

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

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

Species (test system)	End point	Results		Reference
		With activation	Without activation	
<u>Kerosene</u>				
Prokaryotic organisms:				
<i>Salmonella typhimurium</i> (TA98)	Gene mutation	+	No data	Blackburn et al. 1986
<u>Marine Diesel Fuel</u>				
Prokaryotic organisms:				
<i>S. typhimurium</i> (TA1535, TA1537, TA98, TA100)	Gene mutation	-	-	NTP/NIH 1986
<i>S. typhimurium</i> (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
<u>JP-5 Fuel</u>				
Prokaryotic organisms:				
<i>S. typhimurium</i> (TA1535, TA97, TA98, TA100)	Gene mutation	-	-	NTP/NIH 1986
<i>S. typhimurium</i> (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
<u>Fuel Oil No. 2</u>				
Prokaryotic organisms:				
<i>S. typhimurium</i> (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		Reference
		With activation	Without activation	
Mammalian cells:				
Mouse lymphoma (L5178Y)	Gene mutations	-	+/-	Conaway et al. 1984
<u>Kerosene</u>				
Prokaryotic organisms:				
<i>S. typhimurium</i> (TA1535, TA1537, TA1538, TA98, TA100)	Gene mutations	-	-	Conaway et al. 1984
Mammalian cells:				
Mouse lymphoma (L5178Y)	Gene mutations	-	-	Conaway et al. 1984
<u>Diesel Fuel</u>				
Prokaryotic organisms:				
<i>S. typhimurium</i> (TA1535, TA1537, TA1538, TA98, TA100)	Gene mutations	-	-	Conaway et al. 1984
Mammalian cells:				
Mouse lymphoma (L5178Y)	Gene mutations	-	-	Conaway et al. 1984
<u>Diesel Fuel No. 1</u>				
Prokaryotic organisms:				
<i>S. typhimurium</i> (TA98)	Gene mutation	-	No data	McKee et al. 1994
<u>Diesel Fuel No. 2</u>				
Prokaryotic organisms:				
<i>S. typhimurium</i> (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	
<u>Home Heating Oil</u>				
Prokaryotic organisms: <i>S. typhimurium</i> (TA98)	Gene mutation	+	No data	McKee et al. 1994

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

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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 B6C3F₁ 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

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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-thiothiazolidine-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.

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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.

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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

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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

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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.

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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).

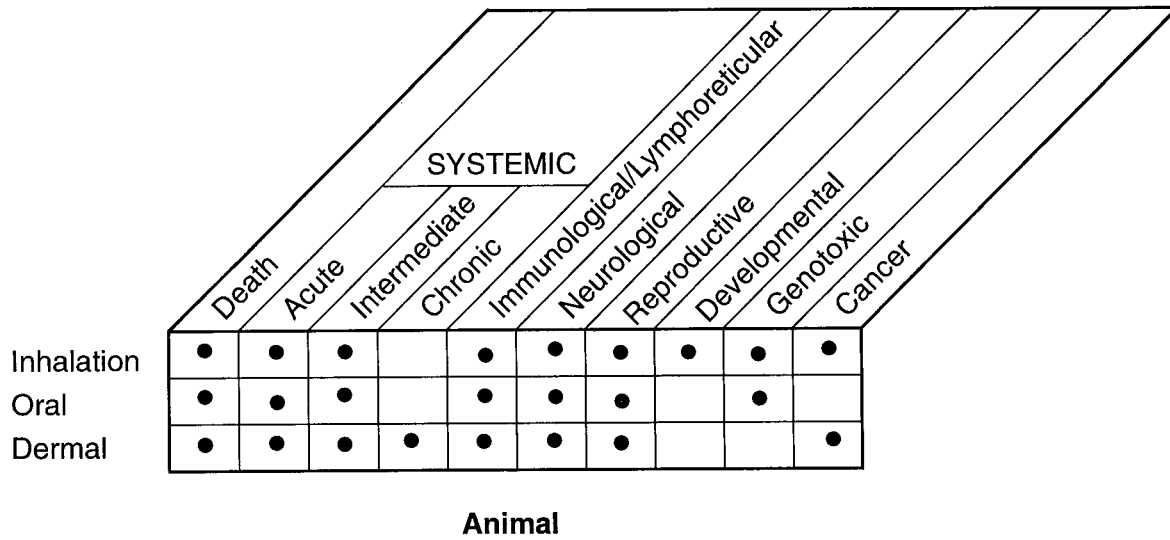
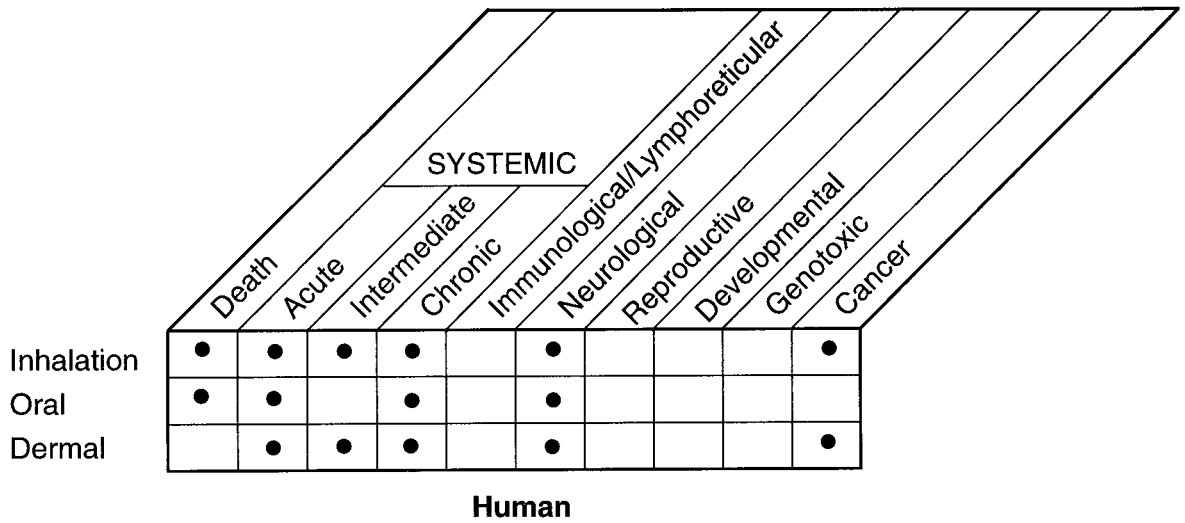
Information is available on acute, intermediate, and chronic systemic effects, as well as neurological and cancer effects, following inhalation exposure to fuel oils; death, acute systemic, and neurological effects following oral exposure to fuel oils; and acute, intermediate, and chronic systemic and 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.

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



● Existing Studies

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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 LD₅₀ 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

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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 α_{2u} -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.

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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.

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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

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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 of 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 Dermatitis (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

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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.

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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; Easley 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 LD₅₀ 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.

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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.