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 fuel oils and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for fuel oils based on toxicological studies and epidemiological investigations.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies, LOAELs have been classified into “less serious” or “serious” effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user’s perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with “serious” effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on the lowest levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been

observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with the carcinogenic effects of fuel oils are indicated in Table 2-3. Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive non-cancer effect for each exposure duration. MRLs include adjustments to reflect human variability and extrapolation of data from laboratory animals to humans.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990e), 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.

Fuel oils are petroleum products whose composition varies with the refinery streams from which they are blended (Air Force 1989). Fuel oils, which have auto-ignition temperatures between 177°C and 329°C (Coast Guard 1985), are composed primarily of aliphatic hydrocarbons (64%), aromatic hydrocarbons (35%), and olefinic hydrocarbons (l-2%) (Air Force 1989). The aliphatic constituents consist of *n*-alkanes (*n*-paraffins), branched alkanes (isoparaffins), and cyclic alkanes (cycloparaffins or naphthenes). Aromatic hydrocarbons include benzene and polycyclic hydrocarbons. These petroleum products are used both for residential heating oil and for diesel fuel. Diesel fuels are graded according to the type of engine in which they are used and range from no. 1-D for higher speed and frequent load changes to no. 4-D for low speed engines.

The purpose of this chapter is to discuss the toxicological effects of fuel oils. There are six types of fuel oils discussed in this profile: (1) fuel oil no. 1, (2) fuel oil no. I-D, (3) fuel oil no. 2, (4) fuel oil no. 2-D, (5) fuel oil no. 4, and (6) fuel oil UNSP. However, there are no toxicity data for fuel oils in general; the available toxicity data are specific for particular fuel oils. Therefore, the toxicity of fuel oils will be discussed in this chapter by referring to the following fuel oils for which there are data: (1) fuel oil no. 1, which is also called kerosene, straight-run kerosene, kerosene, range oil, Deobase®, deodorized kerosene, coal oil, and JP-5 (jet fuel); (2) fuel oil no. l-D, which is also known as diesel

fuel and diesel fuel oil no. 1; (3) fuel oil no. 2, which is also called home heating oil, gas oil, and no. 2 burner oil; (4) fuel oil no. 2-D, which is also known as diesel fuel oil no. 2, diesel fuel no. 2, diesel oil no. 2, and no. 2 diesel; (5) fuel oil no. 4, which is also known as diesel fuel oil no. 4, heavy residual fuel oil, marine diesel fuel, and residual fuel oil no. 4; and (6) fuel oil UNSP. Exposure to individual fuel oil components or combustion products will not be discussed as it is not known whether the components or combustion products behave in a toxicologically similar manner to the fuel oils from which they are derived. For more information regarding the potential toxicity of some fuel oil components, the Air Force document (1989) and previous ATSDR profiles on benzene (ATSDR 1989), toluene (ATSDR 1990a), xylenes (ATSDR 1991a), and polycyclic aromatic hydrocarbons (ATSDR 1991b) can be consulted. Since fuel oils are complex and somewhat variable mixtures, it is not possible to identify the molecular weight for these oils. As such, airborne concentrations of fuel oils are reported as milligrams per cubic meter (mg/m^3).

2.2.1 Inhalation Exposure

Fuel oils can enter the respiratory system as a vapor or an aerosol; in addition, products formed during the combustion of fuel oils can be inhaled in smoke. A vapor is the gaseous phase of a substance that is a liquid at standard temperature. Fuel oils have a low vapor pressure (e.g., the saturation concentration of kerosene in air is approximately 100 mg/m^3). An aerosol is the suspension of solid or liquid particles in a gas (usually air), with particles ranging in size from 0.0001 to over 100 μm. Smoke is an aerosol formed during incomplete combustion. Due to the low volatility of fuel oils, human exposure to vapor concentrations above 100 mg/m^3 is unlikely. Higher concentrations can be achieved, however, by increasing the ambient temperature or modifying other physical parameters. Thus, exposure of the general population to high concentrations of airborne fuel oils would probably occur only in unusual situations.

2.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to fuel oils.

Mortality occurred in 3 of 10 mice exposed by inhalation 8 hours/day for 5 days to diesel fuel no. 2 vapors at a concentration of 204 mg/m^3; inhalation of 65 or 135 mg/m^3 was not lethal to mice (Kainz and White 1984). Acute inhalation of either 86.9 or 408.8 ppm fuel oil UNSP vapor or 101.8 or

401.5 ppm diesel fuel vapor did not induce death in rats (API 1979c, 19798). Inhalation of 8,000-16,000 mg/m^3 diesel fuel aerosol for 2 or 4 hours was lethal to rats (Dalbey and Lock 1983). No lethality occurred following single-exposure inhalation of 6,000 mg/m^3 diesel fuel aerosol for 4 hours or 2,700 mg/m^3 for 6 hours. However, inhalation of 4,000 mg/m^3 for 6 hours was lethal (Dalbey and Lock 1983).

No deaths occurred in rats exposed to 5,000 mg/m3 kerosene (physical form not specified) for 4 hours (Vernot et al. 1990d). This study is limited because only one concentration level was tested. It is useful, however, because the concentration used is very high. Inhalation of diesel fuel aerosol 4 hours/day, 2 days/week, for 13 weeks at concentrations up to 1,500 mg/m^3 did not induce mortality in rats (Lock et al. 1984). Intermediate exposures (once per week for 9 weeks or 3 times per week for 3 weeks) to diesel fuel aerosol induced mortality in 6.25% of the rats exposed to a concentration time product (Ct) of 12,000 mg hour/m^3 (Ct = [airborne concentration of aerosolized diesel fuel in mg/m^3] x [duration of exposure in hours]). However, no rats died at a Ct of 8,000 mg hour/m^3 (Dalbey et al. 1987). The Ct of 8,000 mg hour/m^3, under these conditions, was based on repeated 2- or 6-hour exposures to 4,000 or 1,330 mg/m^3, respectively. The Ct of 12,000 mg hour/m^3 was based on repeated 2- or 6-hour exposures to 6,000 or 2,000 mg/m^3, respectively. However, dose-response data were not reported for the individual exposure concentrations used to produce each Ct.

No rats died during 90-day inhalation exposures to 50 or 300 mg/m^3 marine diesel fuel vapor (Cowan and Jenkins 1981) or to 150 or 750 mg/m^3 JP-5 vapor (Cowan and Jenkins 1981; Gaworski et al. 1984). No mice died during a 90-day inhalation exposure of 150 or 750 mg/m^3 JP-5 vapor (Cowan and Jenkins 1981; Gaworski et al. 1984). One rat died of pneumonia out of 25 male rats exposed to 100 mg/m3 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 (Carpenter et al. 1976).

The NOAEL and LOAEL values for death after inhalation exposure to fuel oils are recorded in Table 2-l and plotted in Figures 2-1 and 2-2.

TABLE 2-1. Levels of Significant Exposure to Fuel Oils - Inhalation

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL[b] (mg/m3)		LOAEL[b] Less serious (mg/m3)		LOAEL[b] Serious (mg/m3)		Reference/ Chemical Form
ACUTE EXPOSURE										
Death										
1	Rat Sprague-Dawley	1d 6 hr/d						4000	(sex not specified, 30% mortality)	Dalbey and Lock 1983 FO5DFU
2	Mouse CD-1	5 d 8 hr/d						204 M	(30% mortality)	Kainz and White 1984 FO4DF2
Systemic										
3	Rat	10 d 6 hr/d	Other	408.8 (ppm)	F					API 1979c FO5
4	Rat [CRL: COBS CD(SD) BR]	10 d 6 hr/d	Other			401.5 (ppm)	F (decreased food intake)			API 1979g FO5DFU
5	Rat NS	10 d 6 hr/d	Other	400 (ppm)	F					Beliles and Mecler 1983 FO2HHO
6	Mouse CD-1	5 d 8 hr/d	Cardio	65	M	135	M (vasodilation)			Kainz and White 1984 FO4DF2
			Bd Wt	135	M	204	M (decreased water and food consumption with subsequent weight loss of 30%)			
Neurological										
7	Mouse CD-1	5 d 8 hr/d				65[c]	M (ataxia; disturbed gait)			Kainz and White 1984 FO4DF2

TABLE 2-1. Levels of Significant Exposure to Fuel Oils - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL[b] (mg/m3)		LOAEL[b] Less serious (mg/m3)	LOAEL[b] Serious (mg/m3)	Reference/ Chemical Form
	Developmental							
8	Rat	10 d 6 hr/d		408.8 (ppm)	F			API 1979c FO5
9	Rat [CRL: COBS CD(SD) BR]	10 d 6 hr/d		401.5 (ppm)	F			API 1979g FO1DOK
10	Rat NS	10 d 6 hr/d		400 (ppm)	F			Beliles and Mecler 1983 FO2HHO
	INTERMEDIATE EXPOSURE							
	Systemic							
11	Rat Albino 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			

TABLE 2-1. Levels of Significant Exposure to Fuel Oils - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL[b] (mg/m3)	LOAEL[b] Less serious (mg/m3)	LOAEL[b] Serious (mg/m3)	Reference/ Chemical Form
12	Rat Sprague-Dawley	13 wk 2d/wk 4hr/d	Resp	750	1500 (increase in relative weight of right lobe of lung)		Lock et al. 1984 FO5DFU
			Cardio	1500			
			Gastro	1500			
			Hemato	1500			
			Hepatic	1500			
			Renal	1500			
			Dermal	1500			
			Bd Wt		250 (decreased body weight)		
13	Rat Wistar	14 wk 6 d/wk 6 hr/d	Hepatic		58[d] M (decreased blood glucose levels)		Starek and Vojtisek 1986 FO-1
			Other		231 M (decreased metabolism of phenacetin; decrease in lactate and pyruvate)		
14	Mouse C57BL/6	90 d 24 hr/d	Hepatic		150 F (hepatocellular fatty changes and vacuolization)		Gaworski et al. 1984 FD1JP5
			Other	750 F			
15	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		20 M (increased body weight)		

TABLE 2-1. Levels of Significant Exposure to Fuel Oils - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL[b] (mg/m3)	LOAEL[b] Less serious (mg/m3)	LOAEL[b] Serious (mg/m3)	Reference/ Chemical Form
	Neurological						
16	Rat Harlan-Wistar	13 wk 5 d/wk 6 hr/d		100			Carpenter et al. 1976 FO1DOK
17	Rat Sprague-Dawley	13 wk 2d/wk 4hr/d			250	(increased response time/startle reflex assay)	Lock et al. 1984 FO5DFU
18	Dog Beagle	13 wk 5 d/wk 6 hr/d		100 M			Carpenter et al. 1976 FO1DOK
	Reproductive						
19	Rat Sprague-Dawley	13 wk 2d/wk 4hr/d		1500			Lock et al. 1984 FO5DFU

[a]The number corresponds to entries in Figures 2-1 or 2-2.
[b]Units are in mg/m^3, unless specified otherwise. In some studies, the units were given in ppm. Since the molecular weight of fuel oils is not known, the ppm units could not be converted to mg/m^3. Data from the studies with exposures in ppm are shown in Figure 2-1; data from studies with exposures in mg/m^3 are shown in Figure 2-2.
[c]Used to derive an acute inhalation Minimal Risk level (MRL) of 0.02 mg/m^3; exposure concentration adjusted for 24 hours per day exposure divided by an uncertainty factor of 1000 (10 for interspecies variability, 10 for intraspecies variability, and 10 for use of a LOAEL (less serious effect) for MRL derivation).
[d]Used to determine an intermediate Minimal Risk Level (MRL) of 0.01 mg/m^3; exposure concentration adjusted for 24 hours per day, 7 days per week exposure divided by an uncertainty factor of 1000 (10 for interspecies variability, 10 for intraspecies variability, and 10 for use of a LOAEL (less serious effect) for MRL derivation).

Cardio = cardiovascular; d = day(s); F = female; FO-1 = fuel oil no. 1; FO1DOK = deodorized kersoene; FO5DFU = unspecified diesel fuel; FO2HHO = home heating oil no. 2; FO1JP5 = JP-5 (jet fuel); FO4DF2 = fuel oil no. 2-D; FO5 = unspecified fuel oil; 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 Fuel Oils – Inhalation

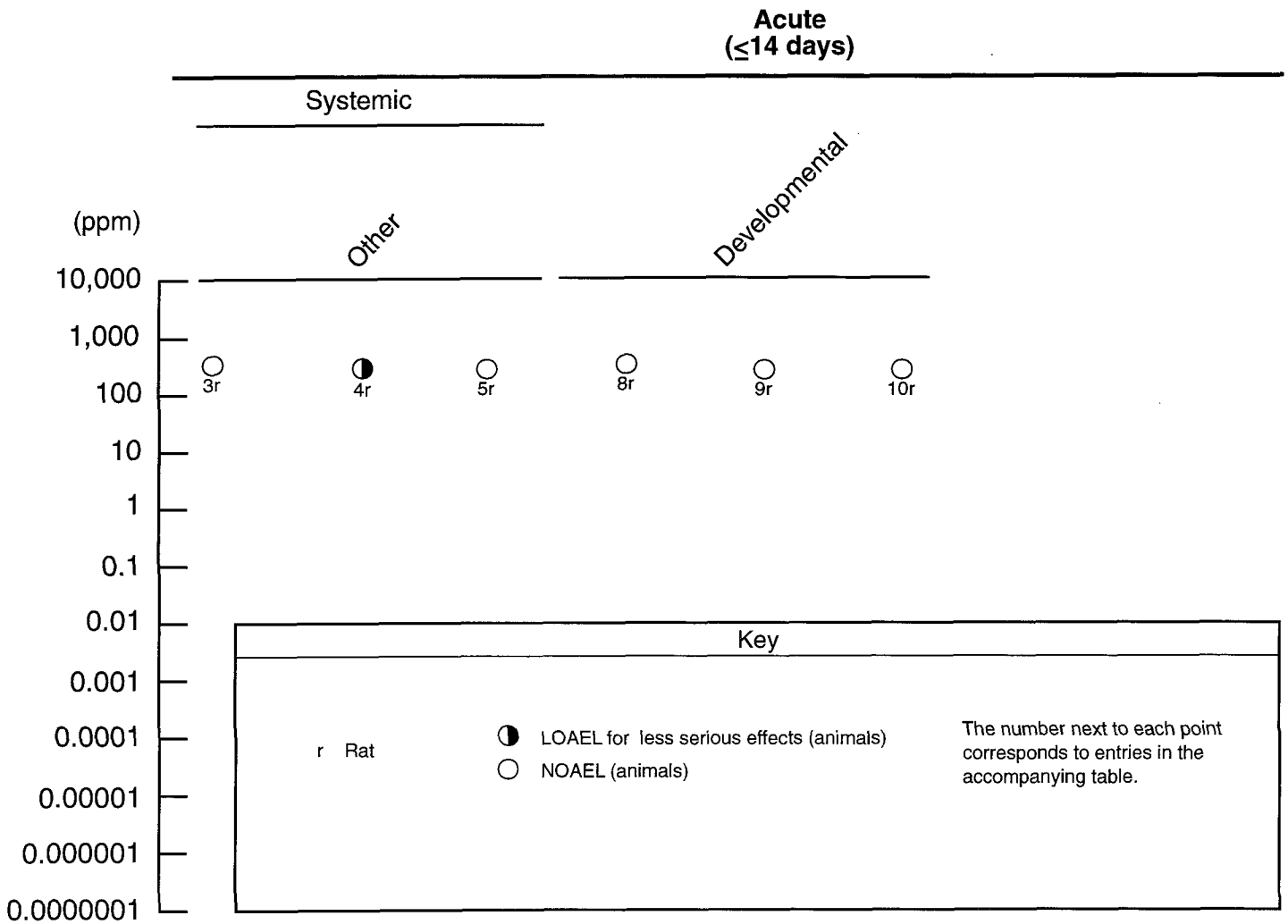


Figure 2-2. Levels of Significant Exposure to Fuel Oils – Inhalation

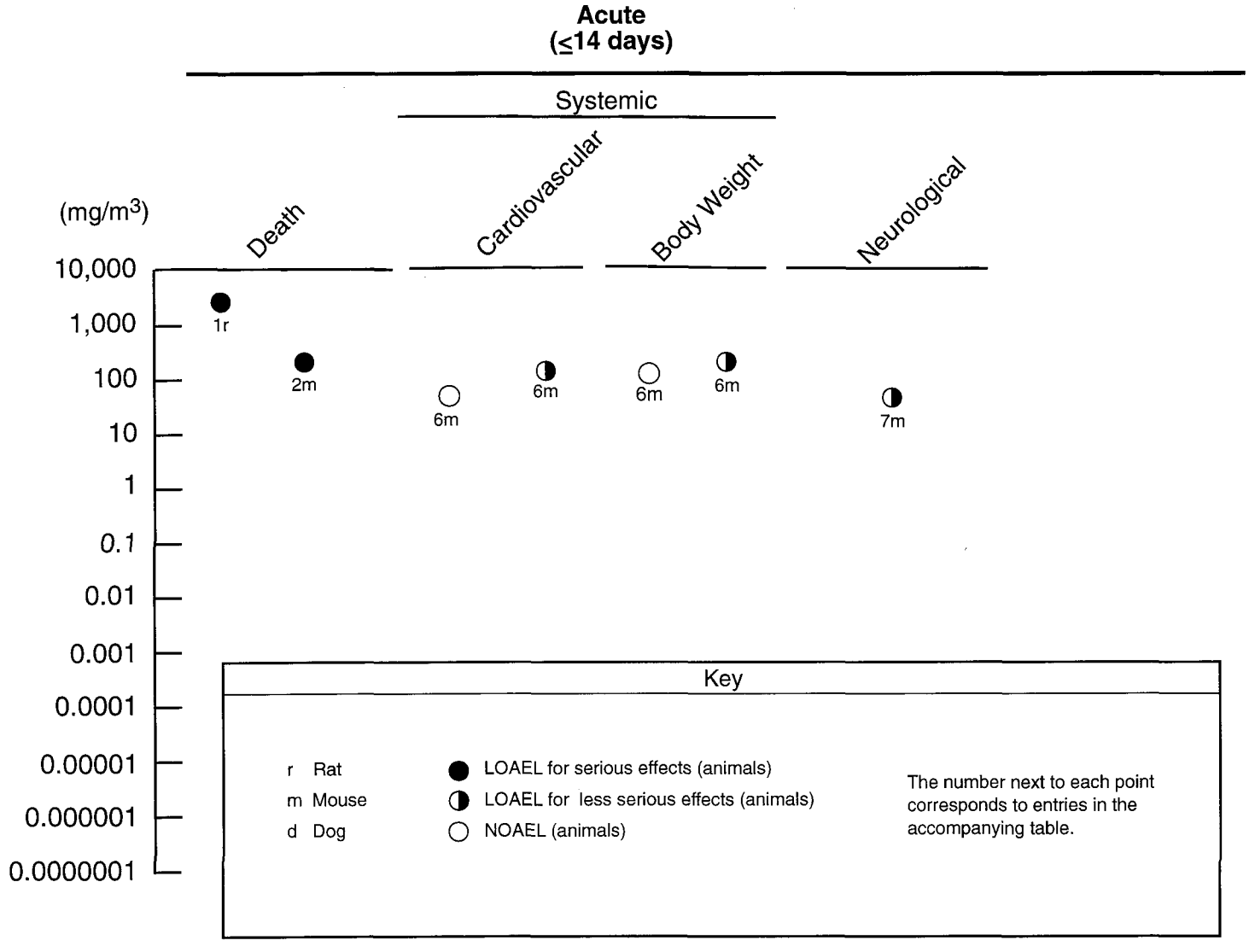
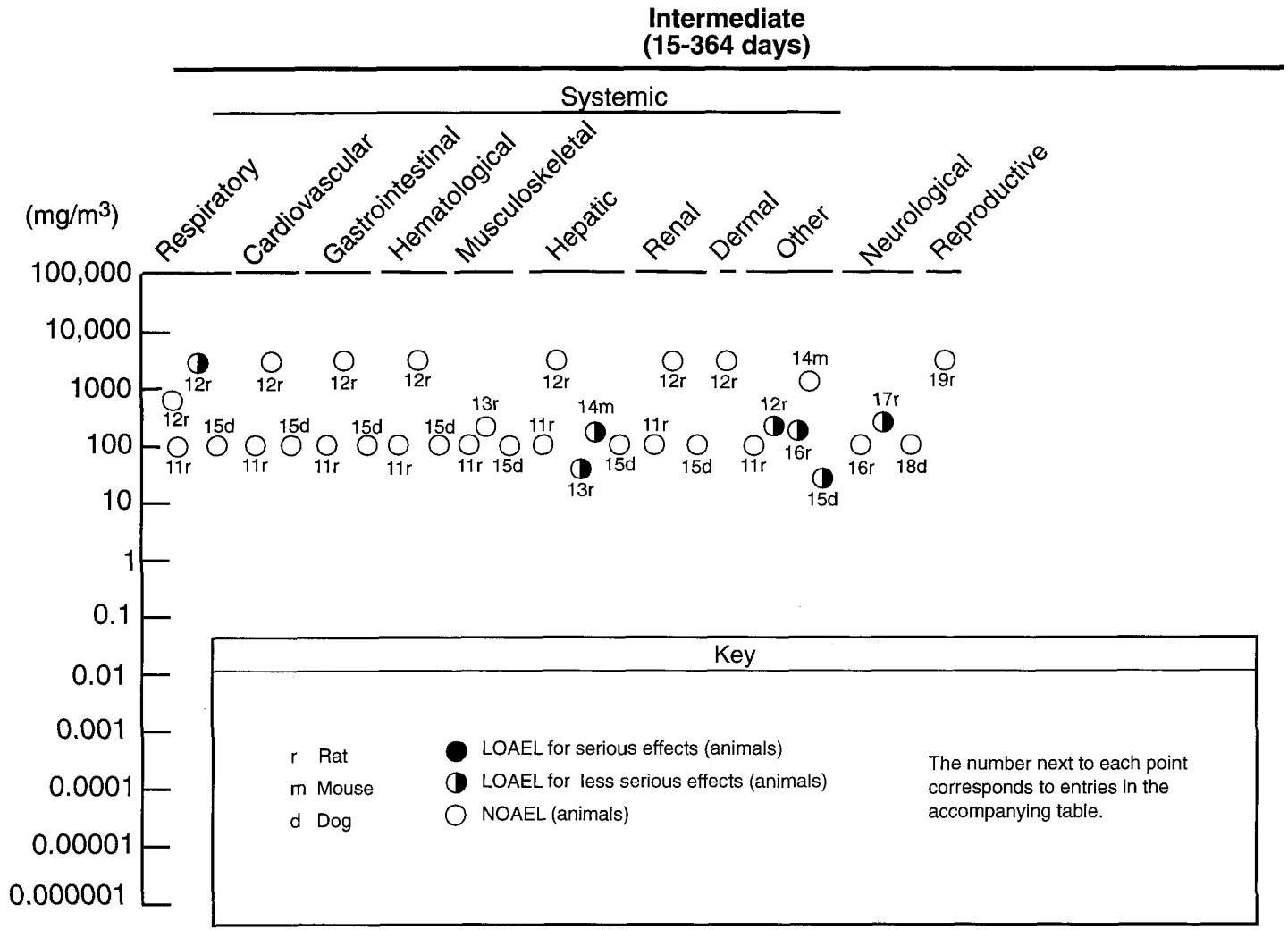


Figure 2-2. Levels of Significant Exposure to Fuel Oils – Inhalation (continued)



2.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category for inhalation exposure to fuel oils are recorded in Table 2-l and plotted in Figures 2-l and 2-2.

Respiratory Effects. Pleural effusions and alveolar infiltrations were noted in a man who had washed his hair with an unknown amount of diesel fuel (Barrientos et al. 1977). The relative contributions from inhalation and dermal exposure could not be distinguished in this case. There was no throat irritation in six volunteers following a 15-minute exposure to a concentration reported to be 140 mg/m^3 of deodorized kerosene vapor (Carpenter et al. 1976). The authors used a hot nichrome wire for the volatilization of their test material and reported that the concentration was probably the "highest attainable concentration at which vapor analysis is representative of liquid analysis." The air saturating concentration of kerosene is considered to approximate 100 mg/m^3 (room temperature and 760 mmHg) and is dependent on the constituents of the mixture.

An epidemiological study examined the effects of chronic exposure to jet fuels in factory workers (Knave et al. 1978). This study found a significant increase in a feeling of heaviness in the chests of exposed subjects when compared to unexposed controls from the same factory. The data are limited because the jet fuels were not specified and may not include JP-5, which is the jet fuel of concern in this profile, and the study did not adjust for the presence of other chemicals. Inhalation exposure is likely, since jet fuel vapor was detected by the authors; however, dermal and oral (i.e., from eating contaminated food) exposures cannot be excluded. An estimated time-weighted average of 128-423 mg/m^3 was detected in the breathing zones of the workers. However, it is not possible to associate the specific concentrations with specific effects.

Limited epidemiological data suggest that chronic human inhalation exposure to kerosene vapor and/or kerosene combustion products from cooking with kerosene stoves does not induce asthmatic respiratory effects. The presence of kerosene stoves in the homes of Malaysian children was not associated with chronic cough, persistent wheeze, asthma, or chest illness (Azizi and Henry 1991). Asthmatic bronchitis and frequent common colds in 3-year-old Japanese children were not associated with the presence of kerosene stoves in their homes (Tominaga and Itoh 1985). The latter study

corrected for exposure to passive smoke. These data are of limited usefulness because the duration of exposure was not reported and the levels of kerosene exposure could not be quantified. Finally, it cannot be determined whether actual exposure to kerosene occurred in these individuals because kerosene exposure was assumed to occur if kerosene was used during cooking or if a kerosene stove was present in the home.

Animal data that pertain to respiratory effects following acute exposure to kerosene by inhalation are limited, because only one concentration level was tested in each study. Reductions in tidal volume and dynamic lung compliance, bronchoconstriction, and an increase in pulmonary resistance occurred in rabbits following inhalation of 32,500 mg/m^3 kerosene aerosol (Casaco et al. 1982). Bronchoconstriction was also induced in guinea pigs that were exposed to 20,400 mg/m^3 kerosene aerosol (Garcia et al. 1988b).

No histopathological changes were noted in the respiratory system of rats or dogs exposed to up to 100 mg/m^3 deodorized kerosene vapor for 13 weeks (Carpenter et al. 1976). Inhalation of diesel fuel aerosol 4 hours/day, 2 days/week, for 13 weeks at concentrations up to 1,500 mg/m^3 did not impair pulmonary function or induce histopathological changes in rats (Lock et al. 1984). However, there was a dose-related increase in the relative weight of the right lobe of the lung, which was only significant at the highest exposure level. Elevated numbers of alveolar macrophages in the low- and high-dose groups were not dose related. Intermediate exposures to diesel fuel aerosol induced damage to the lung parenchyma of rats exposed to a Ct of 8,000 or 12,000 mg hour/m^3 (Dalbey et al. 1987). In general, respiratory effects were more severe after three exposures/week for 3 weeks than one exposure/week for 9 weeks at various exposure levels and durations. Thus, the study found that the respiratory effects were generally more dependent upon the frequency of exposure than the exposure dose or duration. Dose-response data were not reported for the individual exposure concentrations used to produce each concentration time product (see discussion in Section 2.2.1.1).

Cardiovascular Effects. Two case studies were found that reported mild hypertension in humans from acute inhalation exposures to fuel oils. Mild hypertension was noted for 4 days in one of two individuals following a l-hour exposure to JP-5 vapor while flying a small airplane (Porter 1990). Delayed mild hypertension was also noted in a man who was exposed to diesel fuel vapor for 10 days while driving a truck with a fuel injector leak (Reidenberg et al. 1964). The concentration of vapor was not reported in either study. Palpitations were noted in workers chronically exposed to jet fuel

according to one epidemiological study (Knave et al. 1978). The limitations of this study are discussed in detail in Section 2.2.1.2 under Respiratory Effects.

Vasodilation was seen in the ear and tail veins of mice exposed via acute inhalation to 204 or 135 mg/m^3 diesel fuel no. 2 vapors. The effect was not seen at 65 mg/m^3 (Kainz and White 1984). Inhalation of kerosene aerosol for an intermediate duration induced aortic plaques in guinea pigs that resemble those seen in atherosclerosis (Noa and Illnait 1987a). Significant increases in total serum cholesterol and decreases in high-density lipoprotein (HDL) were also noted. Similar effects were induced following exposure to kerosene aerosol or kerosene smoke. This study was limited because only one concentration of kerosene aerosol, within a range of 20,400-34,000 mg/m^3, was tested and the actual exposure level of kerosene smoke was not reported. Inhalation of diesel fuel aerosol 4 hours/day, 2 days/week, for 13 weeks at concentrations up to 1,500 mg/m^3 did not induce histopathological changes in the cardiovascular system of rats (Lock et al. 1984). However, a statistically significant decrease in blood cholesterol levels was reported in females of the high-dose group immediately after exposure compared to controls. The authors did not consider this effect to be treatment related; no data were presented. No microscopic or histopathological changes were noted in the cardiovascular system of rats or dogs exposed to up to 100 mg/m^3 deodorized kerosene vapor for 13 weeks (Carpenter et al. 1976).

Gastrointestinal Effects. Several studies were identified that described gastrointestinal effects in humans after inhalation exposure to unknown quantities of fuel oils. In one case study, 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). This effect subsided within 24 hours. Abdominal cramps, vomiting, and diarrhea occurred in a man who was exposed to diesel fuel vapor for 10 days while driving a truck with a fuel injector leak (Reidenberg et al. 1964). Also, nausea, abdominal cramps, and diarrhea were reported for a man who had washed his hair with a diesel fuel. “On examination” (no further description of the examination was provided), the abdomen was normal (Barrientos et al. 1977). A history of epigastric (upper abdominal) pain was noted in a male subsequent to washing his hands with diesel fuel over several weeks (Crisp et al. 1979). Effects resulting from inhalation versus dermal exposure could not be distinguished in the two latter cases.

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 13 weeks (Carpenter et al. 1976). Inhalation of diesel

fuel aerosol 4 hours/day, 2 days/week, for 13 weeks at concentrations up to 1,500 mg/m^3 did not induce histopathological changes in the gastrointestinal system of rats (Lock et al. 1984).

Hematological Effects. Three case studies were found that addressed possible hematological effects due to acute inhalation exposure to unknown quantities of fuel oils by humans. There were no blood chemistry changes in either of two individuals following a l-hour exposure to JP-5 vapor while flying a small airplane (Porter 1990). Subcutaneous hemorrhage, mild nose bleeds, low platelet counts, and retinal arteriole constriction were reported for a man who was exposed to diesel fuel vapor for 10 days while driving a truck with a fuel injector leak (Reidenberg et al. 1964). The latter effect was delayed, occurring 4 weeks after initial exposure. These effects may be indicative of blood clotting problems. Decreased hemoglobin concentration and an increase in erythrocyte sedimentation rate were noted in one man after washing his hands with diesel fuel over several weeks (Crisp et al. 1979). Effects resulting from inhalation versus dermal exposure cannot be distinguished in this case.

No exposure-related hematological effects were noted in rats or dogs exposed to up to 100 mg/m^3 deodorized kerosene vapor for 13 weeks (Carpenter et al. 1976). Inhalation of diesel fuel aerosol (4 hours/day, 2 days/week, for 13 weeks) at concentrations ranging up to 1,500 mg/m^3 failed to produce histopathological changes, splenic weight changes, or other hematological effects in rats (Lock et al. 1984). Intermediate exposures to diesel fuel aerosol induced decreases in the mean red blood cell count in rats exposed to a Ct of 8,000 or 12,000 mg hour/m^3 3 times/week for 3 weeks (Dalbey et al. 1987). However, the statistical significance of this effect was not clearly reported in the study. There was no significant effect on white blood cell count in these rats. Dose-response data were not reported for the individual exposure concentrations used to produce each Ct (see discussion in Section 2.2.1.1).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to fuel oils.

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 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 fuel oils.

In a study designed to evaluate the effects of kerosene hydrocarbons on the tissue metabolism of rats after acute and subchronic exposure, Starek and Vojtisek (1986) exposed groups of male Wistar rats (131 total animals for both acute and subchronic studies) to kerosene vapors in average concentrations of 58 (range 33.3-75.0) or 231 (range 181.3-250.2) mg/m^3 for 6 hours/day, 6 days/week for 14 consecutive weeks. Food and water were available *ad lib* throughout exposure, but animals were fasted for 18 hours prior to post-dosing tests. Twenty hours after termination of exposure, two types of tests were conducted: (1) the effects of kerosene on the rate of biotransformation of hexobarbital and phenacetin were examined by looking at hexobarbital sleeping time and measuring the antipyritic activity of phenacetin in intact animals; and (2) blood, liver, and muscle tissue were obtained for *in vitro* tests to examine pyruvate, lactate, and glucose activity/levels. In the first experiments, hexabarbital sleeping time remained unchanged in both treatment groups, and the antipyretic activity of phenacetin was significantly prolonged only in the high-dose (concentration) group. In the second group of tests, the blood glucose concentration was found to be decreased in both the 58 mg/m^3 and 231 mg/m^3 exposure groups, while lactate and pyruvate were found to be increased only in the high concentration group. (This study was used as the basis for derivation of an intermediate MRL for fuel oil no. 1 for the inhalation route of exposure.) The authors suggest that the decreased circulating glucose levels may be associated with both increased glycolysis and the inhibition of gluconeogenesis (kerosene exposure effecting increased glycolysis is supported by the findings of increased concentrations of lactate and pyruvate in the blood and liver, as well as increased lactate dehydrogenase activity in the liver). Further, the authors suggest that the increased glycolysis may be the result of the inhibition of cellular respiration by kerosene, and it was noted that cellular respiration was inhibited in liver and kidney slices subsequent to the addition of kerosene to the incubation solution.

When exposed to up to 100 mg/m^3 deodorized kerosene vapor 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). Inhalation of diesel fuel aerosol 4 hours/day, 2 days/week for 13 weeks at concentrations up to 1,500 mg/m^3 did not induce histopathological or organ weight changes in the livers of rats (Lock et al. 1984).

Renal Effects. Renal effects were tested by urinalysis in two individuals who were exposed to JP-5 vapor for approximately 1 hour while flying a small airplane (Porter 1990). No abnormalities in the urine were reported in this case study for either of these individuals. Acute renal failure was reported in a man who was exposed to diesel fuel vapor for 10 days while driving a truck with a fuel injector leak (Reidenberg et al. 1964). Acute renal failure also occurred in a man after washing his hair with an unknown amount of diesel fuel (Barrientos et al. 1977). In addition, he had oliguria; biopsy revealed mitosis and vacuolization in renal cells, tubular dilation, and some cellular proliferation in the glomerulus. Another man developed acute tubular renal necrosis after washing his hands with an unspecified diesel fuel over several weeks (Crisp et al. 1979). Specifically, patchy degeneration and necrosis of the proximal and distal tubular epithelium with preservation of the basement membranes were noted. Also, increased blood urea and serum creatinine levels were noted in this individual. Effects resulting from inhalation versus dermal exposure could not be distinguished in the two latter cases. Based upon these case studies and the finding of kidney damage in mice dermally exposed to fuel oils (see Section 2.2.3.2 under Renal Effects), it may be possible to absorb fuel oil vapor through the skin. However, no studies were located that tested dermal absorption of fuel oil vapor in humans (see Section 2.3.1.3).

Several studies have identified a hydrocarbon-induced nephropathy in male rats that is associated with exposure to hydrocarbon vapors, including some fuel oils (Bruner 1984; Cowan and Jenkins 1981; 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). When male rats are exposed to certain hydrocarbons, including JP-5 and marine diesel fuel, $\alpha_{2\mu}$,-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 (Bruner 1984; Cowan and Jenkins 1981; Gaworski et al. 1984) and 50 or 300 mg/m^3 marine diesel fuel vapor (Bruner 1984; Cowan and Jenkins 1981) 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 and marine diesel fuel-induced nephropathy, dose-dependent formation of cytoplasmic hyaline droplets of the proximal tubules in the renal cortex is 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 1981). Since humans do not possess $\alpha_{2\mu}$ -globulin, this effect in male rats is not considered germane to human health risk assessment.

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). This nephropathy does not appear to be induced by deodorized kerosene or diesel fuel, at least not under subchronic exposure conditions. No histopathological changes were noted in the renal system of rats or dogs exposed to up to 100 mg/m^3 deodorized kerosene vapor for 13 weeks (Carpenter et al. 1976). No organ weight or histopathological changes of the renal system were noted in rats following inhalation of diesel fuel aerosol 4 hours/day, 2 days/week, for 13 weeks at concentrations up to 1,500 mg/m^3 (Lock et al. 1984). 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 exposed under similar conditions to either JP-5 or marine diesel fuel vapors (Bruner 1984; Cowan and Jenkins 1981; Gaworski et al. 1984).

Dermal Effects. No studies were located regarding dermal effects in humans after inhalation exposure to fuel oils.

Whole-body inhalation exposure to diesel fuel aerosol 4 hours/day, 2 days/week, for 13 weeks at concentrations up to 1,500 mg/m^3 did not induce skin lesions in rats (Lock et al. 1984).

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). Both individuals experienced a burning sensation in their eyes, and one had itchy, watery eyes 1 day after the exposure. These effects subsided within 24 hours. Hyperemic conjunctiva were also reported for one of the individuals; this effect subsided after 4 days. Another case study describes subconjunctival hemorrhages in a man whom had washed his hair with an unknown amount of diesel fuel (Barrientos et al. 1977). Effects resulting from inhalation versus dermal exposure could not be distinguished in this case. Eye irritation was not induced in six volunteers by a 15-minute exposure to 140 mg/m^3 deodorized kerosene vapor (Carpenter et al. 1976). This study is limited since only one concentration was tested. Eye irritation was also noted in factory workers who were chronically exposed to jet fuel (Knave et al. 1978). The limitations of the study are discussed in detail in Section 2.2.1.2 under Respiratory Effects.

No studies were located regarding ocular effects in animals after inhalation exposure to fuel oils.

Body Weight Effects. No studies were located regarding body weight effects for humans after inhalation exposure to fuel oils.

There was no change in body weight gain in rats exposed to up to 100 mg/m^3 deodorized kerosene vapor for 13 weeks (Carpenter et al. 1976). Inhalation of diesel fuel aerosol 4 hours/day, 2 days/week for 13 weeks at concentrations of 250-1,500 mg/m^3 induced reversible body weight loss at all exposure levels and decreased food consumption in rats exposed to the mid- and high-exposure levels (Lock et al. 1984). There were no histopathological or relative adrenal gland weight changes in these animals. Intermediate exposures to diesel fuel aerosol induced decreases in the mean body weights of rats exposed to a Ct of 8,000 or 12,000 mg hour/m^3 (Dalbey et al. 1987). Weight loss was found to be dependent upon exposure concentration, frequency, and duration in this study. Dose-response data were not reported for the individual exposure concentrations used to produce each Ct (see discussion in Section 2.2.1.1). There was no change in body weight gain in mice or female rats following 90-day inhalation exposure to 750 mg/m^3 JP-5 vapor (Gaworski et al. 1984).

Other Systemic Effects. A man exposed to diesel fuel vapor for 10 days while driving a truck with a fuel injector leak exhibited systemic edema (Reidenberg et al. 1964). Edema of the scrotum and ankle were reported in a man who washed his hands with diesel fuel over several weeks (Crisp et al. 1979). Other effects noted in this man were loin pains, thirst, and severe exhaustion. Effects resulting from inhalation versus dermal exposure could not be distinguished in this case. Inhalation of 400 ppm home heating oil no. 2 vapor, 408.8 ppm fuel oil UNSP vapor, or 401.5 ppm diesel fuel vapor by pregnant rats for 10 days did not induce maternal body weight changes (API 1979c, 1979g; Beliles and Mecler 1983). A dose-response relationship was noted for decreased food and water consumption with subsequent weight loss and dehydration in mice following 5-day, 8-hour/day acute inhalation of 204 mg/m^3 diesel fuel no. 2 vapors (Kainz and White 1984). These effects were not induced by 135 mg/m^3 of the diesel fuel. Decreased food intake was also noted in pregnant rats following inhalation of 401.5 ppm diesel fuel vapor; no effects on maternal food intake were noted following inhalation of 101.8 ppm diesel fuel vapor, 100 or 400 ppm home heating oil vapor, or 86.9 or 408.8 ppm fuel oil UNSP vapor (API 1979c, 1979g; Beliles and Mecler 1983).

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or Lymphoreticular effects in humans or animals after inhalation exposure to fuel oils.

2.2.1.4 Neurological Effects

In one case study, neurological effects in humans resulting from acute exposure to JP-5 vapor were reported (Porter 1990). Coordination and concentration difficulties and fatigue were noted in each of two individuals following a l-hour exposure to JP-5. Other effects included headache, apparent intoxication, and anorexia. Neither experienced any sensory impairment. The effects subsided within 24 hours for one individual, and within 4 days for the other. Anorexia was also reported in a man who washed his hands with diesel fuel over several weeks (Crisp et al. 1979). Effects resulting from inhalation versus dermal exposure could not be distinguished in this case. A man exposed to diesel fuel vapor for 10 days while driving a truck with a fuel injector leak exhibited severe headaches approximately 4 weeks after exposure (Reidenberg et al. 1964). In a study of six volunteers, slight olfactory fatigue was induced in three, while one reported “tasting something,” following a 15-minute exposure to 140 mg/m3 deodorized kerosene vapor (Carpenter et al. 1976). This study is limited since only one concentration was tested.

An epidemiological study tested the effects of chronic exposure to jet fuel in factory workers (Knave et al. 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. Also, attention and sensorimotor speed were impaired in the exposed workers, but no effects were found on memory function or manual dexterity. Results of an electroencephalograph (EEG) suggested that the exposed workers may have had instability in the thalamocortical system. The limitations of the study, which include lack of specification of type of jet fuel and no adjustment for other chemicals, were discussed in greater detail in Section 2.2.1.2 under Respiratory Effects.

Kainz and White (1984) exposed (nose only) groups of CD-l mice to concentrations of 65, 135, or 204 mg diesel vapor/m3 of air for 8 hours/day for 5 consecutive days. General appearance and behavior were observed, as was performance on a series of neurobehavioral tests (square box activity

test, rotating rod test, inclined plane test, cornea1 reflex test, hot plate test) administered 24 hours before exposure, on each day of exposure, and 24 hours after the last exposure. Results of the square box test revealed increased activity at the lowest concentration, little change at the mid-concentration, and decreased activity (up to 50%) in the high-concentration exposed animals. The rotating rod test showed decreased performance at the mid- and high-exposures. Results of the hot plate test indicated an increased sensitivity to heat of the mid- and high-concentration groups on day 1 of exposure, but tolerance was reported on day 6. The corneal reflex and inclined plane tests showed no differences from controls at any air concentration. Some degree of ataxia/disturbed gait was observed in all exposure groups immediately after removal from the exposure chamber, with the severity and duration of the symptom being dose dependent (all mice returned to normal before the next day's exposure). Grooming habits were reported to be poor in the mid- and high-exposure groups. Water consumption was decreased in the high-dose group, which was reported to appear dehydrated on day 3 of exposure, and a 30% loss in body weight was also observed in this group. Vasodilation of the ear and tail veins was seen in the mid- and high-concentration groups on the third day of the experiment. Tremors were reported in 3 of 10 mice in the mid-exposure group and in 5 of 10 mice in the high-concentration group while in motion, and 3 of the high-exposure animals died before the end of the experiment. The results of the Kainz and White (1984) study indicated a time- and dose-dependent response to diesel vapor, with nonlethal effects all being completely reversible within 24 hours of cessation of exposure. (This study was used to derive an acute inhalation MRL for fuel oil no. 2-D.)

No histopathological changes were noted in the nervous system of rats or dogs exposed to up to 100 mg/m^3 deodorized kerosene vapor for 13 weeks (Carpenter et al. 1975, 1976). Inhalation of diesel fuel aerosol 4 hours/day, 2 days/week, for 13 weeks at concentrations up to 1,500 mg/m^3 did not induce histopathological changes in the nervous system of rats (Lock et al. 1984). However, peak response time using the startle reflex assay was increased in rats at all exposure levels, but the greatest increase occurred in the high-dose group. Neurotoxicity, as measured using the landing footspread, tail flick, forelimb grip strength, and startle reflex assays, did not occur in rats exposed to a Ct of 8,000 or 12,000 mg hour/m^3 diesel fuel aerosol for 3 or 9 weeks (Dalbey et al. 1987).

The highest NOAEL and all reliable LOAEL values for neurological effects after inhalation exposure to fuel oils are recorded in Table 2-1 and plotted in Figure 2-2.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to fuel oils.

Inhalation of diesel fuel aerosol 4 hours/day, 2 days/week, for 13 weeks at concentrations up to 1,500 mg/m^3 did not induce relative testes weight changes nor histopathological changes in the reproductive organs of rats (Lock et al. 1984).

The highest NOAEL value for reproductive effects after inhalation exposure to fuel oils is recorded in Table 2-l and plotted in Figure 2-2.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to fuel oils.

No developmental effects (soft tissue changes, skeletal abnormalities, inhibition of fetal growth) were noted in the fetuses of female rats exposed to 400 ppm home heating oil no. 2, 408.8 ppm fuel oil UNSP, or 401.5 ppm diesel fuel vapor by inhalation during gestation days 6-15 (API 1979c 1979g; Beliles and Mecler 1983). Only one study was located for each fuel oil for these effects.

The highest NOAEL values for developmental effects after inhalation exposure to fuel oils are recorded in Table 2-1 and plotted in Figure 2-l.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after inhalation exposure to fuel oils.

In the only *in vivo* animal study located regarding genotoxic effects using inhalation as the route of exposure, male CD-l mice (12/group) exposed to 100 or 400 ppm diesel fuel vapor (6 hours/day, 5 days/week, for 8 weeks) showed no adverse effects with respect to the frequency of dominant lethal mutations (API 1981).

Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

There are limited epidemiological data regarding carcinogenicity in humans following chronic inhalation exposure to kerosene. In one case-control study, there was no association between the use of kerosene stoves for cooking and bronchial cancer in nonsmoking women (Chan et al. 1979). In another case-control study, there was no association between renal cell cancer and occupational exposure to fuel oils, including diesel fuel (Partanen et al. 1991). In the first study, it cannot be determined whether the individuals were actually exposed to kerosene vapor. Also, there may be additional or alternative effects resulting from exposure to the combustion products of kerosene, which may be toxicologically different from the kerosene itself. In the latter study, exposure to other chemicals may have affected the results, since fuel oil exposure was based upon occupation. Both studies are limited because they do not quantify the levels of exposure and cannot accurately determine the duration of exposure to fuel oils. In another study, increased risk of laryngeal cancer was associated with self-reported exposure to diesel oil (Ahrens et al. 1991). However, the data were equivocal. Similarly, exposure to “petroleum products,” including diesel fuel, has been associated with acute leukemia (Lindquist et al. 1991), but the study was very limited in that type of product exposed to was not described, and included a wide range of product types. A third study associated the use of kerosene stoves and exposure to “petroleum products” with oral and pharyngeal cancer (Zheng et al. 1992), but suffers the same limitations as Lindquist et al., with the addition that use of kerosene stoves involves exposure to both kerosene vapor and combustion products.

In a study conducted on rats, no renal tumors were observed during life-time observation following a 90-day continuous exposure to 750 mg/m^3 JP-5 vapor or to 300 mg/m^3 marine diesel fuel vapor (Bruner 1984). Since this study was not designed to test carcinogenicity, these data have limited usefulness.

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 15 years). The deaths are 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 (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 1,890 mg/kg, based on ingestion of 30 mL of kerosene by children 11 months to 2 years of age (Dudin et al. 1991; Santhanakrishnan and Chithra 1978), and as high as 16,789 mg/kg, based on ingestion of 200 mL of kerosene by a l-year-old child (Santhanakrishnan and Chithra 1978). No lethality was reported for children from 10 months to 5 years old following ingestion of estimated doses ranging from 120 to 870 mg/kg and in one instance a dose as high as 1,700 mg/kg of kerosene (Dudin et al. 1991).

Death in rats occurred after acute oral exposure to 12,000 mg/kg kerosene but not after exposures to 8,000-11,200 mg/kg kerosene or 12,150 mg/kg Deobase® (Muralidhara et al. 1982). Oral exposure to 4,000 mg/kg kerosene was lethal to 10-day-old rats; this dose level was not tested in adult rats (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.

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, death occurred following acute oral exposure to 3,760-19,200 mg/kg kerosene. Death in rabbits occurred after acute oral exposure to 12,800-28,800 mg/kg kerosene but not after exposure to 8,000 mg/kg. 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 four out of five male calves; only one dose was tested in this study (Rowe et al. 1973). Mortality in rats was induced by acute aspiration of 0.05-0.25 mL of kerosene; there was a dose response relationship for death in this study (Gerarde 1963). Aspiration is induced by placing the test material into the back of the throat which causes the animal to choke, forcing the test compound into the respiratory tract. The purpose of using aspiration as a route of exposure in animals is to mimic human respiratory exposure which occurs 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.

All reliable LOAEL values for death in each species and duration category after oral exposure to fuel oils are recorded in Table 2-2 and plotted in Figure 2-3.

2.2.2.2 Systemic Effects

No studies were located regarding musculoskeletal effects in humans or animals after oral exposure to fuel oils.

The highest NOAEL and all reliable LOAEL values for systemic effects in each species and duration category for oral exposure to fuel oils are recorded in Table 2-2 and plotted in Figure 2-3.

Respiratory Effects. Even if the kerosene is initially ingested (accidental ingestion of fuel oils 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; Nouri and Al-Rahim 1970). Based on those 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; Annobil 1983; Annobil and Ogunbiyi 1991; 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 a feeling of heaviness in the chests of workers

TABLE 2-2. Levels of Significant Exposure to Fuel Oils - Oral

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat Wistar-CFTRI	1 d (G)				12000 F (minimum lethal dose; 33% mortality)	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 Wistar-CFTRI	1 d (G)	Cardio	12000 F			Muralidhara et al. 1982 FO-1
			Gastro	12000 F			
			Hemato	12000 F			
			Renal	12000 F	NS F (slightly dilated kidney tubules)		
			Hepatic	12000 F	NS F (cellular vacuolization; infiltration)		
			Bd Wt	12000 F	NS F (decreased body weight and food intake)		

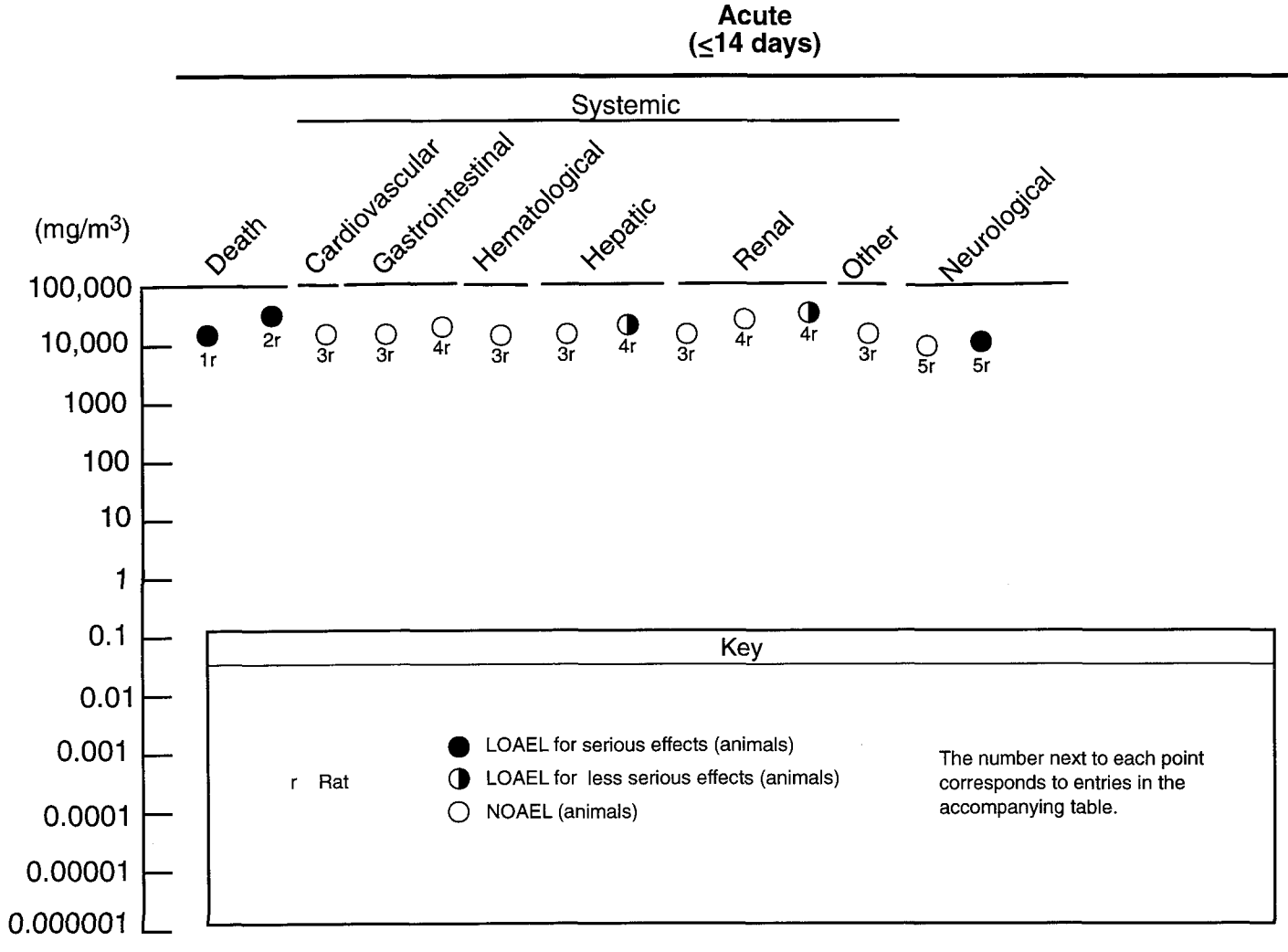
TABLE 2-2. Levels of Significant Exposure to Fuel Oils - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ Chemical Form
4	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)		
	Neurological						
5	Rat Wistar-CFTRI	1 d (G)		8000 F	NS F (anorexia)	9600 F (unsteady gait; drowsiness)	Muralidhara et al. 1982 FO-1

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

Cardio = cardiovascular; Derm - dermal; d = day(s); F = female; FO-1 = fuel oil no. 1; FO1JP5 = JP-5 (jet fuel); (G) = gavage; Gastro = gastrointestinal; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; Resp = respiratory

Figure 2-3. Levels of Significant Exposure to Fuel Oils – Oral



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 in 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 levels of exposure which are usually based on the finding of an empty container near the poisoned child (Agarwal and Gupta 1974; Akamaguna and Odita 1983; Aldy et al. 1978; Coruh and Inal 1966; Dudin et al. 1991; Nouri and Al-Rahim 1970; Saksena 1969; Santhanakrishnan and Chithra 1978), although the effects associated with specific doses were not reported. The Subcommittee on Accidental Poisoning (1962) estimated that ingestion of 10-30 mL 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). These effects also occurred at doses beyond this range. An estimated oral dose of less than 5,300 mg/kg kerosene resulted in the death of a 10-month-old girl. Pneumothorax, pneumomediastinum, and death were believed to be the results of respiratory distress from aspiration of kerosene (Zucker et al. 1986). Respiratory distress was reported to have resulted in the deaths of a 2-year-old child and a l-year-old child after ingestion of 30 mL (1,890-1,959 mg/kg) and 200 mL (15,340-16,789 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 of the 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 authors estimated them as small.

Mononuclear and polymorphonuclear cell infiltration and unspecified pathological lesions were noted in the lungs of guinea pigs after gavage administration of 3,200-8,000 mg/kg kerosene (Brown et al.

1974). In mice, aspiration of 20 μL of Kerosene induced pulmonary consolidation and hemorrhage, pneumonitis, a decrease in pulmonary clearance of *Staphylococcus aureus*, and an increase in relative lung weight (Nouri et al. 1983). Dogs exposed to 0.5 mL/kg kerosene by aspiration exhibited increases in oxygen utilization, intrapulmonary physiologic shunt fraction, and respiratory rate and decreases in arterial oxygen tension (Goodwin et al 1988). In the aspiration studies, the actual dose entering the lungs cannot be determined.

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 under Respiratory Effects.

There were no histopathological changes and no change in the 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 Deobase® (Muralidhara et al. 1982). Data for Deobase® are limited because effects were reported for only one dose.

In another study, decreases in heart rate and mean arterial blood pressure occurred in dogs following a single exposure to 0.5 mL/kg kerosene by aspiration, although 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. The study is limited, however, because only one dose was tested.

Gatrotestinal Effects. The most commonly reported gastrointerinal effect in children following acute ingestion of kerosene in vomiting (Akamaguna and Odita 1983; Aldy et al. 1978; Mahdi 1988; Majeed et al. 1981; Nouri and Al-Rahim 1970; Saksena 1969; St. Johns 1982), including bloody vomit (Nouri and Al-Rahmin 1970). Other effects noted are abdominal pain and/or distension (Akamaguna and Odita 1983; Mahdi 1988; Majeed et al. 1981; Nouri and Al-Rahim 1970; Sakena 1969), gastroenteritis (Sakena 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 Deobase® (Muralidhara et al. 1982).

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).

In rats exposed by gavage to single doses of up to 12,000 mg/kg/ kerosene or 12,150 mg/kg Deobase®, 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 18,912 mg JP-5/kg (Parker et al. 1981).

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to fuel oils.

There was no change in the relative organ weight of the liver in rats following exposure by gavage to single doses of up to 12,000 mg/kg kerosene or 12,150 mg/kg Deobase® (Muralidhara et al. 1982). Histopathological examination revealed slight cellular infiltration and mild vacuolization of the liver, but the kerosene and Deobase exposure levels that induced these effects were not specified. A single exposure to JP-5 induced necrosis in the hepatocytes of rats exposed to 18,912-47,280 mg/kg by gavage (Parker et al. 1981). In another experiment, a single exposure to 18,912 mg JP-5/kg induced vacuolization of the periportal hepatocytes within 2 days of gavage, as well as statistically significant increases in serum glutamic pyruvic transaminase (SGPT), glutamic oxaloacetic transaminase (SGOT), and lactate dehydrogenase levels, suggesting hepatic damage (Parker et al. 1981).

Renal Effects. Several case studies reported normal urinalysis tests in children following acute ingestion of kerosene (Dudin et al. 1991; Mahdi 1988; Nouri and Al-Rahim 1970), although albuminuria was occasionally noted (Dudin 1991; Nouri and Al-Rahim 1970).

There were no changes in relative kidney weights in rats following exposure by gavage to single doses of up to 12,000 mg/kg kerosene or 12,150 mg/kg Deobase® (Muralidhara et al. 1982). Histopathological examination revealed slight cellular infiltration and mild vacuolization in the kidney

tissues and slight dilation of the kidney tubules, but the kerosene and Deobase® exposure levels that induced these effects were not specified. Only one study was located that tested for kidney weight changes.

In another study, 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 within 48 hours of 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, between 2 and 14 days, following exposure. A single exposure to 18,912 mg/kg JP-5 also induced a statistically significant increase in creatinine levels (Parker et al. 1981). These effects are apparently unique to male rats and are not expected to occur in humans (see discussion in Section 2.2.1.2 under Renal Effects).

Dermal Effects. 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 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 exposure by gavage to single doses of 24 mL JP-5/kg (Parker et al. 1981).

Ocular Effects. No studies were located regarding ocular effects in humans or animals after oral exposure to fuel oils.

Other Systemic Effects. Fever has been reported in children following ingestion of kerosene (Akamaguna and Odita 1983; Aldy et al. 1978; Dudin et al. 1991; Mahdi 1988; Majeed et al. 1981; Nouri and Al-Rahim 1970; Saksena 1969; St. John 1982). In one study, fever was reported with pulmonary complications for 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.

There were no histopathological changes and no changes in the relative adrenal gland weights in rats following exposure by gavage to single doses of up to 12,000 mg/kg kerosene or 12,150 mg/kg Deobase® (Muralidhara et al. 1982). Only one study was located that tested for these effects.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after oral exposure to fuel oils.

2.2.2.4 Neurological Effects

In one study, lethargy, semicoma, and/or coma were reported for children and adults who had ingested kerosene (Subcommittee on Accidental Poisoning 1962). Estimated exposure levels of 10-30 mL kerosene were associated with complications of the central nervous system in 18 of the 422 study participants. However, these effects also occurred at doses beyond this range, but the exact exposure levels are not known. Incidences of the effects and the ages associated with the effects or ingested doses were not reported.

Several case studies 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. 1991; 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. 1981; Nouri and Al-Rahim 1970; Saksena 1969; Santhanakrishnan and Chithra 1978).

In one study of 78 children known to have ingested kerosene, coma, convulsions, and death were noted in two children (aged 11-48 months) after each ingested 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. Neither coma nor convulsions occurred in children that ingested 3-20 mL of kerosene (equivalent to 126-1,754 mg/kg in children aged 10 months to 5 years). 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).

An epidemiological study found significant increases in neurasthenia (i.e., fatigue, depressed mood, lack of initiative, dizziness, and sleep disturbances) in workers who were chronically exposed to jet fuels by inhalation, oral, and/or dermal exposure (Knave et al. 1978). Also, attention and sensorimotor speed were impaired, but no effects were found on memory function or manual dexterity. EEG results suggest that the exposed workers may have had instability in the thalamocortical system. The limitations of the 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 Deobase 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 Deobase® data, since only one dose was tested.

In another study in which mice were exposed to a single dose of 20 μL of kerosene followed by aspiration, drowsiness, lack of coordination, and behavioral changes occurred (Nouri et al. 1983). The study is limited because only one dose was tested. The actual dose entering the lungs by aspiration cannot be determined.

The highest NOAEL and all reliable LOAEL values for neurological effects after oral exposure to fuel oils are recorded in Table 2-2 and plotted in Figure 2-3.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after oral exposure to fuel oils.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after oral exposure to fuel oils.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to fuel oils.

Inconclusive evidence that fuel oil no. 2 is clastogenic in rats has been reported (Conaway et al. 1984). Briefly, a bone marrow assay was used in which groups of four Sprague-Dawley rats (sex not specified) received oral doses of 125, 417, or 1,250 mg/kg/day fuel oil no. 2 for 5 consecutive days. Animals were then sacrificed, and bone marrow cells were examined for abnormal chromosome morphology. Marked, but not dose-related, increases in the percentage of aberrant cells and the percentage of cells with chromatid breaks were seen in all treatment groups. The effect was reported to be significant at the low and high dose, and the greatest yield of aberrant chromosome figures occurred in the animals treated with 125 mg/kg/day. Alternatively, cyclohexane/DMSO extract and DMSO extract of diesel 1 (CAS no. 8008-20-6) and home heating oil (CAS no. 68476-30-2), administered orally at doses of 1.0, 2.0, and 5.0 g/kg, did not induce increased frequency of micronuclei in a mouse bone marrow micronucleus assay (McKee et al 1994). It should be noted that the extraction procedure was used to concentrate the aromatic fraction (with particular interest in the polynuclear aromatics) of the fuel oils tested.

Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans or animals after oral exposure to fuel oils.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to fuel oils.

Single dermal exposures to 0.5 mL/kg home heating oil no. 2 or diesel fuel were not lethal to rabbits (API 1979a, 1980a). Daily dermal exposures for 1 week to 0.1 mL kerosene were not lethal to male mice (Upreti et al. 1989). Death in mice occurred after acute dermal exposures to 20,000-40,000 mg/kg/day marine diesel fuel and 30,000-40,000 mg/kg/day JP-5, but not after exposures to 2,000-8,000 mg/kg/day marine diesel fuel or 5,000-20,000 mg/kg/day JP-5 (NTP/NIH 1986). Intermediate exposures to 2,000-8,000 mg/kg/day JP-5 for 13 weeks (NTP/NIH 1986) and to 42.2 mg per application JP-5 or 45.5 mg per application marine diesel fuel 3 times per week for 40 weeks (Schultz et al. 1981), were also lethal to mice. Intermediate exposures (13 weeks) to 500 or 1,000 mg/kg/day JP-5, or 2504,000 mg/kg/day marine diesel fuel (NTP/NIH 1986), or 21.1 mg per application JP-5 3 times per week for 40 weeks, or 22.9 mg per application marine diesel fuel 3 times per week for 40 weeks (Schultz et al. 1981) were not lethal in mice.

A statistically significant increase in the number of deaths was noted only in female mice following chronic exposure to marine diesel fuel and JP-5 at doses of 250 and 500 mg/kg/day for both fuel oils (NTP/NIH 1986). Although the number of deaths in males under these conditions was increased over that of the controls, the effect was not significant. Deaths were observed as early as week 1 of exposure to marine diesel fuel and week 2 of exposure to JP-5. The data are limited for each of these experiments because it was not specified whether the animals were protected against oral exposure and/or removal of the test material.

The highest NOAEL and all reliable LOAEL values for death in each species and duration category after dermal exposure to fuel oils are recorded in Table 2-3.

2.2.3.2 Systemic ,Effects

The highest NOAEL and all reliable LOAEL values for systemic effects in each species and duration category for dermal exposure to fuel oils are recorded in Table 2-3.

TABLE 2-3. Levels of Significant Exposure to Fuel Oils - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL[a] (mg/kg/day)	LOAEL[a] Less Serious (mg/kg/day)	LOAEL[a] Serious (mg/kg/day)	Reference/ Chemical Form
ACUTE EXPOSURE						
Death						
Mouse B6C3F1	2 wk 7 d/wk				20000 (100% mortality)	NTP/NIH 1986 FO1DFM
Mouse B6C3F1	2 wk 7 d/wk				30000 F (100% mortality) M (0% mortality)	NTP/NIH 1986 FO1JP5
Systemic						
Mouse B6C3F1	2 wk 7 d/wk	Derm		2000 (acanthosis; inflammation; parakerotosis; hyperteratosis)		NTP/NIH 1986 FO1DFM
		Other	8000			
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) M (0% mortality)	NTP/NIH 1986 FO1JP5
Mouse C3HF/Bd	40 wk 3x/wk				45.5 F (40% mortality) (mg/app) M (20% mortality)	Schultz et al. 1981 FO1DFM

TABLE 2-3. Levels of Significant Exposure to Fuel Oils - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL[a] (mg/kg/day)	LOAEL[a] Less Serious (mg/kg/day)	LOAEL[a] Serious (mg/kg/day)	Reference/ Chemical Form
Mouse	40 wk				42.2 F (40% mortality)	Schultz et al. 1981
C3HF/Bd	3x/wk				(mg/app) M (13% mortality)	FO1JP5
Systemic						
Mouse	13 wk	Resp	8000			NTP/NIH 1986
B6C3F1	7 d/wk					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)		
Mouse	13 wk	Resp	4000			NTP/NIH 1986
B6C3F1	7 d/wk					FO1DFM
		Cardio	4000			
		Gastro	4000			
		Hemato	4000			
		Hepatic	4000			
		Renal	4000			
		Dermal	2000	4000 (mild chronic active dermatitis)		
		Bd Wt	250M	500 M (9% decrease in body weight gain)		

TABLE 2-3. Levels of Significant Exposure to Fuel Oils - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL[a] (mg/kg/day)	LOAEL[a] Less Serious (mg/kg/day)	LOAEL[a] Serious (mg/kg/day)	Reference/ Chemical Form
Mouse BALC/C	40 wk 3x/wk	Hemato		21.1 (mg/app)	(increased spleen weight)	Schultz et al. 1981 FO1JP5
		Hepatic	42.2 (mg/app)			
		Renal		21.1 (mg/app)	F (increased kidney weight)	
				21.1 (mg/app)	M (decreased kidney weight)	
		Bd Wt		21.1 (mg/app)	(7-11% decrease in body weight)	
Mouse BALB/C	40 wk 3x/wk	Hemato		22.9 (mg/app)	(increased spleen weight)	Schultz et al. 1981 FO1DFM
		Hepatic	45.5 (mg/app)			
		Renal		22.9 (mg/app)	F (increased kidney weight)	
				22.9 (mg/app)	M (decreased kidney weight)	
		Bd Wt		22.9 (mg/app)	(4-21% decrease in body weight)	
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

TABLE 2-3. Levels of Significant Exposure to Fuel Oils - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL[a] (mg/kg/day)	LOAEL[a] Less Serious (mg/kg/day)	LOAEL[a] Serious (mg/kg/day)	Reference/ Chemical Form
CHRONIC EXPOSURE						
Death						
Mouse B6C3F1	84 -103 wk 5 d/wk				250 F (74% mortality) 250 M (54% mortality)	NTP/NIH 1986 FO1DFM
Mouse B6C3F1	90 - 103 wk 5 d/wk				250 F (30% mortality) 250 M (34% mortality)	NTP/NIH 1986 FO1JP5
Systemic						
Mouse B6C3F1	90 - 103 wk 5 d/wk	Resp	500			NTP/NIH 1986 FO1JP5
		Cardio	500			
		Gastro	500			
		Hemato	250	500 (amyloid spleen)		
		Musc/skel	500			
		Hepatic	250	500 (amyloid liver)		
		Renal	250	500 (amyloid kidney)	250	
		Derm			(ulcers; dermatitis)	
		Bd Wt	250	500 (12-25% decrease in body weight gain)		

TABLE 2-3. Levels of Significant Exposure to Fuel Oils - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL[a] (mg/kg/day)	LOAEL[a] Less Serious (mg/kg/day)		LOAEL[a] Serious (mg/kg/day)		Reference/ Chemical Form
Mouse B6C3F1	84 - 103 wk 5 d/wk	Resp	500					NTP/NIH 1986 FO1DFM
		Cardio	500					
		Gastro	500					
		Hemato		250	(hematopoiesis of spleen *and liver*)			
		Musc/skel	500					
		Renal		250	(inflammation of urinary bladder)	250		
		Dermal					(ulcers; dermatitis)	
		Bd Wt		250	(14-23% decrease in body weight gain)			
Immuno/Lymphoret								
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
Mouse B6C3F1	84 - 103 wk 5 d/wk			250	(lymph node plasmocyosis)			NTP/NIH 1986 FO1DFM
Neurological								
Mouse B6C3F1	90 - 103 wk 5 d/wk		500					NTP/NIH 1986 FO1JP5
Mouse *B6C3F1*	84 - 103 wk *5 d/wk*		500					NTP/NIH 1986 *FO1DFM*

TABLE 2-3. Levels of Significant Exposure to Fuel Oils - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL[a] (mg/kg/day)	LOAEL[a] Less Serious (mg/kg/day)	LOAEL[a] Serious (mg/kg/day)		Reference/ Chemical Form
Reproductive							
Mouse B6C3F1	84 - 103 wk 5 d/wk		500				NTP/NIH 1986 FO1DFM
Mouse B6C3F1	90 - 103 wk 5 d/wk		500				NTP/NIH 1986 FO1JP5
Cancer							
Mouse B6C3F1	84 - 103 wk 5 d/wk				250 M	(hepatocellular adenoma or carcinoma)	NTP/NIH 1986 FO1DFM
Mouse B6C3F1	90 - 103 wk 5 d/wk				250	(malignant lymphomas)	NTP/NIH 1986 FO1JP5

[a]Units are in mg/kg/day, unless specified otherwise.

Bd Wt = body weight: Cardio = cardiovascular; d = day(s); Derm = dermal; F = females; FO1DFM = diesel marine fuel; FO1JP5 = JP-5 (jet fuel); Gastro = gastrointestinal; Hemato = hemotological; Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = males; mg/app = mg per application; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); x = time(s)

Respiratory Effects. Effusions and alveolar infiltrations of the lung occurred in a man who had washed his hair with an unknown amount of diesel fuel (Barrientos et al. 1977). Effects resulting from inhalation versus dermal exposure could not be distinguished in this case. An epidemiological study found a significant increase in feelings of "thoracic oppression" (no description provided) 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 under Respiratory Effects.

No histopathological or organ weight changes were noted in the respiratory system of male mice following daily dermal exposures for 1 week to 0.1 mL kerosene (Upreti et al. 1989); 13-week exposures to 2,000-8,000 mg/kg/day JP-5; or chronic exposures to 250 or 500 mg/kg/day of either marine diesel fuel or JP-5 (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. 1978). The limitations of the study are discussed in detail in Section 2.2.1.2 under Respiratory Effects.

No histopathological changes were noted in the cardiovascular system of mice exposed to 2,000-8,000 mg/kg/day JP-5 for 13 weeks or mice chronically exposed to 250 or 500 mg/kg/day of either marine diesel fuel or JP-5 (NTP/NIH 1986).

Gastrointestinal Effects. Nausea, abdominal cramps, and diarrhea occurred in a man who had washed his hair with an unknown amount of diesel fuel (Barrientos et al. 1977). Clinical examination revealed a normal abdomen. Another man had epigastric pain after washing his hands with diesel fuel over several weeks (Crisp et al. 1979). Effects resulting from inhalation versus dermal exposure could not be distinguished in these cases.

No histopathological changes were noted in the gastrointestinal system of mice exposed to 2,000-8,000 mg/kg/day JP-5 for 13 weeks or mice chronically exposed to 250 or 500 mg/kg/day of either marine diesel fuel or JP-5 (NTP/NIH 1986).

Hematological Effects. One case study reported that decreased hemoglobin concentration and an increase in erythrocyte sedimentation rate were noted in one man after washing his hands with diesel fuel over several weeks (Crisp et al. 1979). Effects resulting from inhalation versus dermal exposure could not be distinguished in this case.

A decrease in the splenic relative weight, which was not accompanied by histopathological changes, was noted in male mice following daily dermal exposures for 1 week to 0.1 mL kerosene (Upreti et al. 1989). In addition, decreases in hemoglobin concentration and increases in erythrocyte, white blood cell, and polymorphonuclear leukocyte concentrations were noted. Females were not tested in this study. Hematopoiesis of the spleen (extramedullary hematopoiesis) was noted in mice exposed to 500-8,000 mg/kg/day JP-5 for 13 weeks (NTP/NIH 1986). This effect was dose related and was found to be secondary to dermatitis in mice chronically exposed to 250 or 500 mg/kg/day marine diesel fuel (NTP/NIH 1986). The appearance of extramedullary hematopoiesis indicates a response to a hematological change or effect. Hematopoiesis in the liver in female mice was dose dependent and was directly related to chronic exposures to 250 or 500 mg/kg/day marine diesel fuel (NTP/NIH 1986).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after dermal exposure to fuel oils.

No histopathological changes were noted in the musculoskeletal system of mice chronically exposed to 250 or 500 mg/kg/day of either marine diesel fuel or JP-5 (NTP/NIH 1986).

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to fuel oils.

No histopathological or organ weight changes were noted in the livers of male mice following daily dermal exposures for 1 week to 0.1 mL kerosene (Upreti et al. 1989). Slight hepatic karyomegaly was noted in mice exposed to 500-8,000 mg/kg/day JP-5 for 13 weeks (NTP/NIH 1986). Amyloidosis of the liver occurred in mice chronically exposed to 500 mg/kg/day JP-5 but not in those exposed to 250 mg/kg/day.

Renal Effects. Acute renal failure occurred in a man who washed his hair with an unknown amount of diesel fuel (Barrientos et al. 1977). In addition, he had oliguria; biopsy revealed mitosis and vacuolization in renal cells, tubular dilation, and some cellular proliferation in the glomerulus. Another man developed acute tubular renal necrosis after washing his hands with an unspecified diesel fuel over several weeks (Crisp et al. 1979). Specifically, patchy degeneration and necrosis of the proximal and distal tubular epithelium with preservation of the basement membranes were noted. Also, increased blood urea nitrogen and serum creatinine levels were noted in this individual. Effects resulting from inhalation versus dermal exposure could not be distinguished in these cases.

No histopathological or organ weight changes were noted in the kidneys of male mice following daily dermal exposures for 1 week to 0.1 mL kerosene (Upreti et al. 1989) nor following exposure to 2,000-8,000 mg/kg/day JP-5 for 13 weeks (NTP/NIH 1986). Renal lesions were produced in at least one sex and at one or both doses levels (100% or 50%) in mice dermally treated three times per week for 60 weeks with JP-5 or marine diesel fuel (Easley et al. 1982). However, the lesions could not be duplicated in mice injected intraperitoneally with 100 mg/kg (using a corn oil vehicle) for 3 times per week for days or in mice injected intraperitoneally with 25 microliters of JP-5 for 2 to 8 weeks. In contrast to the case study (Barrientos et al. 1977) in which oliguria was manifested as a symptom of acute diesel fuel toxicity, the dermally treated test animals 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 by intraperitoneal injection led the 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 exposure to petroleum oils was reported to induce a nodular appearance of the kidney as well as induce tubular atrophy of the renal cortex in mice (Schultz et al. 1981). However, it was not reported what petroleum fuels induced the kidney injury, although marine diesel fuel and JP-5 were among those studied. From calculations of the kidney to body weight ratios in mice exposed to 21.l and 42.2 mg JP-5 or 22.9 and 45.5 mg marine diesel fuel for 40 weeks, dose-related trends were noted in female mice for increased relative kidney weights following JP-5 exposure (right kidney only) and marine diesel fuel (both kidneys) (Schultz et al. 1981). There were no dose-response trends for the decreased relative kidney weights in males exposed to either fuel oil. 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.

Lymphocytic inflammation of the urinary bladder was noted in mice chronically exposed to 250 or 500 mg/kg/day marine diesel fuel. Amyloidosis of the kidney was found to be secondary to dermatitis in mice chronically exposed to 500 mg/kg/day JP-5 (NTP/NIH 1986).

Dermal Effects. Experimental data regarding dermal exposure of humans to fuel oils are limited. In one study, there was a dose-dependent increase in dermatitis from acute exposures to 55-85% solutions of kerosene (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. In another study, acute dermal exposure to 1 mL of kerosene impaired protein synthesis, but not deoxyribonucleic acid (DNA) or collagen synthesis, in the epidermis (Lupulescu and Birmingham 1975). Hyperemia, cellular damage of the epidermis, and mild edema also occurred from acute exposure to 1 mL kerosene (Lupulescu and Birmingham 1976; Lupulescu et al. 1973). Histological changes included disorganization of the cells, cytolysis, and enlarged intercellular spaces in the stratum corneum and spinous cells of the epidermis (Lupulescu and Birmingham 1976). Effects had subsided within 72 hours in some individuals (Lupulescu et al. 1973). These studies are limited because each tested only one dose.

Dermal effects of fuel oils from known or suspected short-term dermal exposures are described in several case studies. In one study, erythema, bullae, burning, and itching were reported in a 45-year-old man following a 20-minute dermal exposure to kerosene (Mosconi et al. 1988). In another case study, three males (2-15 years old) and 1 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). A third study reported large blisters, erythema, and peeling skin 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 daily for 1 week with 0.1 mL kerosene had rough skin, edema, and inflammation at the exposure sites (Upreti et al. 1989). Females were not tested in this study. Female mice treated with middle distillates including straight-run kerosene for six weeks developed hyperplasia and necrosis in the epidermis (Ingram et al. 1993) and increased sebocyte counts (Lesnik et al. 1992). Acute dermal exposures to 1% JP-5 or marine diesel fuel induced mild dermal sensitization in guinea pigs (Cowan and Jenkins 1981). Skin irritation was not induced in male rabbits by acute exposure to 0.5 mL JP-5 or marine diesel fuel (Schultz et al. 1981). These studies are limited because only one exposure dose was used in each. Acute dermal exposures to 2,000-40,000 mg/kg marine diesel fuel and unspecified concentrations of JP-5-induced dermatitis (acanthosis, scaly skin, hair loss, inflammation, parakeratosis, and/or hyperkeratosis of the skin) in mice (NTP/NIH 1986). This effect also occurred following 13-week exposures to 4,000 mg/kg/day marine diesel fuel. Intermediate exposure to 500-8,000 mg/kg/day JP-5 induced slight-to-moderate dermatosis in mice which increased with dose. Dermal sensitization did not occur in guinea pigs that were dermally exposed to 9 or 10 doses of diesel fuel (API 1979f; Schultz et al. 1981) or 9 doses of JP-5 (Schultz et al. 1981) over a 3-week period. Dermal application of three types of no. 2 fuel oils (low-catalytic cracked [10%], medium-catalytic cracked [30%], and high-catalytic cracked [50%]) and diesel fuel did not produce skin sensitization in the guinea pig (Beck et al. 1984), although doses were not reported. Erythema and edema occurred during the induction phase in the animals exposed to diesel fuel (API 1979f).

Chronic exposures to 250 and 500 mg/kg/day of both marine diesel fuel and JP-5 induced dermatitis and ulcerations of the skin in mice (NTP/NIH 1986). The incidence and severity of dermatitis and the incidence of ulcers induced by marine diesel fuel were dose dependent for the chronic exposures. The severity, but not the incidence, of dermatitis induced by JP-5 was dose dependent for the chronic exposures. Also, the incidence of ulcers was dose dependent in chronic studies with JP-5. Dermatitis was also noted in another study in mice that were chronically exposed to either JP-5 or marine diesel fuel; effective doses were not reported (Easley et al. 1982).

Ocular Effects. Acute exposure to diesel fuel induced ocular effects in one case (Barrientos et al. 1977). Subconjunctival hemorrhages occurred in a man who had washed his hair in an unknown amount of diesel fuel. Effects resulting from inhalation versus dermal exposure could not be distinguished in this case. Eye irritation was also noted in factory workers who were chronically exposed to jet fuel (Knave et al. 1978). The limitations of this study are discussed in detail in Section 2.2.1.2 under Respiratory Effects.

Ocular irritation was not induced in rabbits by diesel fuel (API 1979b; Beck et al. 1984), marine diesel fuel, JP-5 (Cowan and Jenkins 1981; Schultz et al. 1981), or three types of no. 2 fuel oils (low-catalytic cracked [10%], medium-catalytic cracked [30%], an high-catalytic cracked [50%]) (Beck et al. 1984). Draize scores were not reported in the Cowan and Jenkins (1981) study.

Body Weight Effects. No studies were located regarding body weight effects in humans after dermal exposure to fuel oils.

There was no change in body weight in male mice following daily dermal exposures for 1 week to 0.1 mL kerosene (Upreti et al. 1989). There was no effect on body weight in mice following acute exposures to 2,000-8,000 mg/kg/day marine diesel fuel (NTP/NIH 1986). Acute exposure to at least 10,000 mg/kg/day JP-5, but not 5,000 mg/kg/day, induced decreases in body weight in mice. A dose-related trend in decreased body weight gain was noted in male, but not female, mice exposed to 4,000 and 8,000 mg/kg/day JP-5 and 500-4,000 mg/kg/day marine diesel fuel for 13 weeks. For JP-5 exposure, the changes in weight gain compared to the controls were not large, i.e., 5-7%, and therefore, the significance of the effect could not be determined (NTP/NIH 1986). Dermal application of total weekly doses of 126.6 and 63.3 mg of JP-5 or 136.5 and 68.2 mg of diesel fuel marine three times per week for 40 weeks produced significant weight reduction in mice (Schultz et al. 1981); however, the authors failed to accurately describe the methods and doses. Chronic exposures to 500 (but not 250) mg/kg/day JP-5 and 250 and 500 mg/kg/day marine diesel fuel induced decreases in body weight relative to controls (NTP/NIH 1986). An increased incidence of amyloid in the adrenal cortex was found to be secondary to dermatitis in mice chronically exposed to 500 mg/kg/day JP-5 (NTP/NIH 1986).

Other Systemic Effects. Edema of the scrotum and ankle, loin pains, thirst, and severe exhaustion were reported in a man who washed his hands with diesel fuel over several weeks (Crisp et al. 1979). Effects resulting from inhalation versus dermal exposure could not be distinguished in this case.

There were no abnormal clinical signs, no histopathological or organ weight changes in the adrenal glands, and no effects on food or water intake in male mice following daily dermal exposures for 1 week to 0.1 mL kerosene (Upreti et al. 1989). Amyloidosis of the spleen was found secondary to dermatitis in mice chronically exposed to 500 mg/kg/day JP-5; this effect was not noted following exposure to 250 mg/kg/day JP-5 (NTP/NIH 1986). Mice exposed to a 50% solution of marine diesel

fuel for 60 weeks had increases in daily water consumption (Easley et al. 1982). This effect also occurred in mice exposed to JP-5, but dose levels were not reported. Similarly, dermal application of JP-5 and diesel marine fuel increased water consumption and urine output (accompanied by a loss in osmolarity) in mice. Easley and coworkers (1982) speculated that the increased water consumption may have been the result of impaired renal function (see Section 2.2.3.2 under Renal Effects) and/or the dehydration of these animals.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after dermal exposure to fuel oils.

Decreases in the relative weights of the lymph nodes and thymus were noted in male mice following daily dermal exposures for 1 week to 0.1 mL 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 axial lymph nodes were also present. This study is limited because females were not tested. Chronic exposure to 500 mg/kg/day JP-5 induced granulocytic hyperplasia in the bone marrow in male and female mice and hyperplasia in the lymph nodes of female mice (NTP/NIH 1986). Plasmacytosis of the lymph nodes was found to be secondary to dermatitis in mice chronically exposed to 250 and 500 mg/kg/day of marine diesel fuel.

The highest NOAEL and all reliable LOAEL values for immunological effects after dermal exposure to fuel oils are recorded in Table 2-3.

2.2.3.4 Neurological Effects

In one case study, anorexia was reported in a man who washed his hands with diesel fuel over several weeks (Crisp et al. 1979). Effects resulting from inhalation versus dermal exposure could not be distinguished in this case. An epidemiological study found a significant increase in neurasthenia (i.e., fatigue, depressed mood, lack of initiative, dizziness, and sleep disturbances) in workers who were chronically exposed to jet fuels by either inhalation, oral, and/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 instability in the thalamocortical system. The limitations of the study were discussed in detail in Section 2.2.1.2 under Respiratory Effects.

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

The highest NOAEL values for neurological effects after dermal exposure to fuel oils 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 fuel oils.

No histological changes were noted in the reproductive system of mice dermally exposed to 2,000-8,000 mg/kg/day JP-5 for 13 weeks or in mice chronically exposed to 250 or 500 mg/kg/day of either marine diesel fuel or JP-5 (NTP/NIH 1986).

The highest NOAEL values for reproductive effects after dermal exposure to fuel oils 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 fuel oils.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to fuel oils.

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer in humans after dermal exposure to fuel oils.
Unspecified skin tumors were identified in C3HF/Bd mice under the following exposure conditions: a 40-week exposure to 22.9 mg (but not 42.2 mg) JP-5 or 23.8 and 45.5 mg marine diesel fuel; a 60-week exposure to 5.7-42.2 mg (the highest incidence was at 11.4 mg) JP-5 or 11.9 and 23.8 mg (but not 45.5 mg) marine diesel fuel (Schultz et al. 1981). Tumors were more prevalent in females than males for JP-5 exposure. None of the control animals developed skin tumors and statistical analysis was not conducted. The tumor incidence was not dose related, and historical control data for this strain of mouse were not provided.

No skin cancer was reported in B6C3F_1 mice chronically exposed to 250 and 500 mg/kg/day of JP-5 (NTP/NIH 1986). There was a 2-6% incidence of squamous cell papilloma and/or carcinoma of the skin in B6C3F_1 mice chronically exposed to 250 (females only) or 500 (both sexes) mg/kg/day marine diesel fuel. The effect did not occur in the control groups; the statistical significance of these effects was not reported. Hepatocellular adenoma or carcinoma were noted in males exposed to 250 and 500 mg/kg/day marine diesel fuel. These effects did not occur in female mice at these doses. Malignant lymphomas were noted in females exposed to 250 mg/kg/day, but not 500 mg/kg/day, JP-5; therefore, 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.

The tumorigenic potential of API no. 2 fuel oil was evaluated by dermal application in male and female C3H/Bd_f mice (Witschi et al. 1987). Fifty microliters of the fuel oil was applied neat, or as a 50% or 25% dilution (w/v, in acetone) three times per week. Negative controls consisted of mice treated with acetone or animals that received no treatment. Positive controls received 50, 25, or 12.5 mg of benzo[a]pyrene dissolved in 50 microliters of acetone. Over all the doses, 15 of the 150 mice developed skin tumors (the first tumor appeared at 75 to 80 weeks), while 299 of the 300 mice treated with benzo[a]pyrene developed skin tumors (first tumor appeared at 19 weeks). Neither of the negative control groups developed neoplastic lesions).

Similarly, the dermal carcinogenic activity of 6 Commercial no. 2 heating oils with varied boiling ranges, points of origin, and composition have been evaluated (Biles et al 1988). The heating oils were applied neat to male C3H/HeJ mice in 25 microliter aliquots, 3 times per week for lifetime or until all mice in the test group developed frank carcinomas. The negative controls received a “highly refined white mineral oil," and the positive controls received four concentrations of catalytically cracked clarified oil (known to produce a positive dermal tumorigenic response) diluted in white mineral oil. None of the negative control mice (140 animals) developed tumors, while all of the positive control groups displayed significantly increased incidence of tumor production. All of the Commercial no. 2 heating oils induced a significantly increased incidence of tumors (an incidence of 5 animals with tumor per 50 animals was statistically significant, and the heating oil incidence ranged from 5 to 11 per 50).

No increase in the incidence of tumor-bearing mice was noted in animals treated with 25 mg of undiluted petroleum diesel three times per week for up to 105 weeks in male and female C3H/HeN (diesel-treated had an incidence of 2/27 and mineral oil-treated negative controls did not develop any tumors). Jet A did, however, produce an increased incidence (26%) of tumors (primarily squamous cell carcinoma and fibrosarcoma) (Clark et al. 1988). It was noted that both types of fuels produced inflammatory and degenerative changes at the application 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.

Furnace oil (CAS no. 68474-30-2) was evaluated for skin carcinogenicity with both lifetime skinpainting and an initiation/promotion bioassay (Gerhart et al. 1988). Briefly, in the lifetime skinpainting study, 50 microliters of undiluted furnace oil was applied to 50 male C3H/HeN mice twice weekly for the lifetime of the animals. A sham negative control group of equal size was run concomitantly. In the initiation portion of the initiation/promotion bioassay, 30 CD-l mice received five treatments of 25 microliters or five treatments of 50 microliters of furnace oil, and both groups were subsequently treated with 50 microliters of 0.1 mg/mL phorbol-12-myristate-13-acetate (PMA) twice weekly for 25 weeks. Thirty mice received one treatment of 50 microliters of 9,10-dimethyl-1,2-benzanthracene (DMBA) or 50 microliters of acetone and subsequently were treated with 50 microliters of furnace oil twice weekly for 25 weeks in the promotion component of the investigation. (Note that Gerhart and coworkers [1988] indicated that the two different strains of mice were used: C3H mice, which are not commonly used in initiation/promotion studies, and CD-l mice,

which are considered to be a sensitive model and used extensively in initiation/promotion studies of carcinogenesis.) In the skin-painting studies, furnace oil produced a significant increase in the incidence (9/43 in furnace oil group and 0/49 in negative controls) of confirmed skin tumors (squamous cell carcinoma and fibrosarcoma). Two of the nine tumor-bearing animals developed squamous cell carcinoma in untreated areas of skin. In contrast, when furnace oil as an initiating agent, no increase in tumor incidence was observed in animals treated with either 25 or 50 microliters. However, a significant increase (12/30 vs l/30 in acetone initiated) in histologically confirmed tumor incidence (squamous cell carcinoma) was observed in mice that were treated with DMBA as an initiating agent and received furnace oil as the promoting agent.

The tumorigenic activity of no. 2 type fuel oil and hydrodesulfurized kerosene was examined utilizing an initiation/promotion assay with CD-l mice (API 1989). In the initiation phase of the study, mice received 5-50 microliter consecutive daily applications of the fuel oils and subsequently were treated with PMA (0.1 mg/mL) twice weekly for 25 weeks. In the promotion phase of the study, mice received a single application of DMBA (1.0 mg/mL) and were subsequently treated with one of the fuel oils twice weekly for 25 weeks. No significant difference in tumor incidence was noted in those animals treated with either of the fuel oils, when compared to the negative control (initiation with 50 microliters of acetone). However, both the incidence of confirmed tumor (18/30 in animals treated with no. 2 fuel oil as a promoting agent, 22/30 in animals receiving hydrodesulfurized kerosine as a promoting agent, and 0/30 in acetone-promoted negative controls) and the latency period were significantly different than those of the positive controls. The most prevalent tumors were squamous cell papillomas and keratoacanthomas.

The dermal carcinogenicity of mixtures of petroleum products that have a boiling range approximately equal to or greater than 370°C has been reported to be primarily related to the polycyclic aromatic hydrocarbon (PAH) content of the material (Biles 1988). The boiling ranges of the various fuel oils are as follows: fuel oil no. 1, 175-300°C; fuel oil no. l-D, 193-293°C; fuel oil no. 2, 160-360°C; fuel oil no. 2-D 282-338°C; fuel oil no. 4, l0l-588°C; fuel oil UNSP, 151-588°C (see Table 3-3). Whereas some fuel oils contain cracked stocks that are known to contain biologically active PAH, virgin distillate petroleum products (boiling range approximately 177°C to 370°C), which include various middle distillate fuel oils, primarily contain saturated species (Biles 1988). Although these virgin petroleum materials contain low concentrations of PAH, repeated application can induce dermal tumors. It has been reported that the tumorigenicity of three petroleum- and four coal-derived liquids

were not consistent with the PAH content of the test materials (Witschi et al. 1987). Similarly, the dermal carcinogenicity of 10 petroleum-derived fuels (including 6 formulations of no. 2 heating oil) did not appear to be "directly related" to the aromatic content or the presence of PAH in the materials (Biles et al. 1988). Gerhart and colleagues (1988) reported that furnace oil induced tumors through epigenetic or promotional means, even though it contained no detectable concentrations of four- and five-ring aromatics. In a 2-year skin-painting study of four petroleum middle distillates (including jet fuel), the authors suggested 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 fuel oils is a secondary effect associated with dermal irritation (Biles et al. 1988; Clark et al. 1988; McKee et al. 1989). Biles and coworkers (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 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. 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 was not always predictive of tumorigenicity (Clark et al. 1988). Similarly, even though dermal application of dewaxed heavy paraffinic distillate led to a greater incidence of confirmed tumors than did furnace oil (26/48 and 9/43, respectively), furnace oil induced a greater incidence of nonneoplastic lesions (37/43 vs. 14/48) (Gerhart et al. 1988). McKee and coworkers (1989) ascribed the weak promotional activity of a lightly refined paraffinic oil to the irritation caused by its repeated application to mouse skin, partially based on findings that the whole oil and various fractions of the oil were negative for both mutagenic activity in bacteria and carcinogenic initiating activity.

The role of chronic acanthosis and inflammation in tumor promotion by a middle distillate has been investigated (Skisak 1991). Briefly, male CD-l mice received a single dermal treatment of 50 microliters of DMBA (initiation) and subsequently were treated with 25, 50, or 100 microliters (twice weekly for 25 weeks) of hydrodesulfurized kerosine (HK). Dose, washing after treatment, and topical application of dexamethasone were used to control inflammation. The mice treated with 100 microliters of HK had the greatest tumor incidence (35/53) and the highest degree of acanthosis throughout the study. While the tumor responses of the 25 and 50 microliter treated groups were

similar (14/54 and 13/54, respectively), the degree of acanthosis was much more pronounced in the mice treated with 50 microliters HK. Application of dexamethasone to animals treated with 50 microliters reduced the tumor incidence to 0, although acanthosis was still observed. It is interesting to note that washing the mice (1 to 2 hours after treatment) with an Ivory soap solution with 50 microliters of HK increased tumor incidence (22/53) compared to the group treated with 50 microliters HK but not washed. The 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 microliters 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 when irritation was noted in 20% of the group and resumed when it was resolved in all but 20%) (Freeman et al. 1993). Intermittent dosing 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 and coworkers (1993) stated that chronic skin irritation was necessary, but insufficient for tumor induction. These data indicate that the irritant properties of fuel oils are not the ultimate cause of dermal carcinogenicity, although the irritation induced by the repeated application may play an important role in the mechanism of tumor formation.

Reliable LOAEL values for cancer effects after dermal exposure to fuel oils are recorded in Table 2-3.

2 . 3 TOXICOKINETICS

Few data were available concerning the absorption, distribution, metabolism, and excretion of fuel oils. Indirect evidence suggests that some fuel oils may be absorbed through the respiratory tract, the gastrointestinal tract, and percutaneously. Although data concerning the metabolism of fuel oils in humans could not be located, a single animal study suggested that cytochrome P-448 may be involved in the metabolism of fuel oil no. 2 (Rahimtula et al. 1982). No quantitative data were found regarding the excretion of fuel oils.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding the absorption of fuel oils in humans or animals after inhalation exposure. However, indirect evidence of gastrointestinal, cardiovascular, hematological, renal, and/or dermal/ocular effects from case reports in which two pilots were exposed to JP-5 vapor while flying a small airplane and another man was exposed to diesel fuel vapor while driving a truck indicate that these fuel oils can be absorbed following inhalation exposure in humans (Porter 1990; Reidenberg et al. 1964). Effects on animals acutely exposed to fuel oils by inhalation provide indirect evidence for inhalation absorption in animals (Casaco et al. 1985c; Garcia et al. 1988b; Kainz and White 1984).

2.3.1.2 Oral Exposure

No quantitative data were located regarding the absorption of fuel oils in humans after oral exposure. However, there is evidence that absorption from the gastrointestinal tract occurs following ingestion of kerosene by humans (Subcommittee on Accidental Poisoning 1962). In a study of 422 cases, pulmonary complications were noted in 11 individuals, even though gastric lavage was not administered nor was vomiting reported (vomiting and gastric lavage could cause aspiration of the kerosene, thus contributing to the respiratory effects). In this same report, pulmonary complications occurred in a higher percentage of the individuals that did not receive lavage than in those that were treated by gastric lavage. This suggests that pulmonary effects of fuel oils may also be the result of systemic toxicity. Further, administration of gastric lavage within 30 minutes of ingestion further decreased the number of affected individuals, suggesting that removal of kerosene from the stomach may have prevented its absorption and subsequent toxicity in these cases. In this same study, there is also indirect evidence that aspiration from vomiting may induce pulmonary effects since there were more individuals with respiratory complications when vomiting occurred than when it did not, regardless of the administration of gastric lavage. It is possible that both absorption and aspiration contribute to the respiratory effects in these individuals.

Limited animal data and indirect evidence indicate kerosene is poorly absorbed from the gastrointestinal tract. In one study, kerosene labeled with ^{3}H-toluene or ^{14}C-hexadecane was given to tracheotomized baboons (15 mL/kg) by nasogastric tube (Mann et al. 1977). The isotopes were

recovered after 6 hours from the brain, lung, liver, spleen, heart, and kidney; however, the amounts distributed to the tissue were very small, suggesting that gastrointestinal tract absorption was slight. The potential absorption of ingested kerosene into the lungs was tested by comparing respiratory effects from oral exposures in nontracheotomized and tracheotomized monkeys (Wolfsdorf and Kundig 1972). The tracheotomized monkeys who 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 fuel oils, not absorption, is the underlying cause of the respiratory effects. A lack of pulmonary toxicity was reported in dogs in which aspiration was prevented. This study supports the theory 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

Studies of effects on animals following acute, intermediate, and chronic dermal exposure to marine diesel fuel and JP-5 fuel provide evidence for dermal absorption (NTP/NIH 1986). Case reports concerning a man who washed his hair with an unknown amount of diesel fuel (Barrientos et al. 1977) and a man who washed his hands with an unspecified diesel fuel over several weeks (Crisp et al. 1979) provide possible evidence for dermal absorption, but effects resulting from inhalation versus dermal exposure could not be distinguished in these cases. No other data on the absorption of fuel oils following dermal exposure in humans or animals were located.

Some case studies suggest that dermal exposure to the vapor of diesel fuel may also result in absorption via the skin. The studies identify one individual with only vapor exposure and two others with vapor and/or direct dermal contact with diesel fuel; individuals developed acute renal failure or renal necrosis (Barrientos et al. 1977; Crisp et al. 1979; Reidenberg et al. 1964). Also, dermal exposures to marine diesel fuel and JP-5 in mice induced renal damage (Easely et al. 1982). No studies were located that directly tested dermal absorption of fuel oil vapor.

2.3.1.4 Other Routes of Exposure

Dogs that had undergone transection of the esophagus exhibited no respiratory or gastrointestinal effects after injection by syringe of 5, 10, 20, or 30 mL of kerosene (4-17.9 rnL/kg) directly into the stomach. This study provides indirect evidence that kerosene is poorly absorbed from the gastrointestinal tract (Wolfe et al. 1970), or alternatively, kerosene is adsorbed but not grossly toxic unless it is aspirated.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding the distribution of fuel oils in humans or animals after inhalation exposure.

2.3.2.2 Oral Exposure

No studies were located regarding the distribution of fuel oils in humans after oral exposure.

Very 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 very small (Mann et al. 1977).

2.3.2.3 Dermal Exposure

No studies were located regarding the distribution of fuel oils in humans or animals after dermal exposure.

2.3.3 Metabolism

No studies were located regarding the metabolic pathway of fuel oils in humans. In one animal study, fuel oil no. 2 applied to the skin of rats induced cutaneous aryl hydrocarbon hydroxylase activity in rat skin microsomal preparations by causing a three-fold induction of benzo(a)pyrene (BaP) 3-hydroxylase activity (Rahimtula et al. 1982). In addition, BaP 3-hydroxylase activity was selectively inhibited by α-naphthoflavone, but not by metyrapone, suggesting that cytochrome P-448 enzymes are induced and may participate in the metabolism of this fuel oil (Rahimtula et al. 1982).

2.3.4 Excretion

There is no quantitative information on the excretion of fuel oils following inhalation, oral, or dermal exposure in humans or animals.

2.3.5 Mechanisms of Action

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 the exposure of large concentrations of aerosolized kerosene (Casaco et al. 1982, 1985b, 1985c). It was suggested 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, resulting in bronchoconstriction. Garcia and Gonzalez (1985), based on their observations 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 vesicles and 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 regarding the hematological effects of fuel oils on humans cannot be made, the effect of kerosene on the first two steps of the heme synthetic pathway has been studied in an animal model. Both hepatic δ-aminolevulinic acid (δ-ALA) dehydratase and δ-ALA synthetase activities were decreased in female rats after intraperitoneal injection of kerosene, while heme oxygenase was unaffected (Rao and Pandya 1980). Since δ-ALA synthetase is the rate-limiting enzyme of the heme biosynthesis pathway, hepatic heme biosynthesis may be inhibited by kerosene.

It is conceivable that this may be related to the extramedullary hematopoiesis reported in other studies (NTWNIH 1986); however, there are no direct data to support this.

The biochemical mechanism of CNS depression seen with fuel oils and common to many organic solvents has not been elucidated. The mechanism of carcinogenesis associated with various formulations of fuel oils is unknown.

2.4 RELEVANCE TO PUBLIC HEALTH

Information regarding health effects of fuel oils in humans and 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 to fuel oils. Fuel oils 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 endpoints. Further, a number of the animal studies utilized an aerosol for exposure, and it should be noted that the toxicity from an aerosol will typically vary from that of a vapor (the probable form of exposure). The available epidemiological studies are generally inconclusive, since they cannot exclusively associate exposures to fuel oils with the adverse effects reported.

Minimal Risk Levels for Fuel Oils

Inhalation

- An MRL of 0.02 mg/m^3 has been derived for acute inhalation exposure to diesel fuel (fuel oil no. 2). The MRL is based on dose-related neurobehavioral effects (mild transient ataxia and CNS depression), beginning at 65 mg/m^3, in mice exposed to airborne concentrations of fuel oil of 65, 135, and 204 mg/m^3.

- An MRL of 0.01 mg/m^3 has been derived for the intermediate inhalation exposure to kerosene (also termed fuel oil no. 1). The MRL is based on decreased blood glucose levels noted in male rats subsequent to exposure to airborne concentrations of kerosene averaging

58 mg/m^3 for 6 hours/day, 6 days/week for 14 weeks. Rats exposed to an airborne concentration of kerosene averaging 231 mg/m^3 showed a decrease in blood glucose titers, as well as increased circulating levels of lactate and pyruvate. In addition, mice exposed to 150 or 750 mg/m^3 or airborne JP-5 showed hepatocellular fatty changes and vacuolization at the LOAEL of 150 mg/m^3 (Gaworski et al. 1984). Finally, no systemic or neurological effects were observed in rats or dogs exposed to a deodorized kerosene concentration of 100 mg/m^3 (Carpenter et al. 1976).

No chronic inhalation MRLs were derived for fuel oils because available data were not suitable for MRL derivation. Studies that report lethality or biochemical alterations without attendant pathology cannot be used for MRL determination

Oral

No acute, intermediate, or chronic oral MRLs were derived for fuel oils because available data were not suitable for MRL derivation. Studies that report lethality at the lowest dose tested cannot be used for MRL determinations. Hepatocyte necrosis reported by Parker et al. (1981) occurred at a dose greater than dose levels at which serious effects occurred in other studies, making these data unsuitable for derivation of an MRL.

Death. No quantitative lethality data for humans were located from inhalation or dermal exposure to fuel oils. Based on case studies reporting deaths in humans following ingestion of kerosene, estimated lethal doses of kerosene range from 1,890 to 16,789 mg/kg (Dudin et al. 1991; Santhanakrishnan and Chithra 1978). These lethal doses are based upon specific cases in which 30 or 200 mL of kerosene were ingested by l- and 2-year-old children. No lethality was reported for children from 10 months to 5 years old following ingestion of 126-877.2 mg/kg or 1,754 mg/kg of kerosene, respectively (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 determine a specific oral dose of kerosene at which lethality in humans would not be expected to occur.

A single 6-hour exposure to 4,000 mg/m^3 diesel fuel aerosol (Dalbey and Lock 1983) and repeated exposures (once or three times per week for a total of nine exposures) for 2 hours to 6,000 mg/m^3 or 6 hours to 2,000 mg/m^3 diesel fuel aerosol (Dalbey et al. 1987) were lethal to rats. However, a single

4-hour exposure to 6,000 mg/m^3 diesel fuel aerosol was not lethal to rats (Dalbey and Lock 1983). The variability of these diesel fuel data appear to indicate that the cumulative dose may be more important than the airborne concentration of fuel oil aerosol, although human exposure to such high concentration of a fuel oil aerosol seems unlikely. Acute and intermediate exposures to moderate through high concentrations of marine diesel fuel, diesel fuel vapor or aerosol, fuel oil UNSP, JP-5, and kerosene (API 1979c, 19798; Cowan and Jenkins 1981; Gaworski et al. 1984; Lock et al. 1984; Vernot et al. 1990d) ranging from 50 mg/m^3 marine diesel vapor to 5,000 mg/m^3 kerosene were not lethal to rats. Although it appears that fuel oils may be lethal to humans only at vapor concentrations that occur at elevated temperatures or as the result of exposure to an aerosol, these data are not sufficient for such generalizations to be drawn concerning the lethal concentration or cumulative dose of fuel oils.

The acute oral LD_{50} in guinea pigs and rabbits for kerosene has 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. Similarly, a lethal dose of kerosene of 6,400 mg/kg has been reported in calves (Rowe et al. 1973), but the lethal dose for rats is 12,000 mg/kg (Muralidhara et al. 1982). Comparison of these data is problematic; however, they do suggest that species differences and age sensitivity may exist for oral kerosene toxicity, although such differences have not been established.

For oral exposures, different fuel oils have differing lethality profiles in rats. Acute lethal doses in rats were reported to be 12,000 mg/kg for kerosene (Muralidhara et al. 1982) and 47,300 mg/kg for JP-5 (Parker et al. 1981). However, an oral dose of 12,200 mg/kg of Deobase® was not lethal in rats (Muralidhara et al. 1982). Although differences in the oral toxicity of fuel oils and differences in species thresholds of toxicity may exist, the oral toxicity of fuel oils is relatively low. The intestinal absorption of fuel oils is also relatively low, and aspiration, with its resultant pulmonary effects, is the primary risk from the ingestion of fuel oils.

Daily dermal exposures for 1 week to 0.1 mL kerosene were not lethal to male mice (Upreti et al. 1989). A minimum lethal dose of 30,000 mg/kg/day was reported for JP-5 from acute dermal exposure in mice, but this dose was decreased to 2,000 and 250 mg/kg/day following intermediate and chronic exposures, respectively (NTP/NIH 1986). A similar trend was also reported for dermal

toxicity in mice exposed to marine diesel fuels (NTP/NIH 1986). Conclusions cannot be drawn from the available data regarding dermal exposure by humans to fuel oils near hazardous waste sites.

Systemic Effects

Respiratory Effects. There are epidemiological data that found no evidence of respiratory toxicity in children from exposure to kerosene vapor and combustion products from kerosene stoves used for cooking (Azizi and Henry 1991; Tominaga and Itoh 1985); however, the importance of such exposures to individuals living near hazardous waste sites or in the workplace is uncertain. Another epidemiological study noted thoracic oppression in workers that were chronically exposed to jet fuel by the inhalation, oral, and/or dermal routes (Knave et al. 1978). However, the jet fuels were not specified in this study, and therefore, these exposures may not necessarily include fuel oils such as JP-5. Only one case study was found that reported effusions and alveolar infiltrations from dermal and/or inhalation exposure to diesel fuel when used as a shampoo (Barrientos et al. 1977). A low concentration of deodorized kerosene vapor was not irritating to the throat 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. In one study, intermediate exposure to diesel fuel aerosol induced damage to the lung parenchyma of rats (Dalbey et al. 1987). This study found that an increase in the frequency of exposure was more likely to induce respiratory effects than the exposure dose or duration. However, in each of these cases of respiratory toxicity, relatively high exposure levels were used. Other animal studies have found no histopathological evidence of respiratory toxicity following relatively low to moderate intermediate inhalation or acute, intermediate, and chronic dermal exposures to various fuel oils (Carpenter et al. 1976; Lock et al. 1984; 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 of kerosene or diesel fuel. Relatively low or moderate exposure levels may also affect sensitive members of the population, but this cannot be determined from the data. The data also indicate that humans who are frequently exposed to fuel oils, such as those exposed occupationally, may be at greater risk of developing respiratory lesions than those with single or less frequent exposures.

Ingestion of fuel oils, kerosene in particular, 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

feature of ingestion. Numerous studies in animals and humans have evidenced the introduction of kerosene into the lungs during vomitus and 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). However, limited absorption from the gastrointestinal tract into the lungs 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; Annobil 1983; Annobil and Ogunbiyi 1991; Dudin et al. 1991; 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. Oral exposure data for humans are only available for kerosene; therefore, no conclusions can be made regarding the respiratory toxicity of other fuel oils. However, the similar composition of the various fuel oils suggests that the effects may also be similar.

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). It was indicated that kerosene may induce asthma-like symptoms by acting on the parasympathetic pathway involving a direct effect on the vagus nerve or by inhibiting acetylcholinesterase, thus increasing the acetylcholine level in the trachea, resulting in bronchoconstriction (Casaco et al. 1982, 1985b, 1985c). It has also been reported that kerosene can affect the calcium pump of the rabbit sarcoplasmic reticulum (Garcia and Gonzalez 1985), suggesting that the mechanism of kerosene-induced bronchoconstriction may involve changes in the ionic flow across the cellular membranes to prolong muscle contraction.

Curdiovasculur Effects. Mild hypertension from acute inhalation of JP-5 vapor (Porter 1990) or diesel fuel vapor (Reidenberg et al. 1964) and palpitations from chronic inhalation, dermal, and/or oral exposures to unspecified jet fuels have been reported in humans (Knave et al. 1978). Tachycardia and cardiomegaly were reported in children following acute ingestion of kerosene (Akamaguna and Odita 1983; Coruh and Inal 1966). Most of the available animal studies found no histopathological changes or organ weight changes in the cardiovascular system of rats and mice following inhalation, oral, or dermal exposures to various fuel oils, including kerosene (Carpenter et al. 1976; Lock et al. 1984; Muralidhara et al. 1982; NTP/NIH 1986). However, there are some limited data regarding cardiac effects. Inhalation of 20,400-34,000 mg/m^3 of kerosene vapor induced aortic plaques in guinea pigs.

Further, significant increases in total serum cholesterol and decreases in HDL were noted (Noa and Illnait 1987a). Vasodilation was reported in mice exposed by inhalation to diesel fuel no. 2 aerosol (Kainz and White 1984). Aspiration of kerosene decreased heart rate and mean arterial blood pressure in dogs (Goodwin et al. 1988). Because most of the toxicity findings are specific for kerosene, it is difficult to draw conclusions regarding the cardiac effects of other fuel oils. However, the similar composition of the various fuel oils suggests that the effects may also be similar. The potential for cardiac effects in humans at hazardous waste sites exists; the risk is increased if the individuals are exposed in confined spaces.

Gastrointestinal Effects. Inhalation of JP-5 vapor induced nausea in one individual. Abdominal cramps, vomiting, and diarrhea occurred in another man who was exposed to diesel fuel vapor for 10 days (Reidenberg et al. 1964). Inhalation and/or dermal exposure to diesel fuel induced epigastric pains in a man who washed his hands with diesel fuel (Crisp et al. 1979) and nausea, abdominal cramps, and diarrhea in another individual who used it as a shampoo (Barrientos et al. 1977). Ingestion of kerosene induces more severe effects: vomiting, abdominal pain and/or distension, gastroenteritis, bleeding, and diarrhea (Akamaguna and Odita 1983; Aldy et al. 1978; Mahdi 1988; Majeed et al. 1981; Saksena 1969; St. John 1982; Nouri and Al-Rahim 1970). No histopathological changes in the gastrointestinal system were reported in animals exposed to various fuel oils by the inhalation and dermal routes of exposure (Carpenter et al. 1976; Lock et al. 1984; NTP/NIH 1986). Also, acute oral exposure to kerosene or Deobase did not induce diarrhea in rats (Muralidhara et al. 1982). These data, though limited, indicate that species variations may exist between humans and rats following oral exposure to kerosene. Although the data are largely anecdotal, they strongly suggest that gastrointestinal effects are induced in humans by ingestion of kerosene, inhalation of JP-5 or diesel fuel vapor, and dermal contact with or inhalation of diesel fuel. It has not been determined whether these effects would occur as the result of exposure to other fuel oils and if they did at what exposure levels such effects would occur.

Hematological Effects. Subcutaneous hemorrhage, mild nose bleeds, low platelet counts, and retinal arteriole constriction were reported for a man who was exposed to diesel fuel vapor for 10 days (Reidenberg et al. 1964). These effects may be indicative of blood clotting problems. Decreased hemoglobin concentration and an increase in erythrocyte sedimentation rate were noted in one man after washing his hands with diesel fuel over several weeks (Crisp et al. 1979). Of 12 patients admitted to the pediatric intensive care unit of a children’s hospital during a 5-year period due to

respiratory distress associated with hydrocarbon aspiration, 3 showed signs of intravascular hemolysis. 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 two individuals exposed to JP-5 for a few hours (Porter 1990).

No hematological or splenic effects were reported in rats following oral exposure to kerosene (Muralidhara et al. 1982), nor were hematological and splenic effects noted in rats and dogs following inhalation of deodorized kerosene (Carpenter et al. 1976), in rats that inhaled diesel fuel (Lock et al. 1984), or in rats following oral administration of Deobase (Muralidhara et al. 1982).

Decreases in hemoglobin concentration and increases in erythrocyte, white blood cell, and polymorphonuclear leukocyte concentrations were noted in mice after acute dermal exposure to kerosene. A decrease in the splenic relative weight, which was not accompanied by histopathological changes, was also noted (Upreti et al. 1989). Oral exposure to JP-5 increased hematocrit levels, decreased white blood cell counts, and increased erythrocyte counts in rats (Parker et al. 1981). However, inhalation of diesel fuel aerosol induced decreases in the mean red blood cell count in rats and had no effect on white blood cells (Dalbey et al. 1987).

The effect of kerosene on the first two steps of the heme synthetic pathway was studied in an animal model and demonstrated that hepatic δ-aminolevulinic acid (δ-ALA) dehydratase and δ-ALA synthetase activities were decreased in female rats after intraperitoneal injection of kerosene. Further, heme oxygenase was not affected by kerosene under these conditions (Rao and Pandya 1980). Since δ-ALA synthetase is the rate-limiting enzyme of the heme biosynthesis pathway, hepatic heme biosynthesis may be inhibited by kerosene.

Generalizations regarding the hematological effects of fuel oils on humans cannot be made because the available data suggest that each fuel oil may behave differently, that species variation may exist, and that exposure route may play a role. The similar effects in humans and mice exposed to kerosene suggest that kerosene may not be species specific and may act similarly on the hematopoietic system regardless of the exposure route. However, there are not enough data to determine whether these generalizations can be made. The limited data suggest that inhalation or dermal exposure to diesel fuel and ingestion of kerosene can induce hematological effects in some individuals; however, it is not

known if these effects would occur in most individuals, although Algren and Rodgers suggest that hydrocarbon ingestion may frequently effect intravascular hemolysis.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation, oral, or dermal exposure to fuel oils. 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). Mice treated dermally with marine diesel fuel and JP-5 (up to 500 mg/kg/day) also displayed no detectable adverse effects to the musculoskeletal system (NTP/NIH 1986). The limited information available on animals is not sufficient to assess its relevance to human health.

Hepatic Effects. Histopathological examination revealed slight cellular infiltration and mild vacuolization of the livers of rats following gavage with kerosene or Deobase® organ weights were not affected (Muralidhara et al. 1982). Gavage with JP-5 induced increases in serum levels of hepatic enzymes, hepatocyte necrosis, and vacuolization of the periportal hepatocytes in rats (Parker et al. 1981). Inhalation of 231 mg/m^3 kerosene vapor induced increases in blood lactate and pyruvate levels; exposure to 58 mg/m^3 kerosene vapor induced decreases in blood glucose levels in rats (Starek and Vojtisek 1986). Neither rats nor dogs exhibited histopathological changes in the liver following inhalation exposure to 20, 48, or 100 mg/m^3 deodorized kerosene vapor (Carpenter et al. 1976) or following inhalation of up to 1,500 mg/m^3 diesel fuel aerosol by rats (Lock et al. 1984). No histopathological changes were noted in the livers of mice following acute dermal exposures to 0.1 mL kerosene (Upreti et al. 1989). Slight hepatic karyomegaly was noted in mice dermally exposed to 500-8,000 mg/kg/day JP-5 for 13 weeks (NTP/NIH 1986). These data suggest that fuel oils may be of concern to humans because they affected rats by inhalation and oral exposures and mice by dermal exposures. However, no human data are available for inhalation, oral, or dermal exposures to fuel oils with regard to hepatic toxicity. Therefore, the available information is not sufficient to assess the relevance to human health.

Renal Effects. In one individual, acute renal failure was noted from inhalation and/or dermal exposure to diesel fuel which was used as a shampoo. Biopsy detected tubular dilation, mitosis, and vacuolization in renal cells, and some cellular proliferation in the glomerulus in this individual (Barrientos et al. 1977). Another individual experienced renal failure following inhalation of diesel fuel vapor for 10 days (Reidenberg et al. 1964). Renal necrosis developed in one man after washing

his hands with diesel fuel over several weeks (Crisp et al. 1979). Urinalysis was normal following inhalation of JP-5 by two individuals or ingestion of kerosene by numerous individuals (Dudin et al. 1991; Mahdi 1988; Nouri and Al-Rahim 1970; Porter 1990).

Renal lesions have been produced in mice by dermal application of JP-5 or marine diesel fuel. The inability to duplicate these lesions with intraperitoneal administration suggested that skin application, in particular the alteration of skin following repeated dermal application, was necessary to produce the renal toxicity, and that the renal effects appeared to be 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 or marine diesel fuel (NTP/NIH 1986). However, acute and intermediate dermal exposures to kerosene and JP-5, respectively, were not toxic to the renal system of mice (Upreti et al. 1989; NTP/NIH 1986). Although renal damage has occurred in a few individuals exposed to diesel fuel, it is not known if the general population would exhibit these effects following exposure to these fuel oils. The effects of JP-5 and kerosene on humans is not known.

Inhalation of JP-5 or marine diesel fuel vapors and oral exposure to JP-5 induce a nephropathy that is unique to male rats (Bruner 1984; Cowan and Jenkins 1981; Gaworski et al. 1984; Parker et al. 1981). The progression of this lesion has been noted in several studies, including studies conducted on the hydrocarbon decalin (decahydronaphthalene) (Alden 1986; Bruner 1984; Cowan and Jenkins 1981; 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. 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 to binding with specific substances, such as fuel oils, or their metabolites. The cells die and are sloughed off. 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 under similar conditions to either JP-5 or marine diesel fuel vapors (Bruner 1984; Cowan and Jenkins 1981; Gaworski et al. 1984). There is no evidence of renal necrosis in humans acutely exposed to JP-5 vapor (Porter 1990). In a case report, one individual exposed to an unspecified diesel fuel for several weeks exhibited acute tubular necrosis (Crisp et al. 1979). However, renal necrosis did not occur in

two other individuals acutely exposed to diesel fuel vapor (Barrientos et al. 1977; Reidenberg et al. 1964), although they did exhibit acute renal failure. Based on available data, 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).

Dermal Effects. Oral and/or dermal exposure to kerosene induced blisters, erythema, and peeling skin in two cases (Annobil 1988). Dose-related effects in humans from dermal exposures to fuel oils are based upon limited information. Case studies describe numerous effects in or on the skin following dermal exposure to kerosene. These effects are 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 by impairing protein synthesis, but not DNA or collagen 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. Also, cellular destruction was noted in humans from dermal exposure to kerosene (Lupulescu and Birmingham 1976; Lupulescu et al. 1973), but the implications of these effects have yet to be determined.

Acute, intermediate, and chronic dermal exposures to marine diesel fuel and JP-5 have induced various degrees of dose-dependent dermatitis in mice (Easley et al. 1982; NTP/NIH 1986). Manifestations of the dermatitis include: acanthosis, inflammation, parakeratosis, and hyperkeratosis (NTP/NIH 1986). Dermal irritation was induced in mice by acute dermal exposure to kerosene (Upreti et al. 1989). It is possible that dermal sensitization by fuel oils occurs only following acute exposures since sensitization was noted in guinea pigs acutely exposed to JP-5 or marine diesel fuel vapors but not following intermediate exposures to JP-5 or diesel fuel vapors (API 1979f; Cowan and Jenkins 1981). However, delayed sensitization was not induced in guinea pigs treated with diesel fuel (Beck et al. 1984), three formulations of No. 2 fuel oil (Beck et al. 1984), JP-5 (Schultz et al. 1981), or diesel fuel marine (Schultz et al. 1981). Diesel fuel marine and JP-5 did induce skin irritation in guinea pigs (API 1979f). No signs of dermal lesions were noted in rats following repeated whole-body inhalation exposure to diesel fuel aerosol (Lock et al. 1984). Whereas dermal exposure to fuel oils (liquid or vapor) would be expected to induce irritation or possibly dermatitis, the data are not adequate to evaluate delayed skin sensitization. Furthermore, the data are insufficient to assess the dermal effects of fuel oils when exposure occurs via the oral or respiratory routes.

Ocular Effects. JP-5 vapor were irritating to the eyes of two individuals and were associated with hyperemic conjunctiva in one case (Porter 1990). Eye irritation was also reported in workers who were chronically exposed to unspecified jet fuels, which may or may not include JP-5 (Knave et al. 1978). Deodorized kerosene vapor were shown to induce eye irritation in some individuals (Carpenter et al. 1976). Dermal exposure to diesel fuel and/or inhalation of its vapor was associated with subconjunctival hemorrhages in an individual who used it as a shampoo (Barrientos et al. 1977). In the only available animal studies, rabbits exposed dermally to diesel fuel (API 1979b), marine diesel fuel, or JP-5 (Cowan and Jenkins 1981; Schultz et al. 1981) showed no signs of ocular irritation. These data suggest that fuel oils, in general, may induce eye irritation in some individuals, although only one or two individuals exhibited ocular or dermal effects from airborne exposures to fuel oils. Irritation is likely to be more severe if exposure occurs in confined spaces.

Body Weight Effects. In mice, dose-dependent decreases in body weight were induced by intermediate and chronic dermal exposures to marine diesel fuel. In addition, 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). Both food and water consumption were decreased in mice exposed to diesel fuel no. 2 aerosol for 8 hours/day, 5 consecutive days (Kainz and White 1984); in rats exposed to diesel fuel for 2 or 6 hours, once or 3 times per week (for a total of 9 exposures) (Dalbey et al. 1987); and in rats exposed for 4 hours per day, twice per week for 13 weeks (Lock et al. 1984). None of these effects were noted in mice following acute dermal exposures to kerosene (Upreti et al. 1989). No conclusions can be made regarding human health from the animal data since the significance of decreased body weight and food and water consumption with regard to humans cannot be determined.

Other Systemic Effects. Inhalation and/or dermal exposure to diesel fuel has been associated with edema in two individuals (Crisp et al. 1979; Reidenberg et al. 1964). In one of these cases, loin pains, thirst, and severe exhaustion were also reported (Crisp et al. 1979). 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; Nouri and Al-Rahim 1970; Saksena 1969; St. John 1982; Subcommittee on Accidental Poisoning 1962). The effects of oral exposure to kerosene in children cannot be used to predict possible effects in adults or the effects of other fuel oils by this route without additional information. Similarly, it cannot be determined whether the effects of diesel

fuel noted in humans would occur from exposure to other fuel oils or in the general population since limited information is available.

Immunological and Lymphoreticular Effects. No studies were located regarding immunotoxicity in humans after inhalation, oral, or dermal exposure or in animals following inhalation or oral exposure to fuel oils. Dermal application of JP-5 induced granulocytic hyperplasia in the bone marrow and hyperplasia in the lymph nodes of mice. Dermal treatment of mice with marine diesel fuel induced plasmacytosis in the lymph nodes; this effect was secondary to dermatitis (NTP/NIH 1986). 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 studies indicate that fuel oils may have an effect on the immune system of mice, although the toxicological significance of these effects cannot be determined from the data. There are not enough data to determine whether fuel oils would induce immunological effects in humans.

Data regarding changes in white blood cell counts were found; however, it cannot be determined whether these changes indicate hematological or immunological toxicity. Increases in leukocyte counts from acute ingestion of kerosene (Dudin et al. 1991; Majeed et al. 1981; Nouri and Al-Rahim 1970) have been reported in humans. Increases white blood cell and polymorphonuclear leukocyte concentrations were noted in mice after acute dermal exposure to kerosene (Upreti et al. 1989). Oral exposure to JP-5 decreased white blood cell counts in rats (Parker et al. 1981). However, inhalation of diesel fuel aerosol had no effect on white blood cells in rats (Dalbey et al. 1987). The conflicting changes in white blood cell levels may be due to differences in the toxicity of these fuel oils or to differences in exposure route or both. The similar effects in humans and mice exposed to kerosene suggests that kerosene may not be species specific and that this fuel oil affects white blood cells in a similar manner regardless of the exposure route. However, there are not enough data to determine whether these generalizations can be made.

Neurological Effects. Numerous neurological effects were reported from 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; 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 that ingested 3-20 mL of kerosene. This dose is equivalent to 126-1,754 mg/kg in children aged 10 months to 5 years (Dudin et al. 1991). There are limited data that suggest that the central nervous system effects noted from ingestion of kerosene are due to hypoxia which results from kerosene-induced respiratory impairment (Majeed et al. 1981).

Severe headaches occurred in an individual exposed to diesel fuel vapor for 10 days (Reidenberg et al. 1964). Anorexia occurred in a man following dermal and/or inhalation exposure to diesel fuel over several weeks (Crisp et al. 1979). Other neurological effects were reported following inhalation of JP-5 vapor in two individuals who had fatigue and coordination and concentration difficulties; other effects included headache, apparent intoxication, and anorexia. Effects subsided within 24 hours for one individual and within 4 days for the other (Porter 1990). Sensory impairment did not occur in these individuals. However, experimental data indicate that olfactory fatigue and taste sensation may occur in some individuals after a 15-minute inhalation exposure to 140 mg/m^3 deodorized kerosene vapor (Carpenter et al. 1976). These data suggest that the different types of fuel oils may behave differently under inhalation exposure conditions. The effect of deodorized kerosene may also occur at lower doses, but this cannot be determined from these data.

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). Nevertheless, it is not known to which jet fuels the workers were exposed, and confounding by exposure to other chemicals may have occurred.

Acute inhalation of diesel fuel no. 2 vapor induced dose-dependent ataxia, increased sensitivity to heat, changes in behavior, and tremors in mice. Also, while ataxia occurred, there was no affect on the spinal cord reflex for blink response nor on the integrity of the neuromuscular junction based on responses to the rota rod and inclined plane tests (Kainz and White 1984). In rats, intermediate inhalation of diesel fuel aerosol induced increased peak response time using the startle reflex assay

(Lock et al. 1984); however, histopathological changes of the nervous system were not noted in these rats. Neurotoxicity was not induced using the landing footspread, tail flick, forelimb grip strength, and startle reflex assays under similar exposure conditions (Dalbey et al. 1987). Oral exposure to kerosene and Deobase® induced ataxia and drowsiness in rats (Muralidhara et al. 1982). 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 (Upreti et al. 1989) in mice. No histopathological changes were noted in the nervous system of mice following dermal exposures to JP-5 or marine diesel fuel (NTP/NIH 1986). The information from human and animal studies indicate that neurotoxicity may occur by all routes of exposure and that all fuel oils may be neurotoxic. As is common with hydrocarbons, the primary acute neurotoxic effect is central nervous depression that may be manifest in a number of symptoms.

Developmental Effects. No studies were located regarding developmental effects in humans after inhalation, oral, or dermal exposure to fuel oils. No developmental effects were noted in rat fetuses after inhalation exposure of the gestating female to home heating oil no. 2, fuel oil UNSP, or diesel fuel vapor (API 1979c, 19798; Beliles and Mecler 1983). Since negative effects were noted for several fuel oils in one species, it is possible that none of the fuel oils induce developmental effects by inhalation. However, additional data are needed to assess whether developmental effects would occur in other species, including humans, and/or by oral and dermal exposures.

Reproductive Effects. No studies were located regarding reproductive effects in humans after inhalation, oral, or dermal exposure to fuel oils. No histological changes were noted in the reproductive system of mice dermally exposed to JP-5 for 13 weeks or chronically exposed to marine diesel fuel or JP-5 (NTP/NIH 1986) or in rats following intermediate-duration inhalation of diesel fuel aerosol (Lock et al. 1984). There is not enough information to assess the human reproductive toxicity to fuel oils by oral, inhalation, or dermal exposures.

Genotoxic Effects. No genotoxicity studies involving human exposure to fuel oils were identified. The results from a study employing a human cell line showed that neither 5 nor 50 ppm petroleum-derived JP-5 (PD-JPS) interfered with Snyder-Theilen feline sarcoma virus (ST-FeSV)-directed transformation of human foreskin fibroblastic cells (Blakeslee et al. 1983). Higher concentrations (2100 ppm) were cytotoxic. It was reported that marine diesel fuel failed to inhibit transformation in this assay, but data were not shown. 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 virus by blocking a specific virus gene function (i.e., transformation); noncarcinogens do not inhibit virus-induced cell transformation in this test system.

Animal models have primarily yielded negative genotoxicity data. Inhalation of 100 to 400 ppm diesel fuel 6 hours/day, 5 days/week for 8 weeks did not increase the frequency of dominant lethal mutations. Cyclohexane/DMSO extract and DMSO extract of diesel 1 (CAS no. 8008-20-6), diesel 2 (CAS no. 64742-47-7), and home heating oil (CAS no. 68476-30-2), administered orally at doses of 1.0, 2.0, and 5.0 g/kg, did not induce increased frequency of micronuclei in a mouse bone marrow micronucleus assay (McKee et al. 1994). It should be noted that the extraction procedure was used to concentrate the aromatic fraction (with particular interest in the polynuclear aromatics) of the fuel oils tested. Kerosene, administered intraperitoneally , did not increase the frequency of chromosomal aberrations in bone marrow cells harvested from rats following a one-time exposure to 0.04, 0.13, or 0.4 mL or a 5-day exposure to 0.02, 0.06, or 0.18 ml/day (Conaway et al. 1984). Since the rationale for selection of 0.4 mL (LD,) as the high dose was not provided and there was no information regarding toxic effects in the treated animals or cytotoxic effects on the target organ (i.e., bone marrow cells), the findings do not fully support a negative conclusion for kerosene.

Some data has, however, suggested that fuel oils may have genotoxic activity. Evidence that fuel oil no. 2 is clastogenic in rat bone marrow has been reported (Conaway et al. 1984). Significant increases (Wilcoxon rank test) in the percentage of aberrant cells were observed in a rat bone marrow cytogenetic assay in rats receiving single intraperitoneal (i.p.) injections (2.0 or 6.0 mL/kg diesel fuel) and in rats receiving daily i.p. injections of 6.0 ml/kg/day for 5 days, although the response was not dose-related. Similarly, rats that received doses of fuel oil no. 2 (oral gavage; 125, 417, or 1,250 g/kg/day) for 5 consecutive days demonstrated nondose-related increases in the percentage of aberrant cells and the percentage of cells with chromatid breaks (Conaway et al. 1984). The effect was significant at the low and high dose, and the greatest yield of aberrant chromosome figures occurred in the rats treated with 125 g/kg/day.

The genotoxicity of fuel oil no. 2, kerosene, and diesel fuel was also evaluated with the mouse lymphoma $TK^{+/-}$ forward mutation assay (Conaway et al. 1984). The data reported was insufficient to

permit a full evaluation of the results; however, the authors considered diesel fuel and kerosene to be negative and fuel oil no. 2 to be positive.

The cyclohexane/DMSO extract and DMSO extract of diesel 1 (CAS no. 8008-20-6), diesel 2 (CAS no. 64742-47-7), and home heating oil (CAS no. 68476-30-2) were evaluated for genotoxicity with the Ames assay (McKee et al. 1994). Diesel 1 extracts did not produce significant increases in revertants. The DMSO extract of diesel 2 produced a significant increase in the number of revertants, although the increase was not dose-related. The cyclohexane/DMSO extract of diesel 2 failed to produce a significant increase in the number of revertants. The DMSO-extract of home heating oil produce a significant increase in revertants, that was dose-dependent, while the cyclohexane/DMSO extract induced a dose-related increase in revertants that was less than two times greater than the control. It should be noted that the modifications to the standard Ames mutagenesis included not only the extraction step but also the use of S9 at eight times the recommended concentration, and the use of the TA98 strain exclusively. Kerosene was mutagenic in S. *typhimurium* TA98 in the presence of increased concentrations of hamster S9 and nicotinamide adenine dinucleotide phosphate (NADP) in the S9-cofactor mix (Blackburn et al. 1986).

In contrast to the positive results with kerosene, neither JP-5 nor a marine diesel fuel product were mutagenic in the Ames assay when activated with S9 (Arochlor-induced rat liver enzymes) (Schultz et al. 1981). Similarly, neither marine diesel fuel nor JP-5 were mutagenic in well-conducted *S. typhimurium* preincubation assays (NTP/NIH 1986). Doses of each agent evaluated without S9 activation and with rat or hamster liver fractions ranged from 3 to 333 μg/plate -S9, from 33 to 3,333 μg/plate +S9 (marine diesel fuel), and from 100 to 10,000 μg/plate +/-S9 (JP-5). Further, fuel oil no. 2 was not mutagenic up to the limit of solubility (42 mg/plate) in the *Salmonella/mammalian* microsome mutagenicity assay (Conaway et al. 1984). It was also reported that kerosene (0.001-5 μL/plate +/-S9 [plate test] and 6.25-50 μL/mL +/-S9 [preincubation assay]) and diesel fuel (0.001-5 μL/plate +/-S9 [plate test] and 3.38-25 μL/mL [preincubation assay]) were negative in this microbial test system.

The inconsistent data reported for the animal models, the human cell assays, and the Ames tests with the various fuel oils preclude the use of the data for the prediction of genotoxic hazards to humans (refer to Tables 2-4 and 2-5 for a further summary of these studies).

TABLE 2-4. Genotoxicity of Fuel Oils *In Vivo*

Species (test system)	End point	Results	Reference
Fuel Oil No. 2			
Mammalian cells:			
Rat (bone marrow)	Chromosome aberrations	+/–[a]	Conaway et al. 1984
Diesel Fuel			
Mammalian cells:			
Rat (bone marrow)	Chromosome aberrations	+	Conaway et al. 1984
Mouse (all stages of spermato- and spermiogenesis)	Dominant lethal mutations	–[b]	API 1981
Kerosene			
Mammalian cells:			
Rat (bone marrow)	Chromosome aberrations	–[c]	Conaway et al. 1984
Diesel Fuel No. 1			
Mammalian cells:			
Rat (bone marrow)	Micronucleus increase	–	McKee et al. 1994
Diesel Fuel No. 2			
Mammalian cells:			
Rat (bone marrow)	Micronucleus increase	–	McKee et al. 1994
Home Heating Oil			
Mammalian cells:			
Rat (bone marrow)	Micronucleus increase	–	McKee et al. 1994

[a]Positive after oral exposure but no dose response
[b]Negative after inhalation exposure
[c]Negative after intraperitoneal exposure but study was compromised

+/– = inconclusive result, + = positive result; – = negative result

TABLE 2-5. Genotoxicity of Fuel Oils *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Kerosene				
Prokaryotic organisms:				
Salmonella typhimurium (TA98)	Gene mutation	+	No data	Blackburn et al. 1986
Marine Diesel Fuel				
Prokaryotic organisms:				
S. typhimurium (TA1535, TA1537, 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
JP-5 Fuel				
Prokaryotic organisms:				
S. 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
Fuel Oil No. 2				
Prokaryotic organisms:				
S. typhimurium (TA1535, TA1537, TA1538, TA98, TA100)	Gene mutations	–	–	Conaway et al. 1984

TABLE 2-5. Genotoxicity of Fuel Oils *In Vitro* (*continued*)

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Mammalian cells:				
Mouse lymphoma (L5178Y)	Gene mutations	–	+/–	Conaway et al. 1984
Kerosene				
Prokaryotic organisms:				
S. typhimurium (TA1535, TA1537, TA1538, TA98, TA100)	Gene mutations	–	–	Conaway et al. 1984
Mammalian cells:				
Mouse lymphoma (L5178Y)	Gene mutations	–	–	Conaway et al. 1984
Diesel Fuel				
Prokaryotic organisms:				
S. typhimurium (TA1535, TA1537, TA1538, TA98, TA100)	Gene mutations	–	–	Conaway et al. 1984
Mammalian cells:				
Mouse lymphoma (L5178Y)	Gene mutations	–	–	Conaway et al. 1984
Diesel Fuel No. 1				
Prokaryotic organisms:				
S. typhimurium (TA98)	Gene mutation	–	No data	McKee et al. 1994
Diesel Fuel No. 2				
Prokaryotic organisms:				
S. typhimurium (TA98)	Gene mutation	+/-	No data	McKee et al. 1994

TABLE 2-5. Genotoxicity of Fuel Oils *In Vitro* (*continued*)

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Home Heating Oil				
Prokaryotic organisms:				
S. typhimurium (TA98)	Gene mutation	+	No data	McKee et al. 1994

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

Cancer. Human cancer data from epidemiological studies found only equivocal evidence of an association between cancer and exposures to fuel oils. Several studies examined the association between "fuel and oil expenditures for farm purposes" and various forms of cancer in central Canadian farmers (Morrison et al. 1992, 1994; Semenciw et al. 1993). They reported an association between such expenditures and non-Hodgkin's lymphoma and multiple myeloma incidence, but the association was equivocal and not statistically significant. Furthermore, the type of fuels and oils was not specified, nor was the exposure route described. 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"). One study (Partanen et al. 1991) suggests that other chemicals could be present in the occupational setting, which could alter fuel oil toxicity, though this same study found no significant association between fuel oil exposure and cancer. Chan and coworkers (1979) examined exposure to kerosene from kerosene cooking stoves, but exposure to kerosene combustion products may have occurred instead of, or in addition to, inhalation of kerosene vapor. Therefore, no firm conclusions may be drawn from this data for human health.

No dermal cancer was noted in B6C3F_1 mice following chronic dermal exposure to 250 or 500 mg/kg/day JP-5 (NTP/NIH 1986). However, unspecified skin tumors were noted in C3HF/Bd mice, but the tumors were not dose related in most exposure conditions (Schultz et al. 1981). There was an increased incidence of squamous cell papilloma and/or carcinoma in mice chronically exposed to 250 or 500 mg/kg/day marine diesel fuel (NTP/NIH 1986). Hepatocellular adenoma and carcinoma were noted in male, but not female, mice exposed to 250 or 500 mg/kg/day marine diesel fuel (NTP/NIH 1986). Although a significant increase in hepatocellular carcinomas were observed in mice dermally treated with middle distillates, the increase was not substantially greater than the incidence noted in "historical" data from negative control groups (Biles et al. 1988). API no. 2 fuel oil demonstrated low tumorigenic activity (15/150) in male and female mice dermally treated with the undiluted material or as a 50% or 25% solution in acetone (Witschi et al. 1987). A low, but significant increase in the incidence of dermal tumor was noted in male mice treated with six no. 2 fuel oils that varied in composition (Biles et al. 1988). No increase in tumor incidence occurred in mice receiving dermal applications of diesel fuel; however, dermal application of Jet A induced an increased incidence (26%) of neoplastic lesions (Clark et al. 1988). An increase in tumor incidence was noted in mice receiving

DMBA as an initiating agent and furnace oil as a promoting agent; further, furnace oil produced a significant increase in the incidence of confirmed skin tumors in a skin-painting assay (Gerhart et al. 1988). An increase in the incidence of confirmed tumor was also noted in animals receiving DMBA as an initiator and either hydrodesulfurized kerosine or no. 2 fuel oil as a promoting agent (API 1989). These data suggest that fuel oils can act as a skin or liver carcinogen. However, only one species has been investigated, limiting the data. Further investigation utilizing other species is required to more fully elucidate the mechanism of dermal carcinogenesis and the impact of dermal exposure of fuel oils on humans. (See Section 2.2.3.8 for a more complete review of carcinogenesis data.)

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance, its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. Examples of the types of biomarkers indicated above include blood lead (the xenobiotic), urinary excretion of 2-thiothizolidine-4-carboxylic acid (a metabolite of carbon disulfide), or a DNA adduct (the product of an interaction between an exogenous material and a macromolecule). Several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to fuel oils are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by fuel oils are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a change in target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "Populations That Are Unusually Susceptible."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Fuel Oils

No biomarkers of exposure were identified for fuel oils in general. However, there have been suggestions for potential markers 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 odor of distillate fuels are so similar, however, that the sensitivity and specificity of these markers would be extraordinarily low. Some components of kerosene, other fuel oils, and their metabolites may be detected in the blood and urine, although neither the route of exposure nor the origin can be determined. For information on biomarkers of exposure for some of the constituents of fuel oils, the ATSDR toxicological profiles on benzene, toluene, total xylenes, and polycyclic aromatic hydrocarbons (ATSDR 1989, 1990a, 1991a, 1991b) can be consulted.

2.5.2 Biomarkers Used to Characterize Effects Caused by Fuel Oils

No specific, quantitative biomarkers of effect for fuel oils were identified.

2.6 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 fuel oils. However, kerosene vapor has been shown to increase the effects of hexobarbital (a sleeping agent), following acute exposure, and phenacetin (an antipyretic), following subchronic exposure, in rats (Starek and Vojtisek 1986).

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

No information was located regarding the toxicity of fuel oils in susceptible populations. The human data, in general, were based upon case studies that reported ingestion of kerosene by children. Although children were not shown to be particularly susceptible to kerosene in these studies, it was obvious that children are more likely to be exposed to kerosene accidentally than adults. In particular, children that are 5 years old or younger often mistakenly drank kerosene because it was accessible to them.

In one animal study, it was found that younger rats are more susceptible to kerosene toxicity than are older rats. A single oral dose of 22,400 mg/kg kerosene killed 27% of the adult rats, 66% of the 5-week-old rats, and 100% of the 10-day-old rats (Deichmann et al. 1944). It is not known whether kerosene would also be more toxic in younger humans as compared to older humans.

2.8 METHODS OF REDUCING TOXIC EFFECTS

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

2.8.1 Reducing Peak Absorption Following Exposure

The mitigation procedures for fuel oils 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 1991) including 100% humidified supplemental oxygen as required (HSDB 1991).

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 fuel oils or kerosene is hydrocarbon aspiration either during ingestion or during gastric decontamination. 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 decontamination 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; Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; HSDB 1991; 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 of how and/or whether to decontaminate the stomach should be based on the state of the patient, the hydrocarbon’s viscosity, and the involvement of other more dangerous chemicals. For conscious patients with operational gag reflexes and without spontaneous emesis, induced vomiting

seems to be the preferred method of gastric emptying (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; Ng et al. 1974; Shirkey 1971; Zieserl 1979); otherwise, endotracheal intubation followed by gastric lavage has been suggested (Ellenhorn and Barceloux 1988; Haddad and Winchester 1990).

For ingestion of large amounts (greater than 30 mL in children) of home or diesel fuel oils, gastric decontamination has been contraindicated since these hydrocarbons have a high viscosity and are poorly absorbed (Ellenhorn and Barceloux 1988). The low viscosity of kerosene, however, has produced conflicting opinions. Some recommend induced emesis to prevent gastrointestinal absorption (Ellenhorn and Barceloux 1988). On the other hand, others suggest that the low viscosity of kerosene increases the risk of aspiration (Gerarde 1959; Litovitz and Greene 1988) and therefore do not recommend gastric decontamination regardless of volume (Bronstein and Currance 1988; CONCAWE 1985; Haddad and Winchester 1990; Litovitz and Greene 1988; Macnamara 1968).

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 1991; 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 1991) 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 and/or corticosteroids does not appear useful in treating hydrocarbon pneumonitis (Brown et al. 1974; Goldfrank et al. 1990; Haddad and Winchester 1990; HSDB 1991; 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 1991; Zieserl 1979).

If the skin is exposed to fuel oils, washing the area of contact with large amounts of soapy water is recommended (CONCAWE 1985; Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; HSDB 1991; 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 1991; Stutz and Janusz 1988) and, if necessary, using proparacaine hydrochloride to assist the irrigation (Bronstein and Currance 1988) are the recommended treatment protocols.

2.8.2 Reducing Body Burden

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

2.8.3 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 fuel oils as well as their mechanisms are not well defined. As such, no known therapies are available that disrupt the mechanisms of action.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of fuel oils 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 fuel oils.

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

2.9.1 Existing Information on Health Effects of Fuel Oils

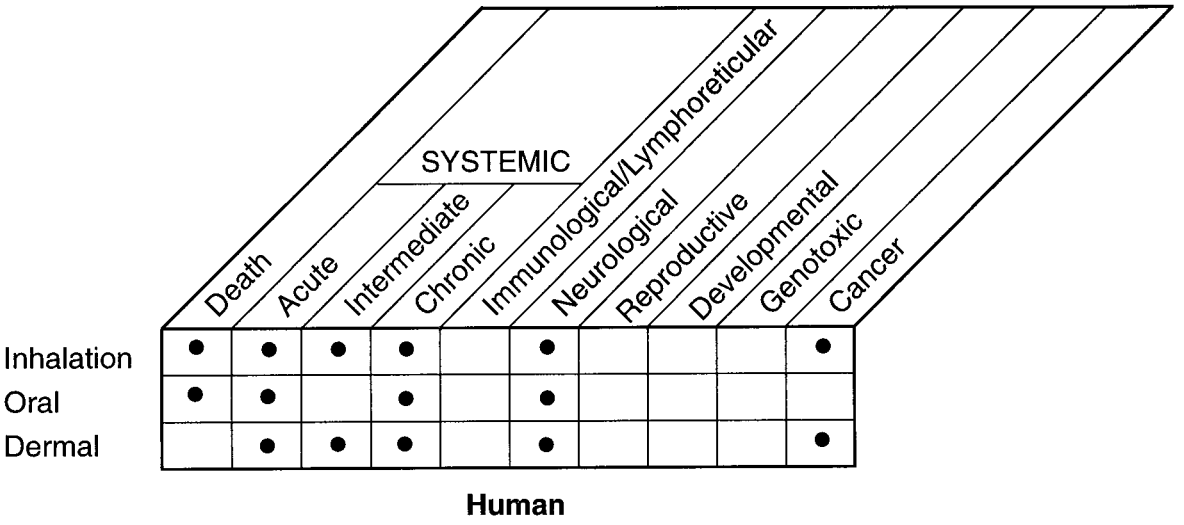
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to fuel oils are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of fuel oils. Each dot in the figure indicates that one or more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

Information is available on acute, intermediate, and chronic systemic effects, as well as neurological and cancer effects, following inhalation exposure to fuel oils; death, acute systemic, and neurological effects following oral exposure to fuel oils; and acute, intermediate, and chronic systemic and neurological effects following dermal exposure to fuel oils in humans. Information is available on death, and acute and intermediate systemic effects, as well as neurological, developmental, reproductive, genotoxic, and cancer effects following inhalation exposure to fuel oils; death, acute systemic effects, as well as neurological and genotoxic effects following oral exposure to fuel oils; and death, acute, intermediate, and chronic systemic effects, as well as immunological, neurological, reproductive, and cancer effects following dermal exposure to fuel oils in animals. Therefore, as Figure 2-4 shows, the majority of the data on health effects of fuel oils concern inhalation or dermal exposure of animals; however, there are some data for all routes of exposure in both animals and humans.

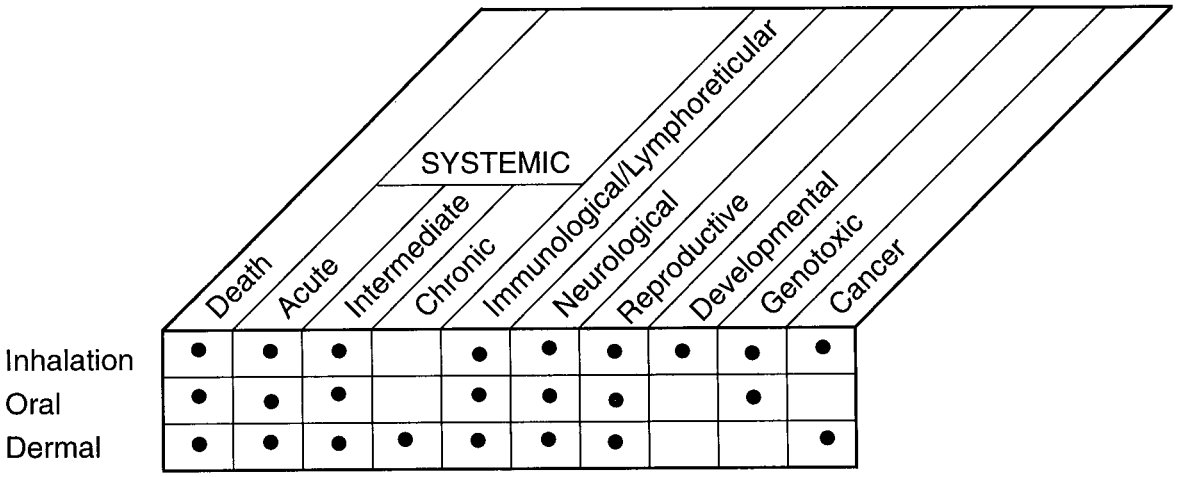
2.9.2 Identification of Data Needs

The following are topical sections that identify gaps in the present state of knowledge concerning the toxicology of fuel oils. Each of the sections identifies specific areas in which additional data are needed to gain a greater understanding of the toxicity of fuel oils and its constituents as well as of the biochemical mechanisms of their toxicity. It must be noted, however, that there are finite monies available for all toxicological research. Hard decisions must be made to determine how (e.g., the material to be studied, the effect to be investigated, whether human study or animal model) these funds would best be invested.

FIGURE 2-4. Existing Information on Health Effects of Fuel Oils



Human



Animal

● Existing Studies

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 fuel oils, 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 (Barrientos et al. 1977; Porter 1990). Dermal irritation is also well documented for both humans (Annobil 1988; Barrientos et al. 1977; Mosconi et al. 1988; Tagami and Ogino 1973) and animals (NTP/NIH 1986; Upreti et al. 1989) by the dermal route of exposure. A few case studies indicate that cardiovascular, hematological, and renal effects may occur in humans exposed to the vapors of JP-5 or diesel fuel (Barrientos et al. 1977; Porter 1990; Reidenberg et al. 1964). Renal toxicity may also occur following dermal contact with diesel fuel (Barrientos et al. 1977).

Dose-response data are largely lacking for the effects noted in both humans and animals. A few animal studies do contain dose-response data. Decreased food and water consumption, vasodilation, and neurological effects (reduced coordination, increased sensitivity to heat, changes in behavior, tremors) were found to be dose-dependent in mice exposed to diesel fuel no. 2 aerosol (Kainz and White 1984). Dose-response lethality data were found for inhalation exposures to diesel fuel aerosols (Dalbey and Lock 1983). In addition, there was a dose-response relationship following a single exposure to kerosene by oral gavage for death, unsteady gait, and drowsiness in rats (Muralidhara et al. 1982). However, the majority of the animal studies contain negative data (Beliles and Mecler 1983) that have not been verified by more than one study using the same fuel oil, species, and/or route of exposure, or 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). 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 fuel oils noted in a few individuals.

Intermediate-Duration Exposure. Only one case study was identified that described intermediate exposure in one individual who washed his hands with diesel fuel over several weeks (Crisp et al. 1979). The man exhibited epigastral pain, hematological effects, renal necrosis, edema of the scrotum and ankle, loin pains, thirst, and severe exhaustion. Effects resulting from inhalation versus dermal exposure could not be distinguished in this case. This is the only study found that identifies renal

necrosis in humans. The renal necrosis described in this individual resembles a renal nephropathy that was previously found only in male rats from vapor inhalation and oral exposure to JP-5 and marine diesel fuel (Bruner 1984; Cowan and Jenkins 1981; Gaworski et al. 1984; Parker et al. 1981). There are data that show the $\alpha_{2\mu}$-globulin protein, which is responsible for the necrosis in rats, may not exist in humans (Alden 1986). Also, data are needed to determine whether mechanisms of toxicity, other than those involving this protein, may exist for the induction of this lesion in both humans and rats. Also, data from well conducted studies are needed to determine which fuel oils induce this lesion in various species. Finally, in future cases of human exposure to fuel oils, signs of renal toxicity should be carefully monitored and results from histological examinations of renal tissue should be reported, if available.

Animal data are available for intermediate exposures by the inhalation and dermal routes of exposure. No animal data were located by the oral route. Most of these studies found no evidence of toxicity in any of the exposure conditions used in each (Carpenter et al. 1976; Bruner 1984; Lock et al. 1984; NTP/NIH 1986). However, the lack of toxicity in these studies has not been verified by more than one study using the same fuel oil, species, and/or route of exposure. In one aerosol inhalation study (Dalbey et al. 1987) there were positive findings for respiratory, hematological, and body weight effects at higher doses than those used in the studies by Carpenter et al. (vapor) (1979) and Lock et al. (aerosol) (1984). However, MRLs cannot be derived from these data because the Dalbey et al. study was not designed to test for a dose-response relationship, and therefore, the exact LOAEL(s) could not be determined for these effects. In another aerosol study with positive findings, only one concentration level was tested (Noa and Illnait 1987a).

One well-conducted study in mice describes effects (death, hepatic karyomegaly, and dermatitis) from dermal exposures to either JP-5 or marine diesel fuel (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). In a third study, dose-related increases in the relative weight of the right lobe of the lung were noted from inhalation of diesel fuel aerosol (Lock et al. 1984). None of these studies can be used for MRL derivation since the data were obtained by dermal exposures in one study and the biochemical and organ weight effects induced by inhalation of the fuel oils were not supported by pathological changes. More data are needed in animals, and especially in humans, for all routes of exposure to identify the primary toxic effects of fuel oils from intermediate exposures.

Chronic-Duration Exposure and Cancer. Epidemiological data regarding respiratory and dermal effects from chronic exposures to fuel oils 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 to fuel oils. A single animal study addressed carcinogenicity in animals via inhalation (Bruner 1984); however, the study did not adequately investigate the subject. Animal model data were available for the carcinogenic effects of chronic dermal exposure. It is apparent that chronic dermal application of fuel oils can induce tumorigenesis; however, both the mechanism of induction and the relevance of fuel oil tumor induction to humans are poorly defined. Equivocal data were available for the induction of hepatic tumors following dermal exposure. The data were so limited that the effect could not be evaluated. As such, further elucidation of the biochemical pathway, the relevance of dermal exposure to humans, and the incidence of induction of systemic tumorigenesis subsequent to dermal exposure would be of value.

The demonstration of renal toxicity in animal models has been considered significant due, at least in part, to case studies reporting 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 fuel oils rather than systemic toxicity. Data that clarifies this effect would be of interest.

Genotoxicity. No definite conclusions can be reached from the *in vitro* human cell and whole animal genetic toxicology studies that have been performed with fuel oils. Data from bacterial *in vitro* assays are inconsistent (see Section 2.4, Genotoxic Effects). A study of the genotoxicity/mutagenicity of commercially available fuel oils and the various component petroleum streams used in their formulation would be of value.

Reproductive Toxicity. No information was found regarding reproductive toxicity in humans from inhalation, oral, or dermal exposures to fuel oils. There were no pathological changes on the reproductive organs of mice following chronic and/or intermediate dermal exposures to marine diesel fuel and JP-5 (NTP/NIH 1986) or in rats following intermediate inhalation of diesel fuel aerosol (Lock et al. 1984). Additional data are needed to identify the toxic potential of fuel oils 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 fuel oils. Several studies were identified that tested developmental effects in animals, but only using the inhalation route of exposure. These studies found no developmental effects in the fetuses of female rats that had been exposed to heating oil, fuel oil UNSP, or diesel fuel vapors by inhalation during gestation days 6-15 (API 1979c, 19798; Beliles and Mecler 1983). Additional data are needed to identify the toxic potential of fuel oils regarding developmental effects by all routes of exposure.

Immunotoxicity. No information was found regarding immunotoxicity in humans from inhalation, oral, or dermal exposures to fuel oils. Only two animal studies were identified that tested immunological effects, both using mice. These 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 chronic dermal exposures to JP-5 and marine diesel fuel (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 fuel oils on the immune system by all routes of exposure and in different animal systems.

Neurotoxicity. Epidemiological data regarding neurological effects from chronic exposures to fuel oils 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; 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 (Muralidhara et al. 1982) or aspiration (Nouri et al. 1983).

Some information is available to identify 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), headaches may be induced by diesel fuel vapor (Reidenberg et al. 1964), and sensory impairment may be induced by deodorized kerosene vapor (Carpenter et al. 1976). In animals, a few studies were found that document neurological effects from inhalation of fuel oils. Acute inhalation of diesel fuel no. 2 vapor produced

behavioral changes, tremors, ataxia, reduced coordination, and increased sensitivity to heat in mice (Kainz and White 1984). In another study (Lock et al. 1984), peak response time, based on the startle reflex assay, was increased in rats after intermediate inhalation of diesel fuel aerosol, but at higher exposure levels than those used in the Kainz study. These studies conflict with the negative neurotoxicity findings of a second intermediate-duration study in which diesel fuel aerosol was tested in rats at even higher concentrations (Dalbey et al. 1987). Thus, MRLs cannot be derived from these data.

Neurotoxicity in humans from dermal exposures has been reported in 1 case study in which anorexia was noted (Crisp et al. 1979); inhalation exposure may have also occurred. One animal study found no histopathological changes in the organs of the nervous system in mice following chronic and/or intermediate dermal exposures to marine diesel fuel and 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 fuel oils on the nervous system in both animals and humans.

Epidemiological and Human Dosimetry Studies. There were limited data that indicated that the use kerosene stoves in the home is not associated with increased respiratory illness (Azizi and Henry 1991; Tominaga and Itoh 1985), although chronic dermal exposure to kerosene has been related to Dermatosis (Jee et al. 1985). These studies are of limited use, however, since neither exposure nor duration of exposure were reported.

A number of effects have been associated with chronic exposure to jet fuel in factory workers (Knave et al. 1978). These effects included increases in the occurrence of neurasthenia (anxiety and/or mental depression, fatigue, depressed mood, lack of initiative, dizziness, palpitations, thoracic oppression, sleep disturbances) and 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. However, the type of jet fuels were not noted nor was there a control for exposure to other

compounds. Inhalation exposure is likely since jet fuel vapor was detected by the study authors; however, dermal and oral (i.e., eating with contaminated hands) exposures may also be possible.

Limited epidemiological information exists for carcinogenicity in humans following inhalation exposure to kerosene (vapor) (Chan et al. 1979) and other fuel oils such as diesel fuel (vapor) (Partanen et al. 1991). These studies either test kerosene exposure by use of kerosene stoves, and so are limited for the same reasons as the respiratory studies described above, or measure fuel oil exposures according to occupation. In the latter case, confounding from exposure to other chemicals, such as gasoline, exists. Both studies are limited since the duration and level of fuel oil exposure were not identified. Other available data are also reported to be inadequate to assess the carcinogenic potential of fuel oils (IARC 1989; Lam and Du 1988).

Exposures to fuel oils generally occur in the occupational setting. For this reason, it is difficult to control for confounding by other chemicals and to identify levels and durations of exposure to specific fuel oils. Exposure to kerosene may occur in the general population through the use of kerosene stoves and kerosene heaters. Aside from accidental poisonings in children, however, quantitative exposures to kerosene are difficult to determine because exposures are likely to be by inhalation or dermal routes. Also, there is much variability in the ventilation systems, cooking patterns, and smoking habits in individual homes of the general population, which makes determination of the level of exposure difficult. Finally, it is not possible to control for confounding by combustion products of kerosene when testing the effects of kerosene by the inhalation route. Therefore, if future studies are going to yield useful data concerning the toxicity of fuel oils in humans, rigorous controls must be planned for any confounding factors.

Biomarkers of Exposure and Effect. No biomarkers of exposure or effect were identified for fuel oils. Although no standard procedures exist for identifying and quantifying exposure to fuel oils in general, procedures do exist for identifying and quantifying the hydrocarbon components of fuel oils, 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 distinct odor of kerosene on the breath or clothing (Annobil 1988; Tagami and Ogino 1973; Zucker et al. 1986). Studies delineating the metabolism and excretion of fuel oils are needed to identify potential biomarkers of exposure.

Although not specific for kerosene, aminolevulinic acid (ALA) could potentially be used as an adjunct or supplemental biomarker for kerosene exposure. Kerosene may affect heme metabolism by decreasing the activities of enzymes in the heme biosynthetic pathway (hepatic δ-ALA dehydratase and δ-ALA synthetase) (Rao 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 fuel oils.

Absorption, Distribution, Metabolism, and Excretion. No quantitative data were located regarding the absorption, distribution, metabolism, or excretion of fuel oils following inhalation, oral, or dermal exposure in humans. No quantitative data were located regarding absorption and distribution of fuel oils following inhalation or dermal exposure in animals. 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. There is also some suggestion from case studies that renal toxicity may occur in humans following exposure to diesel fuel vapor (Barrientos et al. 1977; Reidenberg et al 1964), although this possibility appears remote. Renal toxicity may occur following dermal contact with diesel fuel (Barrientos et al. 1977; Easely et al. 1982). No data were located regarding the metabolism or excretion of fuel oils following any of the three routes of exposure. Acute, intermediate, and chronic data are needed to assess the relative rates and extent of absorption, distribution, and excretion of fuel oils with respect to all three routes of exposure, as well as with respect to time or dose. Also, data are needed to determine whether dermal absorption of diesel fuel vapor can occur to induce renal toxicity.

Comparative Toxicokinetics. Limited data are available regarding comparative toxicokinetics. The acute oral LD_{50} values in guinea pigs and rabbits for kerosene has 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; however, more data would be needed to thoroughly examine species variation in toxicokinetics. This information would be useful to identify similar target organs and to adequately assess which animals can serve as the best models for humans, as well as to define mechanisms of action.

Methods for Reducing Toxic Effects. The mitigation procedures for fuel oils 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, and specifically kerosene-induced, pneumonitis (Brown et al. 1974; Goldfrank et al. 1990; Haddad and Winchester 1990; HSDB 1991; 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 kerosene's toxicokinetic properties of absorption 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.

2.9.3 On-going Studies

No on-going studies evaluating the health effects or toxicokinetics of fuel oils were located.