2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of JP-5 and JP-8. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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

Minimal Risk Levels or MRLs have been established for JP-5 and JP-8. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when sufficient, reliable data exist to identify the most sensitive health effect(s) reported for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs may be revised.

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

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

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

2.2.1 Inhalation Exposure

2.2.1.1 Death

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

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

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

2.2.1.2 Systemic Effects

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

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

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

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

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

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

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

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

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

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

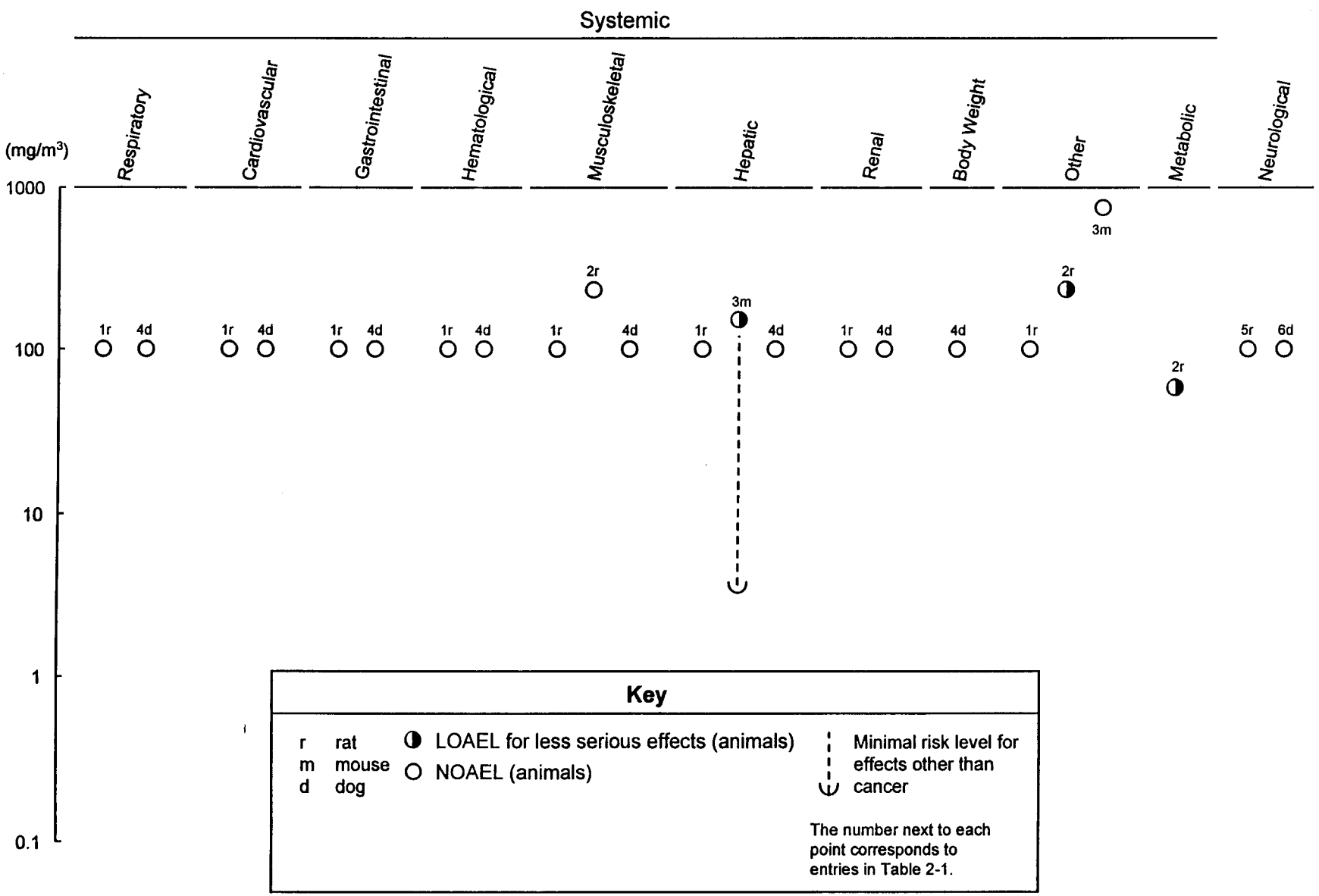
[a]The number corresponds to entries in Figure 2-1.

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

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

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

Intermediate (15-364 days)



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2.2.1.3 Immunological and Lymphoreticular Effects

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

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

2.2.1.4 Neurological Effects

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

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

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

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

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

2.2.1.5 Reproductive Effects

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

2.2.1.6 Developmental Effects

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

2.2.1.7 Genotoxic Effects

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

2.2.1.8 Cancer

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

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

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

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

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

2. HEALTH EFFECTS

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

2.2.2 Oral Exposure

2.2.2.1 Death

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

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

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

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

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

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

2.2.2.2 Systemic Effects

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Acute (≤14 days)

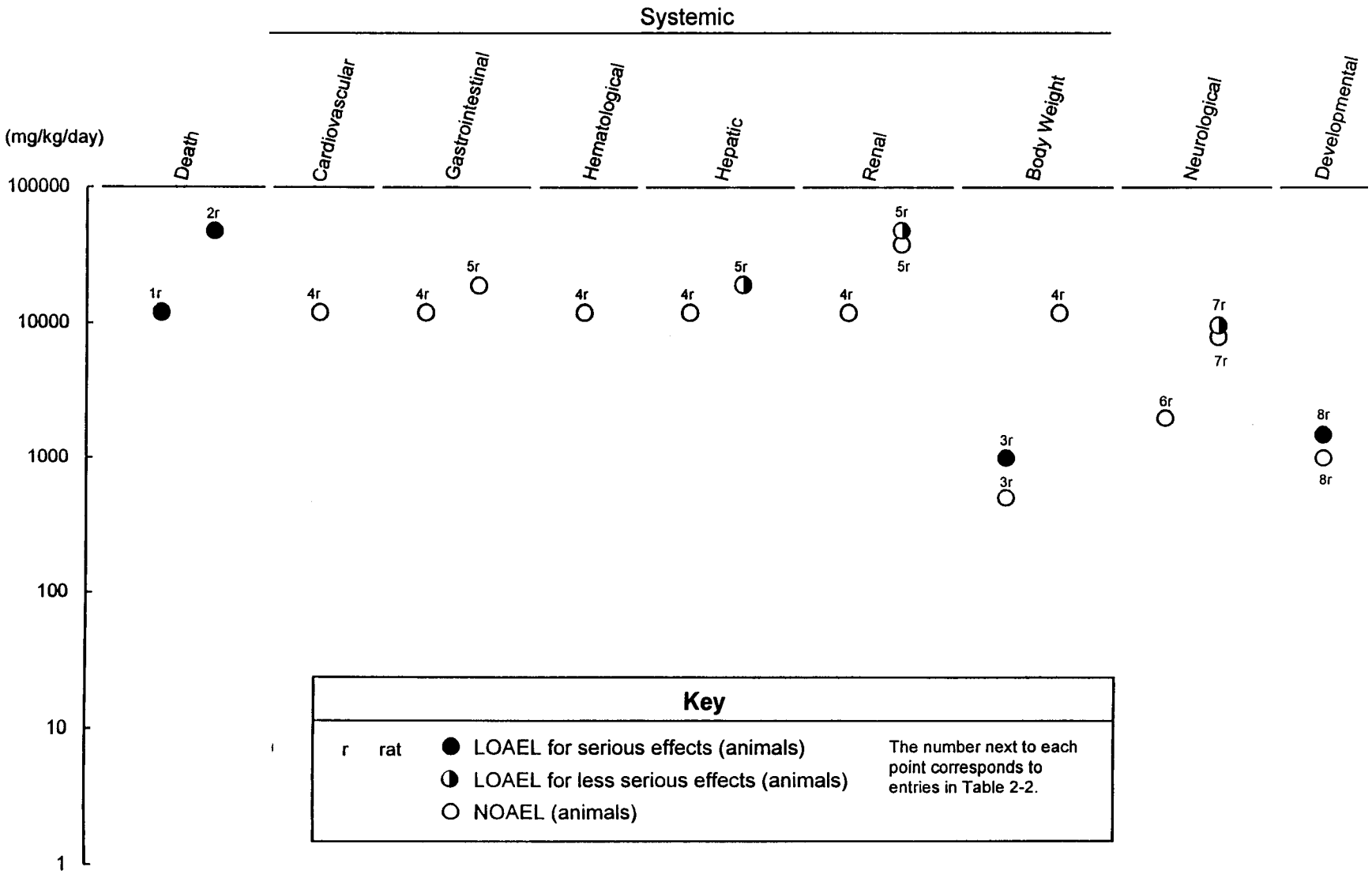
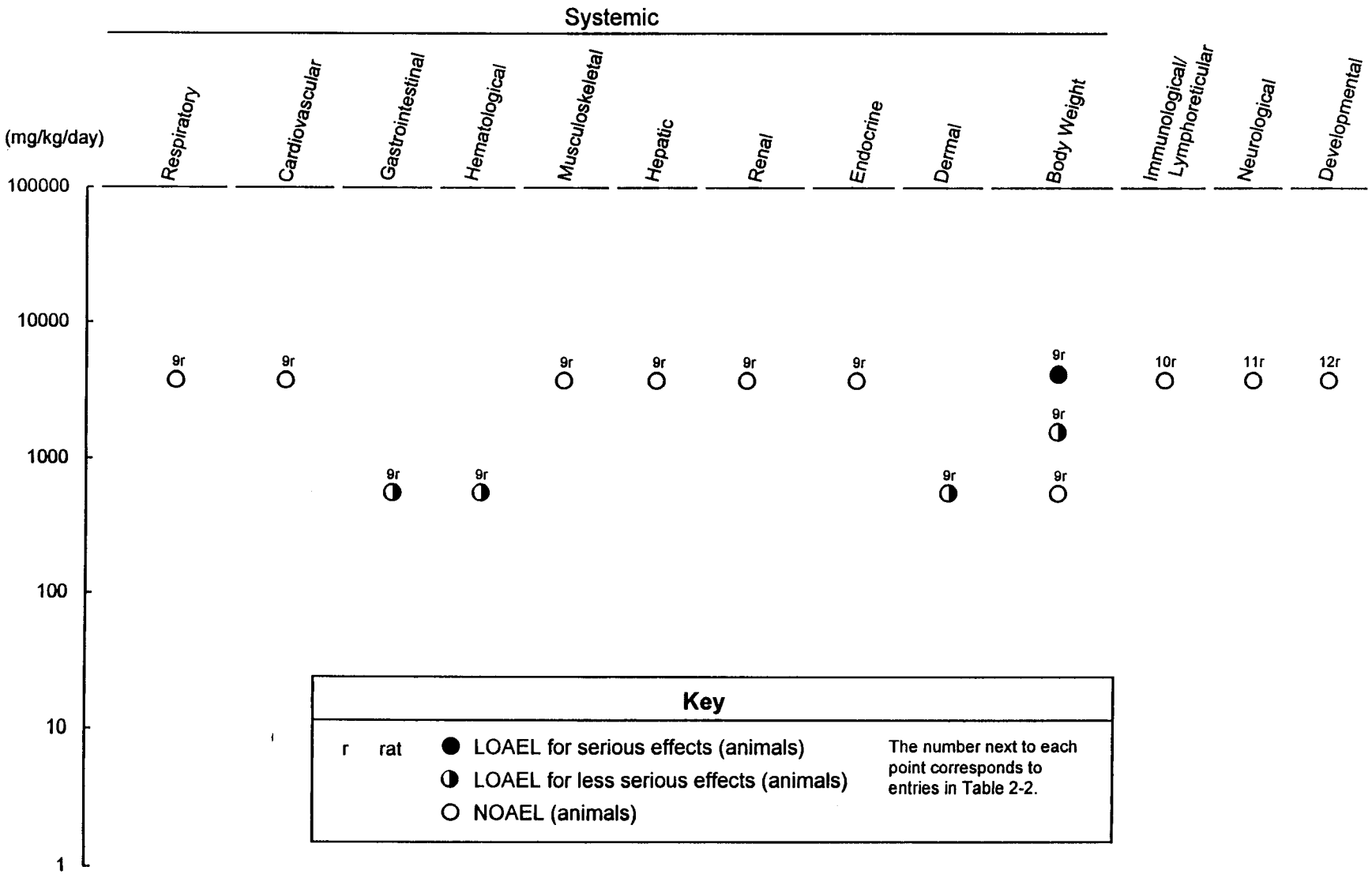


Figure 2-2. Levels of Significant Exposure to JP-5 & JP-8 - Oral

Intermediate (15-364 days)



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2.2.2.3 Immunological and Lymphoreticular Effects

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

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

2.2.2.4 Neurological Effects

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

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

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

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

2.2.2.5 Reproductive Effects

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

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

2.2.2.6 Developmental Effects

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

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

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

2.2.2.7 Genotoxic Effects

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

2.2.2.8 Cancer

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

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

2.2.3 Dermal Exposure

2.2.3.1 Death

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

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

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

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

2.2.3.2 Systemic Effects

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2.2.3.3 Immunological and Lymphoreticular Effects

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

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

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

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

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

2.2.3.4 Neurological Effects

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

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

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

2.2.3.5 Reproductive Effects

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

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

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

2.2.3.6 Developmental Effects

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

2.2.3.7 Genotoxic Effects

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

2.2.3.8 Cancer

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

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

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

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

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

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

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

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

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

2 .3 TOXICOKINETICS

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

2.3.1 Absorption

2.3.1 .l Inhalation Exposure

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

2.3.1.2 Oral Exposure

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

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

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

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

2.3.1.3 Dermal Exposure

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

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

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

2.3.2.2 Oral Exposure

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

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

2.3.2.3 Dermal Exposure

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

2.3.3 Metabolism

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

2.3.4 Elimination and Excretion

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

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

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

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

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

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

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

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

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

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

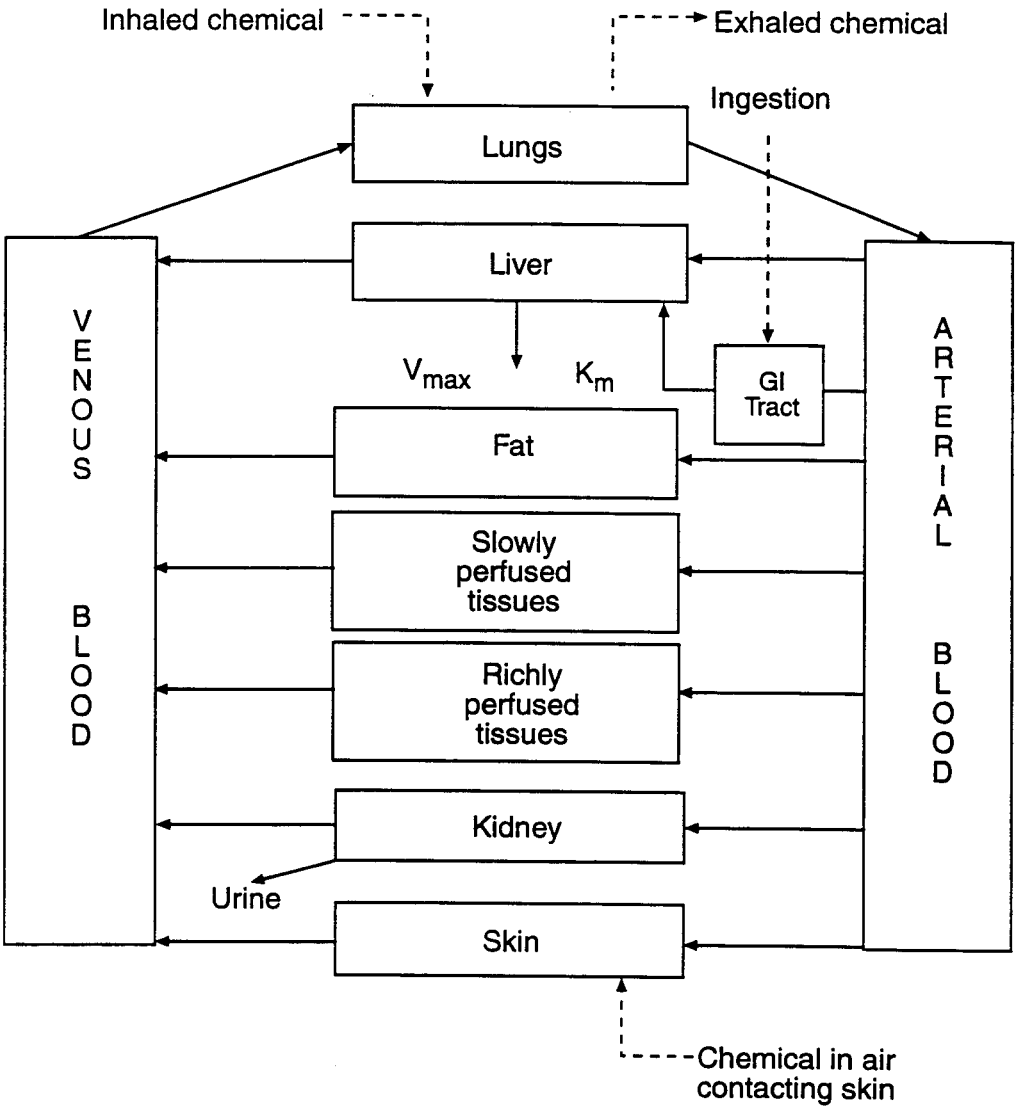
No studies were identified concerning the pharmacokinetic mechanisms of either JP-5 or JP-8.

2.4.2 Mechanisms of Toxicity

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

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

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



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

2.4.3 Animal-to-Human Extrapolations

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

2.5 RELEVANCE TO PUBLIC HEALTH

Overview.

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

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

2. HEALTH EFFECTS

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

Inhalation MRLs.

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

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

Oral MRLs.

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

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

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

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

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

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

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

Systemic Effects.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[a]Negative after intraperitoneal exposure but study was compromised

– = negative result

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

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

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

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

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

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

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

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

body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to JP-5 and JP-8 are discussed in Section 2.6.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical and cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. However, such markers are not often substance specific. They also may not be directly adverse, but can still indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by JP-5 and JP-8 are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organis m^3s ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8, Populations That Are Unusually Susceptible,

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

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

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

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

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

2.7 INTERACTIONS WITH OTHER CHEMICALS

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

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population is considered to be one that will exhibit a different or enhanced response to JP-5 and JP-8 than will most persons exposed to the same level of JP-5 or JP-8 in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of JP-5 and JP-8, or compromised function of target organs affected by JP-5 and JP-8. Populations who are at greater risk due to their unusually high exposure to JP-5 and JP-8 are discussed in Section 5.6, Populations With Potentially High Exposure.

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

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

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section describes clinical practice and research concerning methods for reducing toxic effects of exposure to JP-5 and JP-8. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to JP-5 and JP-8. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to JP-5 and JP-8: Bronstein AC, Currance PL. 1988. Emergency care for hazardous materials exposure. Washington, DC: The C.V. Mosby Company, 175-176. Ellenhom MJ, Barceloux DG. 1988. Medical Toxicology: Diagnosis and treatment of human poisoning. New York, NY. Elsevier Publishing, 944-945. Stutz PR, Janusz SJ. 1988. Hazardous materials injuries: A handbook for pre-hospital care. 2nd ed. Beltsville, MD: Bradford Communications Corporation, 360-36 1.

2.9.1 Reducing Peak Absorption Following Exposure

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

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

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

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

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

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

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

2.9.2 Reducing Body Burden

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

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

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

2.10 ADEQUACY OF THE DATABASE

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

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

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

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

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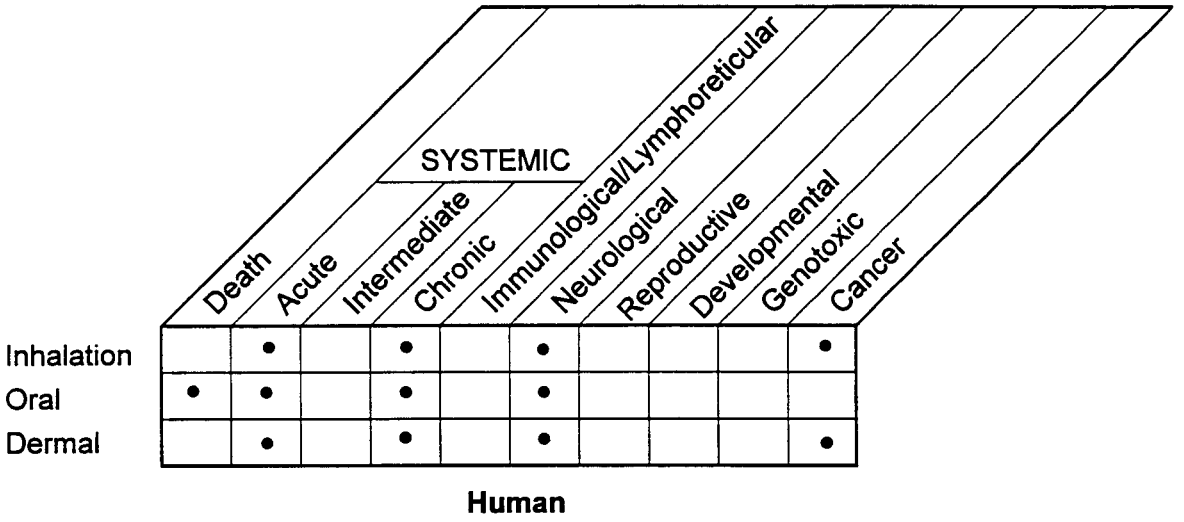
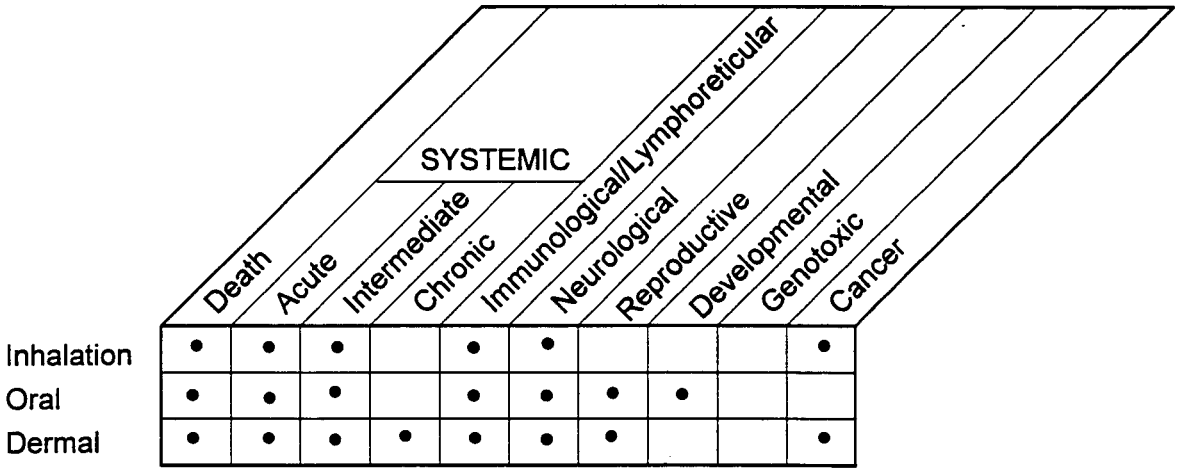
Information is available in humans on acute, intermediate, and chronic systemic effects as well as on neurological and carcinogenic effects following inhalation exposure to JP-5 and JP-8 or some of their compositional analogs; on death, acute systemic, and neurological effects following ingestion; and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

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



Human



Animal

• Existing Studies

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

2.10.2 Identification of Data Needs

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2.10.3 Ongoing Studies

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