels JP-4 and JP-7

No biomarkers of exposure were identified for JP-4 or JP-7. No standard procedures exist for identifying or quantifying exposure to JP-4 or JP-7. For information on biomarkers of exposure for the individual components in JP-4 and JP-7, the ATSDR profiles on benzene (ATSDR 1991a), toluene (ATSDR 1990), total xylenes (ATSDR 1991c) and polycyclic aromatic hydrocarbons (ATSDR 1991b) can be consulted. However, the biomarkers of exposure for these chemicals are not specific for JP-4 or JP-7 exposure.

2.5.2 Biomarkers Used to Characterize Effects Caused by Jet Fuels JP-4 and JP-7

No biomarkers of effect were found for JP-7. Potential biomarkers for neurological effects of JP-4 are mild muscular weakness, staggering gait, and decreased sensitivity to painful stimuli (Davies 1964). Those effects are not specific enough to be useful as biomarkers for JP-4 exposure since they are a component of the clinical signs associated with the exposure to most volatile organic compounds. For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.6 INTERACTIONS WITH OTHER CHEMICALS

When benzene was added to a JP-4 inhalation mixture, experimental animals did not demonstrate any difference in hematological, blood chemistry, or histopathological results when compared to airexposed controls (Air Force 1974, 1976). No other information was located regarding the influence of other chemicals on the toxicity of JP-4 or JP-7.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to JP-4 and JP-7 than will most persons exposed to the same level of JP-4 and JP-7 in the environment. Reasons include genetic make-up, developmental stage, health and nutritional status, and chemical exposure history. These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic and renal) or the pre-existing compromised function of target organs. For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

Review of the literature regarding the effects of exposure to JP-4 or JP-7 does not indicate susceptibility of specific populations to these chemicals. There are very limited data on exposure of humans to JP-4 or JP-7; however, the results from animal studies do not indicate sensitivity in specific groups to the toxicity of these mixtures.

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2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to JP-4 or JP-7. 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-4 or JP-7. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.8.1 Reducing Peak Absorption Following Exposure

Following dermal contact with JP-4 or JP-7, the skin should be wiped off and washed with soap and warm water. After washing, hand cream may be applied to the exposed skin to restore lost oils. If the eyes have been exposed, it is recommended that they be flushed with copious amounts of cool, clean water for at least 15 minutes. Common treatments of the eyes include application of antibiotic creams to prevent secondary infection and a soothing or anesthetic agent. Following ingestion, it is recommended that the victim drink water or milk. Vomiting should not be induced because of the risk of aspiration of jet fuel hydrocarbons. Following inhalation of jet fuel vapors, it has been suggested that the victim be administered oxygen (Tupper 1989; Weiss 1986).

2.8.2 Reducing Body Burden

There is no specific method for enhancing the elimination of JP-4 or JP-7 because the metabolic pathways and excretion pathways for these jet fuels is essentially unknown. Interventions designed to increase elimination may be of limited effectiveness because many of the components of JP-4 and JP-7 are lipophilic. However, it may be possible to increase the elimination of the highly volatile components of the fuels by increasing the respiratory frequency,

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

No information on interfering with the mechanism of action for toxic effects of either JP-4 or JP-7 is provided because the metabolic pathways and excretion pathways for these jet fuels is essentially unknown.

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2.9 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-4 and JP-7 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-4 and JP-7.

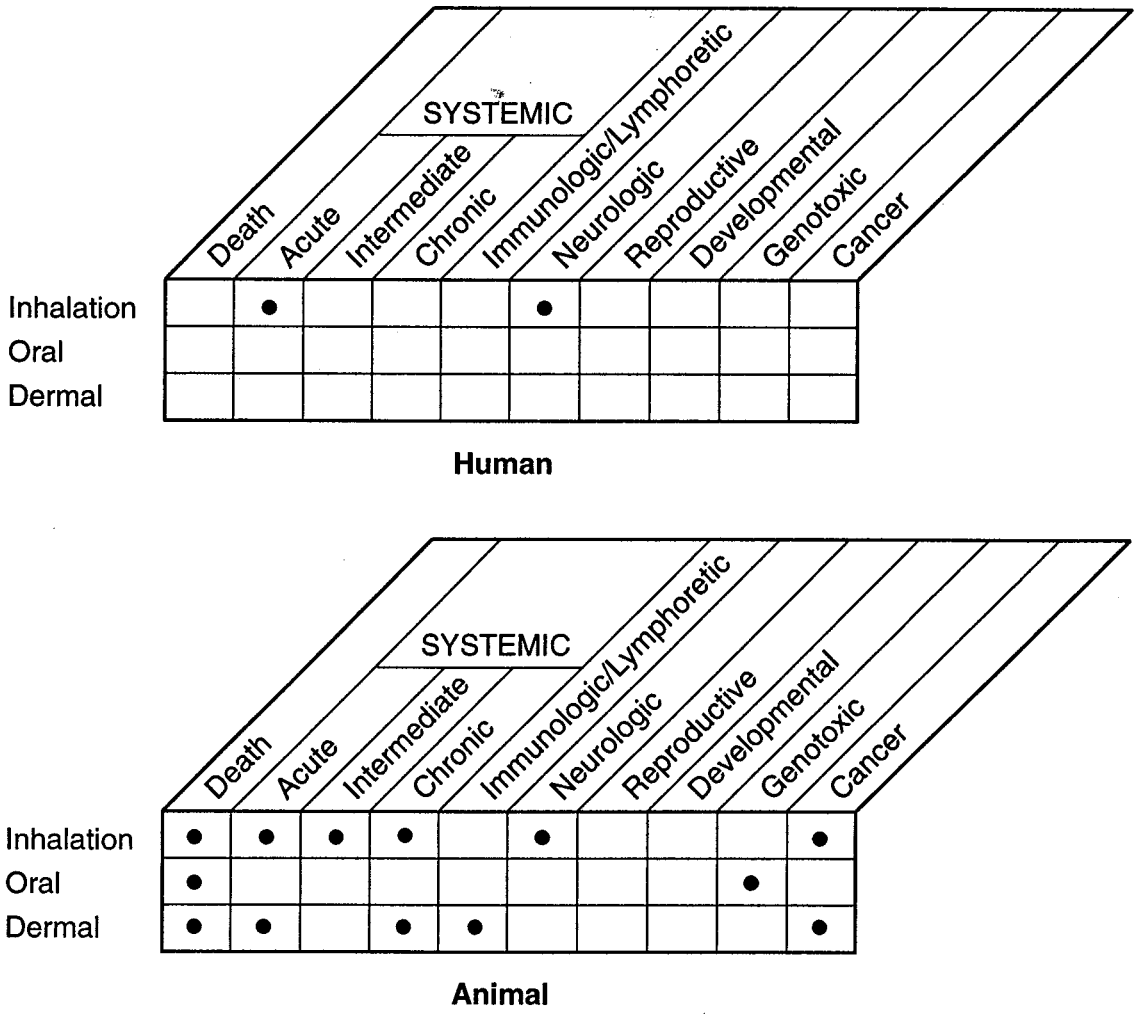
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted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

2.9.1 EXISTING INFORMATION ON HEALTH EFFECTS OF JET FUELS JP-4 AND JP-7

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to JP-4 and JP-7 are summarized in Figures 2-2 and 2-3. The purpose of the figures is to illustrate the existing information concerning the health'effects of JP-4 and JP-7. Each dot in the figures indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in the figures should not be interpreted as "data needs" information (i.e., data gaps that must necessarily be filled).

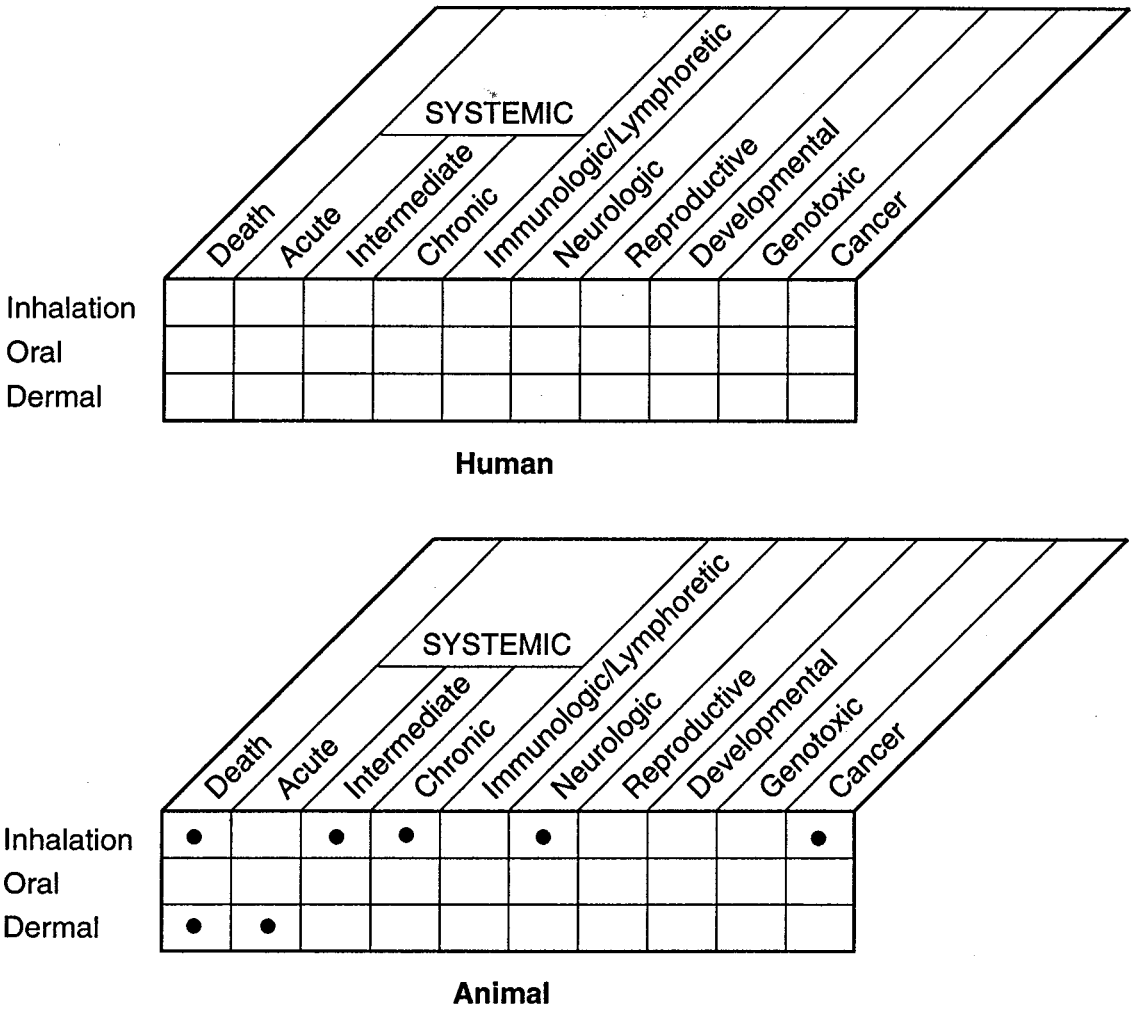
One case study was located detailing the acute neurological effects of accidental JP-4 exposure (Davies 1964). No other data were found on the health effects of inhalation exposure to JP-4 or JP-7 in humans. Animal data exist for death and for intermediate and chronic neurological, and cancer effects following inhalation exposure to JP-4; for death and genotoxic effects following oral exposure to JP-4; and for death and acute and chronic cancer effects following dermal exposure to JP-4. Therefore, as can be seen in Figure 2-2, the majority of the available information for JP-4 is on the health effects of inhalation and dermal exposure in animals. Very limited information exists on the effects of oral exposure in animals. No data were found on the health effects of oral and dermal exposure in

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



● Existing Studies

FIGURE 2-3. Existing Information on Health Effects of JP-7



● Existing Studies

humans. The only available information for JP-7 was on death and intermediate, chronic, and cancer effects following inhalation exposure in animals. As can be seen in Figure 2-3, limited data were found on the health effects of inhalation exposure in animals to JP-7. Data on dermal exposure to JP-7 exist for death and acute effects. No other health effects data were found for either humans or animals.

2.9.2 Identification of Data Needs

Acute-Duration Exposure. The central nervous system appears to be the target of JP-4 toxicity following acute-duration inhalation exposure in humans. Acute inhalation exposure to JP-4 is characterized by a groggy, weak, intoxicated state including staggering gait, mild muscular weakness, and decreased sensitivity to painful stimuli (Davies 1964). Accidental inhalation exposure of a pilot to a high concentration of JP-4 from a fuel leak did not result in any abnormalities in hematological or clinical chemistry tests (Davies 1964). No information was available on acute-duration oral or dermal exposure of humans to JP-4 or JP-7, or on acute-duration inhalation, oral, or dermal exposure of humans to JP-7. Animals acutely exposed by inhalation to very high concentrations of JP-4 (38,000 mg/m^3) exhibited neurotoxic effects including poor coordination and convulsions (Air Force 1974). Acute dermal exposures to JP-4 and JP-7 indicate that both substances are skin irritants (Air Force 1984a; Clark et al. 1989; Dennis 1982a, 1982b; Walter 1982c). No pharmacokinetic data were available for either substance to support the identification of target organs across routes of exposure for animals or humans. No evidence was seen of primary ocular irritation following acute exposure to JP-4 or JP-7 (Air Force 1984a; Clark et al. 1989; Dennis 1982c; Walter 1982a). Petroleum-derived JP-4 was not a dermal sensitizer in guinea pigs (Clark et al. 1989; Walter 1982c). However, JP-7 and shale-derived JP-4 have sensitizing potential (Air Force 1984a). Acute exposure to high levels of JP-4, by all three routes, did not result in any mortality (Clark et al. 1989; Dennis 1982a). No quantitative information was available on acute-duration inhalation or oral exposure of animals to JP-7. No acute MRLs have been developed because of the absence of quantitative information regarding acuteduration inhalation or oral exposure to JP-4 or JP-7. More quantitative information on the levels of exposure that elicit various acute-duration oral, inhalation, or dermal exposure effects in humans and animals would be helpful, as would information on what the thresholds are for these effects.

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Intermediate-Duration Exposure. No information is available on the effects of intermediate-duration exposure to JP-4 or JP-7 in humans. No pharmacokinetic data were available to support the identification of target organs across routes of exposure for either humans or animals. Intermediateduration inhalation exposure to JP-4 or JP-7 did not result in any dose-dependent pathophysiological responses in routine hematological tests in monkeys, dogs, or rats (Air Force 1974, 1980, 1984b, 1984c) with the exception of a decrease in white blood cell count after intermediate- or chronicduration exposure in rats (Air Force 1980). Increased blood urea nitrogen was measured in rats exposed continuously by inhalation for 90 days to 500 or 1,000 mg/m^3 JP-4 (Air Force 1980, 1984c). That effect was not repeated in later studies using intermittent exposure to 5,000 mg/m^3 JP-4 (Air Force 1981i). In that study, blood urea nitrogen was found to be decreased after exposure. Kidney weight was increased in male rats exposed by inhalation to JP-4 for an intermediate duration (Air Force 1976, 1980). Histopathological changes related to $\alpha_{2\mu}$-globulin nephropathy were seen in these male rats. The results of dominant lethal studies in rats and mice orally exposed to JP-4 were negative (Air Force 1978a). More information is needed on the effects of intermediate-duration inhalation, oral, and dermal exposures to JP-4 and JP-7 in humans and animals in order to adequately identify target organs. This is especially true for neurological effects, one of the most sensitive end points for JP-4 (Air Force 1974; Davies 1964) and, most likely, JP-7 exposures. Sufficient inhalation data exist to calculate an intermediate-duration inhalation exposure MRL of 9 mg/m^3.

Chronic-Duration Exposure and Cancer. No chronic-duration exposure studies were found in humans for exposure to JP-4 or JP-7 following inhalation exposure. No chronic-duration exposure studies in humans were found for exposure to JP-4 or JP-7 by the oral or dermal routes.

No chronic-duration exposure studies were found that identified the central nervous system as the target of JP-4 or JP-7 toxicity in animals. Chronic-duration inhalation exposure studies using JP-4 or JP-7 in rats and mice showed no increase in mortality during the exposure period or 12 months postexposure (Air Force 1981i, 1982f, 1982g, 1983e, 1991; Bruner et al. 1993). Chronic inhalation of JP-4 did not result in statistically significant respiratory tract irritation or pulmonary lesions in rats or mice (Bruner et al. 1993). Chronic inhalation exposure to JP-4 resulted in decreased white blood cell count in rats (Bruner et al. 1993). Hepatic inflammation of female mice was seen after inhalation exposure to JP-7 (Air Force 1991).

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No information is available on the carcinogenicity of JP-4 or JP-7 in humans following chronic inhalation, oral, or dermal exposure. Chronic inhalation exposure to JP-4 or JP-7 did not result in an increased incidence of cancer in animals except for an increase in hepatocellular adenomas in female mice exposed high doses of JP-4 (Bruner et al. 1993). The incidence of this cancer is of unknown significance in mice (EPA 1986b). There was equivocal evidence for alveolar/bronchiolar tumors after inhalation exposure of rats (Bruner et al. 1993). JP-7 inhalation exposure did not result in significant increases in the incidence of cancer in rats (Air Force 1991). However, there were slight increases in the incidence of C-cell adenomas and kidney adenomas in the groups of male rats exposed to 750 mg/m^3 of JP-7 (Air Force 1991). Dermal application of undiluted JP-4 to the skin on a chronic basis resulted in increased incidence of squamous cell carcinoma and fibrosarcoma formation in mice at the site of application. There were no oncogenic effects in other organs (Clark et al. 1988). No information is available on the carcinogenicity of JP-4 or JP-7 in animals following chronic oral exposure. Further chronic inhalation or oral studies are recommended to help elucidate the carcinogenic potential of JP-4 and JP-7. Sufficient inhalation data exist to calculate a chronic exposure MRL of 0.3 mg/m^3.

Genotoxicity. JP-4 does not appear to be highly genotoxic in in vitro studies; however, there are no human data to indicate whether this substance acts by a genotoxic mechanism. Consistently negative results were gathered for gene mutations in both microbial species (Air Force 1978a; EPA 1982a, 1982b; Jagannath 1982; Rabenold 1982) and mammals (Air Force 1978a, 1979b; Cifone 1982a, 1982b; EPA 1982b; Galloway 1982a, 1982b). In addition, JP-4 was not clastogenic in Chinese hamster ovary cells (Jagannath 1982; Rabenold 1982). Although significant UDS was observed in human WI-38 cells (Air Force 1978a), more research is needed in order to determine the nature of the DNA damage. The only two *in vivo* (oral) studies obtained were inconclusive for JP-4's effects on the germinal cells of rats and mice due to small sample size of test animals (Air Force 1978a). Testing for sister chromatid exchange chromosome aberrations, UDS, and gene mutations in animals exposed to JP-4 *in vivo* would be helpful in determining whether or not this jet fuel poses a genotoxic threat to humans. Epidemiology studies of exposed workers, pilots, military personnel, or Air Force personnel would help even further in evaluating JP-4 as a potential human genotoxin. No studies were found in which JP-7 was used as a test chemical in genotoxicity experiments. Therefore, research is needed in order to evaluate the toxicity of this particular jet fuel.

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Reproductive Toxicity. No information is available on the reproductive effects of-JP-4 or JP-7 in humans or animals following inhalation, oral, or dermal exposure. No pharmacokinetic data were located to support the potential of JP-4 or JP-7 to affect reproduction across routes of exposure. Reproductive organ toxicity data from studies of acute, intermediate (90-day), and chronic duration are needed for all three routes of exposure in order to establish whether JP-4 or JP-7 has the potential to induce reproductive effects.

Developmental Toxicity. No information is available on the developmental effects of JP-4 or JP-7 in humans or animals following inhalation, oral, or dermal exposure. No pharmacokinetic data were located to support the potential of JP-4 or JP-7 to affect development across routes of exposure. Developmental toxicity data are needed for all three routes of exposure in order to establish whether JP-4 or JP-7 has the potential to induce developmental effects in humans.

lmmunotoxicity and Lymphoreticular Effects. Data regarding the immunological effects of JP-4 are limited to the dermal sensitization tests conducted in guinea pigs (Air Force 1984a; Clark et al. 1989; Walter 1982c). In these studies petroleum-derived JP-4 was not found to be a dermal sensitizer. However, JP-7 and shale-derived JP-4 have weak-to-mild and mild-to-moderate sensitization potential, respectively (Air Force 1984a). No studies were located regarding the immunological effects in humans after inhalation, oral, or dermal exposure to JP-7. It is not possible to determine the likelihood of immunological effects occurring in humans because of the paucity of data. These results suggest that JP-4 may affect immune function. Thus, assessing the effects of oral or inhaled JP-4 on immune function in laboratory animals would be helpful.

Neurotoxicity. No information is available on the neurotoxic effects of JP-4 or JP-7 following oral or dermal exposure in humans and animals, or of JP-7 following inhalation exposure in humans. The central nervous system appears to be the target of JP-4 toxicity following acute inhalation exposure in humans. Acute exposure to a very high concentration of JP-4 produced a groggy, weak, intoxicated state in a pilot exposed to a fuel leak (Davies 1964). The pilot had a staggering gait, mild muscular weakness, and decreased sensitivity to pain; these effects were no longer evident by 36 hours postexposure (Davies 1964). No information was found on neurotoxic effects of JP-4 or JP-7 in humans following intermediate-duration or chronic-duration exposure. Long-term exposure of experimental animals to JP-7 does not result in overt signs of neurotoxicity or any gross pathological

responses (Air Force 1991). Acute exposure of rats to very high concentrations of JP-4 by inhalation produced poor coordination and convulsions (Air Force 1974).

Additional studies in humans and animals using all modes of exposure that examine sensitive neuropathological end points specifically for JP-4 or JP-7 would be useful to definitely determine the symptoms associated with both fuels.

Epidemiological and Human Dosimetry Studies. Limited epidemiological information exists from an early study regarding acute-duration exposure to JP-4 (Davies 1964). Exposure levels in this study were only grossly approximated. No chronic-duration epidemiological studies were located regarding exposure to JP-4 or JP-7. Exposure to JP-4 or JP-7 is thought to occur primarily in a small segment of the population, namely Air Force personnel. Thus, collecting sufficient numbers of exposed persons for meaningful epidemiological studies is difficult. However, because the population most likely to be exposed consists mainly of Air Force personnel, follow-up studies may be more easily performed. Thus, studies examining chronic-duration neurological, immunological, developmental, and systemic effects would be valuable if a sufficient number of exposed persons are identified. In the absence of studies on persons exposed to JP-4 or JP-7, epidemiological studies on persons exposed to the individual components of JP-4 or JP-7 are not a priority because the results of the genetic toxicology tests with JP-4 were negative.

Biomarkers of Exposure and Effect.

Exposure. No biomarkers of exposure were identified for JP-4 or JP-7. No standard procedures exist for identifying or quantifying exposure to JP-4 or JP-7. Studies delineating the metabolism and excretion of JP-4 or JP-7 are needed in order to identify potential biomarkers of exposure following acute, intermediate, and chronic exposures to these chemicals.

Effect. No biomarkers of effect were found for JP-7. Potential biomarkers for neurological effects of JP-4 are mild muscular weakness, staggering gait, and decreased sensitivity to painful stimuli (Davies 1964). Studies of acute, intermediate, and chronic exposures are needed in order to identify biomarkers of effects for specific target organs following exposure to JP-4 or JP-7.

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Absorption, Distribution, Metabolism, and Excretion. No quantitative data were located regarding the absorption, distribution, metabolism, or excretion of JP-4 or JP-7 following inhalation, oral, or dermal exposure in humans or animals. Therefore, acute, intermediate, and chronic data are needed in order to assess the relative rates and extent of absorption, distribution, metabolism, and excretion with respect to all three routes of exposure, as well as with respect to time or dose.

Comparative Toxicokinetics. No studies were located regarding comparative toxicokinetics of JP-4 or JP-7. Human and animal data are needed in order to examine toxicokinetics across species (i.e., in humans and animals and in multiple species). This information is needed in order to identify similar target organs and to adequately assess which animals can serve as the best models for humans.

Mitigation of Effects. All of the treatment methods currently available for use in jet fuel exposure are supportive in nature (Tupper 1989; Weiss 1986). Since the mechanism(s) of jet fuel toxicity are not known, there are currently no methods specifically tailored to mitigating the effects of jet fuels by interfering with the mode of action. Additional information on the ultimate mechanism of jet fuel toxicity is needed before insights can be gained regarding treatment of exposure victims.

2.9.3 Ongoing Studies

No ongoing studies evaluating either the health effects or toxicokinetics of JP-4 or JP-7 were located.