

**TOXICOLOGICAL PROFILE FOR
GASOLINE**

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry**

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DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for Gasoline was released on September 6, 1994. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and the Environmental Protection Agency (EPA) and in support of Department of Defense information needs. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, when known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are significant to protect public health will be identified by ATSDR and the EPA. The focus of the profiles is on health and toxicologic information; therefore, we have included this information in the beginning of the document.

Each profile must include the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects.
- (C) When appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that might present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). Section 211 of SARA also amended Title 10 of the U. S. Code, creating the Defense Environmental Restoration Program. Section 2704(a) of Title 10 of the U. S. Code directs the Secretary of Defense to notify the Secretary of Health and Human Services of not less than 25 of the most commonly found unregulated hazardous substances at defense facilities.

Section 2704(b) of Title 10 of the U. S. Code directs the Administrator of the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare a toxicological profile for each substance on the list provided by the Secretary of Defense under subsection (b).

Foreword

This profile reflects our assessment of all relevant toxicologic testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

- 1 . Green Border Review. Green Border review assures the consistency with ATSDR policy.
- 2 . Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying endpoints.
- 3 . Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.
- 4 . Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

PEER REVIEW

A peer review panel was assembled for gasoline. The panel consisted of the following members:

1. Dr. Carson Conaway, Research Scientist, Division of Pathology/Toxicology, American Health Foundation, Valhalla, New York
2. Dr. Carroll Snyder, Director, Laboratory of Inhalation Carcinogenicity and Toxicology, New York University, A.J. Lanza Laboratories, Tuxedo, New York
3. Dr. Charles Ward, Private Consultant, Pittsburgh, Pennsylvania

These experts collectively have knowledge of gasoline's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This statement was prepared to give you information about gasoline and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,397 sites on its National Priorities List (NPL). Gasoline has been found in at least 23 of these sites. However, we do not know how many of the 1,397 NPL sites have been evaluated for gasoline. As EPA evaluates more sites, the number of sites at which gasoline is found may change. This information is important for you to know because gasoline may cause harmful health effects and because these sites are potential or actual sources of human exposure to gasoline.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, may lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous chemical such as gasoline, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, lifestyle, and state of health.

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1.1 WHAT IS GASOLINE?

Gasoline is a complex manufactured mixture that does not exist naturally in the environment. However, for the most part, chemicals that are in gasoline are generally present in several physical states (gaseous, liquid, or others) in human settlements. Gasoline is produced from petroleum in the refining process. The gasoline discussed in this profile is automotive gasoline used as a fuel for engines in automobiles and other vehicles. Aviation gasoline and other types of fuels, such as diesel and jet fuels, fuel oils, and products that result when gasoline is burned, are not discussed in this profile. The ATSDR toxicological profiles on jet fuels, Otto Fuels II, and fuel oils have further information on other types of fuels.

Typically, gasoline contains more than 150 chemicals including small amounts of benzene, toluene, xylene, and sometimes lead. How the gasoline is made determines which chemicals are present in the gasoline mixture and how much of each is present. The actual composition varies with the source of the crude petroleum, the manufacturer, and the time of year.

Gasoline is a colorless, pale brown, or pink liquid. Gasoline is very flammable; it catches on fire quite easily, evaporates quickly, and forms explosive mixtures with air. Most people can begin to smell gasoline at 0.25 parts of gasoline per million parts of air (ppm). Gasoline may be present in the air, groundwater, and soil. Gasoline does not dissolve readily in water. However, some of the chemicals that make up gasoline can dissolve easily in water. See Chapter 3 for more information on the chemical and physical properties of gasoline and Chapter 4 for its production and use.

1.2 WHAT HAPPENS TO GASOLINE WHEN IT ENTERS THE ENVIRONMENT?

Gasoline is a mixture of many different chemicals. Small amounts of these chemicals evaporate into the air when you fill the gas tank in your car or when gasoline is accidentally spilled onto surfaces and soils or into surface waters. Other chemicals in gasoline dissolve in

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water after spills to surface waters or underground storage tank leaks into the groundwater. The movement of individual chemicals in gasoline is influenced by physical and chemical properties, such as how easily they dissolve in water, how quickly they evaporate, and whether they stick to soil. In surface releases, most chemicals in gasoline will probably evaporate; others may dissolve in and be carried away by water; a few will probably stick to soil. The chemicals that evaporate are broken down by sunlight and other chemicals in the air; the completion of this process may take from hours to weeks. The chemicals that dissolve in water also break down quickly by natural processes. Most chemicals in gasoline do not build up to high levels in plants or animals. For more information on what happens to gasoline when it enters the environment, see Chapter 5.

1.3 HOW MIGHT I BE EXPOSED TO GASOLINE?

The most likely way that you might be exposed to gasoline is by breathing its vapors at a service station when you are filling your car's fuel tank. If an attendant fills your car's fuel tank, you may still be exposed to vapors, but not as much as when you fill it yourself. If the hose from the gas tank leaks or you overfill your tank, you may be exposed to more gasoline vapors or some gasoline may spill on your skin. If you work at a service station, you will be exposed to more gasoline and its vapors than someone who just fills the car up occasionally. Air levels as high as 99 ppm were measured at one gas station during filling of a car's tank with gasoline. When you use equipment that runs on gasoline (for example, a lawn mower), you may be exposed to gasoline or its vapors when you fill the gas tank (especially when the engine is hot) or operate the machine.

You may also be exposed to gasoline if you use or drink contaminated water. However, most of the chemicals in gasoline are usually removed by purification processes before the water enters drinking water supplies. Gasoline can seep into groundwater from leaking underground pipelines or storage tanks. There is no information on how much gasoline may be in

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groundwater after a leak, but in some instances gasoline has been found floating on top of groundwater that is used to supply drinking water to homes. According to one estimate, as many as 75,000-100,000 underground storage tanks leak millions of gallons of gasoline into groundwater each year. Some of the chemicals making up the gasoline mix with the water; you would be exposed to these chemicals when you drink the water, bathe or shower with it, or otherwise use it.

Another way you might be exposed to gasoline or its vapors is by being close to a spot where gasoline has spilled or leaked into the soil. Information on the amount of gasoline that has seeped into the soil from spills, storage tanks, or pipelines is not available.

Certain workers have a greater risk of exposure to gasoline vapors. These include service station attendants, drivers of gasoline tank trucks, workers at bulk loading terminals and marine loading docks, workers who remove and service underground storage tanks and gasoline pipelines, workers who find and clean up gasoline spills and leaks, and refinery workers. If you have any of these jobs, you are probably exposed to small amounts of gasoline vapors every day you work. If you work at a job using gasoline-powered equipment or vehicles, you may be exposed to gasoline and its vapors. See Chapter 5 for more information on exposure to gasoline.

1.4 HOW CAN GASOLINE ENTER AND LEAVE MY BODY?

Gasoline can easily enter your body when you breathe in air or drink water that is contaminated with gasoline. No information is available on how much gasoline enters your body when it gets on your skin. When products like gasoline get on your skin, however, they enter your body more slowly than when they are taken into your mouth. Some of the chemicals in gasoline, such as benzene, are expected to penetrate the skin more easily than some of the other chemicals in gasoline. Most of the gasoline that you breathe in or swallow

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is breathed out unchanged, but some of it can enter your blood rapidly. Gasoline in your blood travels throughout your body. When the chemicals in gasoline reach your liver, they are changed into several different chemical substances. Most of these new substances travel in your blood until they reach your kidneys and then leave your body in urine. However, some of the new substances formed in the liver do not leave your body as rapidly.

Chapter 2 has more information on how gasoline enters and leaves your body.

1.5 HOW CAN GASOLINE AFFECT MY HEALTH?

Many of the harmful effects seen after exposure to gasoline are due to the individual chemicals in the gasoline mixture, such as benzene and lead in very small amounts. Inhaling or swallowing large amounts of gasoline can cause death. The levels of gasoline that killed people are about 10,000-20,000 ppm when breathed in and about 12 ounces when swallowed. High concentrations of gasoline are irritating to the lungs when breathed in and irritating to the lining of the stomach when swallowed. Gasoline is also a skin irritant. Breathing in high levels of gasoline for short periods of time or swallowing large amounts of gasoline may also cause harmful effects on the nervous system. These effects become more serious as the amount of gasoline breathed in or swallowed increases. Less serious nervous system effects include dizziness and headaches, while more serious effects include coma and the inability to breathe. Effects on the nervous system have also occurred in people exposed to gasoline vapors for long periods of time, either in their jobs or because they intentionally sniff gasoline for its ability to cause hallucinations. Harmful effects on the lungs can occur when a person swallows large amounts of gasoline because the gasoline in the stomach can enter the lungs during vomiting.

Some laboratory animals that breathed high concentrations of unleaded gasoline vapors continuously for 2 years developed liver and kidney tumors. However, there is no evidence that exposure to gasoline causes cancer in humans. There is not enough information available

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to determine if gasoline causes birth defects or affects reproduction. For more information on the health effects of gasoline, see Chapter 2 and the ATSDR toxicological profiles for benzene, toluene, xylene, ethylbenzene, 1,2-dibromoethane, 1,3-butadiene, and lead.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO GASOLINE?

There are laboratory tests that can determine if you have been exposed to gasoline. However, these tests are not generally available in your doctor's office. The tests involve measuring elevated blood or urine levels of lead (as an indication of exposure to leaded gasoline only), benzene, or other substances that may result from exposure to gasoline or other sources. These methods are sensitive enough to measure background levels and levels when health effects may occur. If you have these substances in your body, however, they may be there as the result of exposure from sources other than gasoline. Nevertheless, these tests are useful if exposure to gasoline is suspected. Refer to Chapters 2 and 6 for more information on tests to determine whether you have been exposed to gasoline. Also, for more information on the tests for measuring exposure to the individual components in gasoline, refer to the ATSDR toxicological profiles on lead, benzene, toluene, xylene, and ethylbenzene.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The government has developed regulations and guidelines for gasoline. EPA has established many regulations 'to control air pollution. These are designed to protect the public from the possible harmful health effects of gasoline. To protect workers, the Occupational Safety and Health Administration (OSHA) has set a legal limit of 300 ppm for workroom air.

The Occupational Safety and Health Administration (OSHA) regulates levels of gasoline in the workplace. The maximum amount of gasoline allowed in workroom air during an 8-hour

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workday of a 40-hour workweek is 900 milligrams of gasoline vapor per cubic meter of air (mg/m^3), or 300 ppm. However, this level is not intended to be used as a standard for pollutants outside the workplace. See Chapter 7 for more information on recommendations the federal government has made to protect human health from the effects of gasoline.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, Georgia 30333

This agency can also tell you where to find the nearest occupational and environmental health clinic. These clinics specialize in the recognition, evaluation, and treatment of illnesses resulting from exposure to hazardous substances.

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 on the toxicology of gasoline 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 gasoline 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

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

Levels of exposure associated with the carcinogenic effects of gasoline are indicated in Table 2-1 and Figure 2- 1.

This chapter discusses the health effects associated with exposure to automotive gasoline. Please see the ATSDR toxicological profiles on jet fuels, Otto fuels II, and fuel oils (ATSDR 1992) for further information on other types of fuels. Furthermore, this chapter will focus on the health effects associated with exposure to the gasoline mixture, and not the individual components of gasoline. For more information on the health effects associated with exposure to specific components of the gasoline mixture, please refer to the ATSDR toxicological profiles on 1,3-butadiene, benzene, 1,2-dibromoethane, ethylbenzene, lead, toluene, and xylene (ATSDR 1989, 1990, 1991). In addition, this profile will not discuss the health effects associated with exposure to automotive gasoline exhaust or combustion products of gasoline because these products contain other substances that are not constituents of gasoline itself.

Gasoline is a complex, highly variable mixture consisting of several hundred hydrocarbons that have boiling points from approximately 40°C to 180°C (Mehlman 1990). The hydrocarbons present in the gasoline mixture include alkanes, or straight-chain C₄ to C₁₂ compounds also known as paraffins, isoparaffins, or branched-chain compounds of the same size; alkenes, or olefins, which are unsaturated linear and branched-chain hydrocarbons; and naphthenics, or saturated cyclic hydrocarbons. Also included in the gasoline are aromatic compounds (principally benzene, toluene, ethylbenzene, and xylene). Tetraethyl and tetramethyl lead are being phased out of gasoline (Mehlman 1990). Many of the toxicological effects associated with exposure to gasoline can be attributed to specific components of the mixture (i.e., organic lead compounds, benzene). For the majority of the studies discussed in this chapter, the exact composition of the gasoline mixture used was not specified. For those studies in which the composition of the test mixture was indicated, the percentages of the components are

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presented in the text when the study is discussed. Many studies (i.e., those sponsored by the American Petroleum Institute [API]) used a gasoline test mixture formulated by API in 1982 known as API PS-6. Compositional data are available for the mixture formulated in 1982, but the percentages of the formulation are probably atypical because of the large content of paraffinic blending stock: 12.3% n-paraffins, 47.4% isoparaffins, 3.1% cyclopentanes, 14.5% cyclohexanes, 6.4% olefins, 28.7% aromatics (benzene-adjusted 2.0%), 11.5% unclassified hydrocarbons (Anonymous 1989). Another composition (expressed as volume percent) given for API PS-6 is as follows: 11.4% n-paraffins, 46.5% isoparaffins, 4.7% cycloparaffins, 9.0% mono-olefins, 28.4% aromatics (Domask 1984). The API PS-6 used in the chronic study conducted by MacFarland et al. (1984) had the same composition as the one used by Domask (1984), but the benzene content of this mixture was specified as 1.69%. A more recent blend of gasoline, API 91-1, has been reported to contain a greater percentage of aromatics (33.2%) and olefins (12.5%) and a lower percentage of saturated hydrocarbons than the API PS-6 blend (Standeven and Goldsworthy 1993).

Details regarding experimental protocol for most of the studies discussed in this section are presented in Tables 2-1, 2-2, and 2-3, and are generally not reiterated in the text.

2.2.1 Inhalation Exposure

2.2.1.1 Death

Several case reports of either accidental or intentional inhalation of gasoline vapors resulting in death have been published (Ainsworth 1960; Boeckx et al. 1977; Poklis 1976; Wang and Irons 1961). Inhalation of $\geq 5,000$ ppm gasoline vapor (20,000 ppm for 5 minutes) has been shown to be lethal (Ainsworth 1960; Wang and Irons 1961). It has been postulated that the cause of death following inhalation of high concentrations of gasoline vapors is either central nervous system depression due to asphyxia leading to respiratory failure, or cardiac sensitization to circulating catecholamines leading to a fatal arrhythmia (Poklis 1976).

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Acute median lethal concentrations (LC₅₀s) of gasoline vapor have not been established in experimental animals. Intermediate-duration exposure (90 days) to up to 1,552 ppm unleaded gasoline vapor was not lethal to rats or monkeys (Kuna and Ulrich 1984), and exposure to up to 2,056 ppm unleaded gasoline vapors for 2 years was not lethal to rats or mice (MacFarland et al. 1984).

The highest NOAEL values for death in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects for each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. Adverse respiratory effects were described in one case report of inhalation of gasoline vapors that resulted in death (Ainsworth 1960). In this case, a 3-year-old boy was found with his head lying in a pool of gasoline, and he died shortly thereafter. Autopsy revealed pulmonary congestion, edema, and intrapulmonary hemorrhage. Hyperemia was evident in the tracheal and bronchial mucosa, and there was hemorrhagic fluid in the bronchi. Intraalveolar hemorrhage and alveolar necrosis were seen upon histopathological evaluation. According to the report, these effects were the result of inhalation of gasoline fumes. No gasoline was found in the stomach, and there was no evidence of oral or pharyngeal mucosal damage, thus ruling out the possibility that the lung damage was due to aspiration of ingested gasoline.

Information on the acute respiratory effects of gasoline inhalation in experimental animals is limited to one study in which rats were exposed to 0.1 mL gasoline in a closed container either once or intermittently for 5-7 days. In both exposure scenarios, widespread hemorrhage of the lungs was noted at necropsy (O'Regan and Turgeon 1986). This study is not included in Table 2-1 because the unusual exposure conditions precluded quantification of the exposure levels; however, this study does provide qualitative evidence of lung damage resulting from acute-duration exposure to gasoline vapors.

TABLE 2-1. Levels of Significant Exposure to Automotive Gasoline - Inhalation

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference/ Chemical form
					Less serious (ppm)	Serious (ppm)	
ACUTE EXPOSURE							
Systemic							
1	Rabbit NS	2 hr	Cardio		70,180	(ECG disturbances, decreased heart rate; decreased myocardial acid phosphatase, sodium, potassium and magnesium; altered myocardial ATPase activity)	Przybylowski 1971 leaded
Neurological							
2	Rabbit NS	2 hr once				70,180 NS (convulsions, restlessness, narcosis)	Przybylowski 1971 leaded
Developmental							
3	Rat CD (SD) BR	10d Gd 6-15 6hr/d		1600			Litton Bionetics 1978 unleaded

2. HEALTH EFFECTS

TABLE 2-1. Levels of Significant Exposure to Automotive Gasoline - Inhalation (continued)

Key to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference/ Chemical form
					Less serious (ppm)	Serious (ppm)	
INTERMEDIATE EXPOSURE							
4	Monkey Squirrel	90 d 5d/wk 6hr/d	Resp	1552			Kuna and Ulrich 1984 unleaded
			Cardio	1552			
			Hemato	1552			
			Hepatic	1552			
			Renal	1552			
			Endocr	1552			
			Bd wt	1552			
5	Rat Sprague-Dawley	90 d 6hr/d 5d/wk	Cardio	3866			Halder et al. 1984 unleaded
			Hemato	3866			
			Hepatic	3866			
			Renal	40 M 3866 F	379 M	(renal tubular dilation and necrosis)	
			Endocr	3866			
			Bd wt	3866			

TABLE 2-1. Levels of Significant Exposure to Automotive Gasoline - Inhalation (continued)

Key to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference/ Chemical form
					Less serious (ppm)	Serious (ppm)	
6	Rat Sprague-Dawley	21 d 5d/wk 6hr/d	Cardio	3316			Halder et al. 1984
			Hemato	3316	29 M (mild tubular degenerative and regenerative changes with hyaline droplets)	unleaded	
			Hepatic	3316			
			Renal	3316 F			
	Endocr Bd wt	3316 3316					
7	Rat Sprague-Dawley	90 d 5d/wk 6hr/d	Resp	1552			Kuna and Ulrich 1984
					384 M (regenerated epithelium; dilated tubules)	unleaded	
			Cardio	1552			
			Hemato	1552			
	Hepatic	1552					
	Renal	1552 F					
	Endocrine	1552					
	Body wt	1552					
8	Rat Wistar	5-45 d 8hr/d 5d/wk	Resp		100 F (decreased levels of surfactant)		Le Mesurier et al. 1979
						leaded	
9	Rat NS	12 wk 5d/wk 8hr/d	Resp			100 F (respiratory distress; fibrosis; alveolar collapse)	Lykke et al. 1979
						leaded	

TABLE 2-1. Levels of Significant Exposure to Automotive Gasoline - Inhalation (continued)

Key to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference/ Chemical form
					Less serious (ppm)	Serious (ppm)	
10	Rat F344	3 wk 5d/wk 6hr/d	Renal	20 M	200 M	(hyperplasia; necrosis of proximal tubular cells)	Short et al. 1987 unleaded
11	Rat Sprague-Dawley	3-50 wk 5d/wk 6hr/d	Renal	300 F	10 M	α 2 μ -globulin	Short et al. 1989a unleaded
12	Mouse B6C3F ₁	13 wk 5d/wk 6hr/d	Hepatic	300 F	2039 F	(increase liver weight, microsomal enzyme induction, hypertrophy)	Standeven and Goldsworthy 1993 unleaded
13	Mouse B6C3F ₁	16 wk 5d/wk 6hr/d	Hepatic	292 F	2056 F	(increase liver weight, hypertrophy, increase sorbitol dehydrogenase)	Standeven et al. 1994a unleaded
14	Mouse B6C3F ₁	13 wk 5d/wk 6 hr/d	Hepatic	292F	2056 F	(increase liver weight, hepatocyte cell proliferation)	Tilbury et al. 1993 unleaded
15	Immuno/Lymphoret Monkey Squirrel	90 d 5d/wk 6hr/d		1552			Kuna and Ulrich 1984 unleaded
16	Rat Sprague-Dawley	90 d 5d/wk 6hr/d		1552			Kuna and Ulrich 1984 unleaded

TABLE 2-1. Levels of Significant Exposure to Automotive Gasoline - Inhalation (continued)

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference/ Chemical form
					Less serious (ppm)	Serious (ppm)	
Neurological							
17	Monkey Squirrel	90 d 5d/wk 6hr/d		1552			Kuna and Ulrich 1984 unleaded
18	Rat Sprague- Dawley	90 d 5d/wk 6hr/d		1552			Kuna and Ulrich 1984 unleaded
Reproductive							
19	Mouse CD-1	8 wk 5d/wk 6hr/d		1600 M			Litton Bionetics 1980 unleaded
20	Mouse B6C3F ₁	16 wk 5d/wk 6hr/d		2056 F			Standeven et al. 1994a unleaded
Cancer							
21	Rat F344	24 wk 5d/wk 6hr/d				300 M (CEL-renal cell adenomas)	Short et al. 1989b unleaded
22	Mouse CrBr	13 wk 5d/wk 6 hr/d				2039 F (promotion of preneoplastic hepatic foci)	Standeven and Goldsworthy 1993 unleaded

TABLE 2-1. Levels of Significant Exposure to Automotive Gasoline - Inhalation (continued)

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference/ Chemical form
					Less serious (ppm)	Serious (ppm)	
23	Mouse B6C3F ₁	16 wk 5d/wk 6hr/d				2056 F (promotion of preneoplastic altered hepatic foci)	Standeven et al. 1994a unleaded

TABLE 2-1. Levels of Significant Exposure to Automotive Gasoline - Inhalation (continued)

Key to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference/ Chemical form
					Less serious (ppm)	Serious (ppm)	
CHRONIC EXPOSURE							
Systemic							
24	Rat F344	107-109 wk 5d/wk 6hr/d	Resp	292 F	2056 F	(mild multifocal pulmonary inflammatory response)	MacFarland et al. 1984 unleaded
			Resp	2056 M			
			Cardio	2056			
			Gastro	2056			
			Hemato	2056			
			Musc/skel	2056			
			Hepatic	2056			
			Renal	2056 F	67 M	(nephropathy)	
			Dermal	2056			
			Bd wt	292	2056	(decreased body weight gain)	
25	Mouse B6C3F ₁	103-113 wk 5d/wk 6hr/d	Resp	2056			MacFarland et al. 1984 unleaded
			Cardio	2056			
			Gastro	2056			
			Hemato	2056			
			Musc/skel	2056			
			Hepatic	2056			
			Renal	2056			
			Dermal	2056			
			Body wt	292 M	2056 M	(decreased body weight)	
				2056 F			

TABLE 2-1. Levels of Significant Exposure to Automotive Gasoline - Inhalation (continued)

Key to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference/ Chemical form
					Less serious (ppm)	Serious (ppm)	
Immuno/Lymphoret							
26	Rat F344	107-109 wk 5d/wk 6hr/d		2056			MacFarland et al. 1984 unleaded
27	Mouse B6C3F ₁	103-113 wk 5d/wk 6hr/d		2056			MacFarland et al. 1984 unleaded
Neurological							
28	Rat F344	107-109 wk 5d/wk 6hr/d		2056			MacFarland et al. 1984 unleaded
29	Mouse B6C3F ₁	103-113wk 5d/wk 6hr/d		2056			MacFarland et al. 1984 unleaded
Reproductive							
30	Rat	107-109 wk 5d/wk 6hr/d		2056			MacFarland et al. 1984 unleaded
31	Mouse B6C3F ₁	103-113wk 5d/wk 6hr/d		2056			MacFarland et al. 1984 unleaded

TABLE 2-1. Levels of Significant Exposure to Automotive Gasoline - Inhalation (continued)

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference/ Chemical form
					Less serious (ppm)	Serious (ppm)	
32	Mouse B6C3F ₁	103-113 wk 5d/wk 6hr/d		2056 F			MacGregor et al. 1993 unleaded
	Cancer						
33	Rat F344	107-109 wk 5d/wk 6hr/d				292	(CEL renal adenomas, carcinomas, and sarcomas) MacFarland et al. 1984 unleaded
34	Mouse B6C3F ₁	103-113wk 5d/wk 6hr/d				2056 F	(CEL hepatocellular adenomas, and carcinomas) MacFarland et al. 1984 unleaded

^aThe number corresponds to entries in Figure 2-1.

Bd wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); ECG = electrocardiogram; Endor = endocrine; F = female(s); Gastro = gastrointestinal; Gd = gestation day; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = time(s)

Figure 2-1. Levels of Significant Exposure to Automotive Gasoline – Inhalation

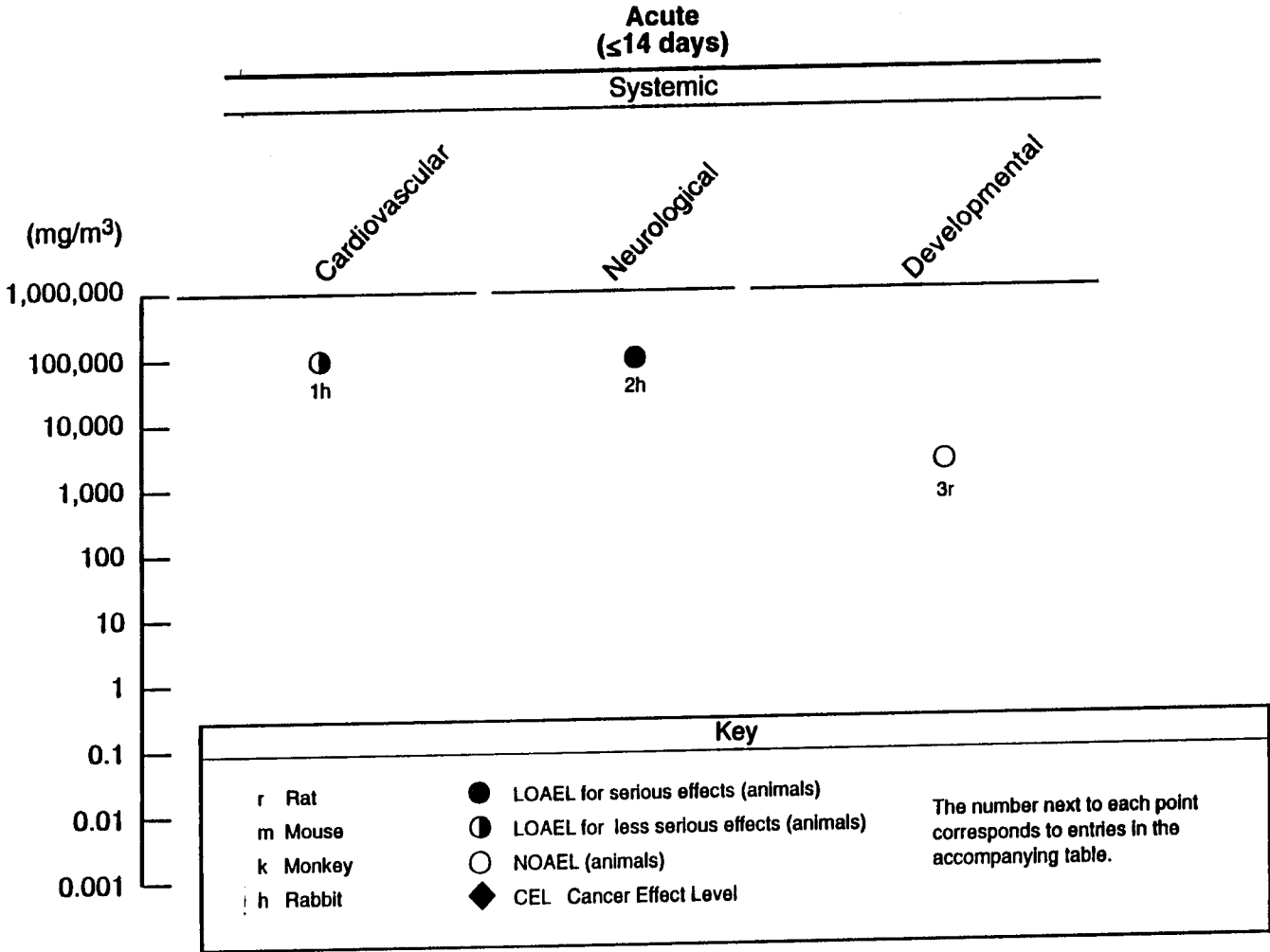


Figure 2-1. Levels of Significant Exposure to Automotive Gasoline – Inhalation (continued)

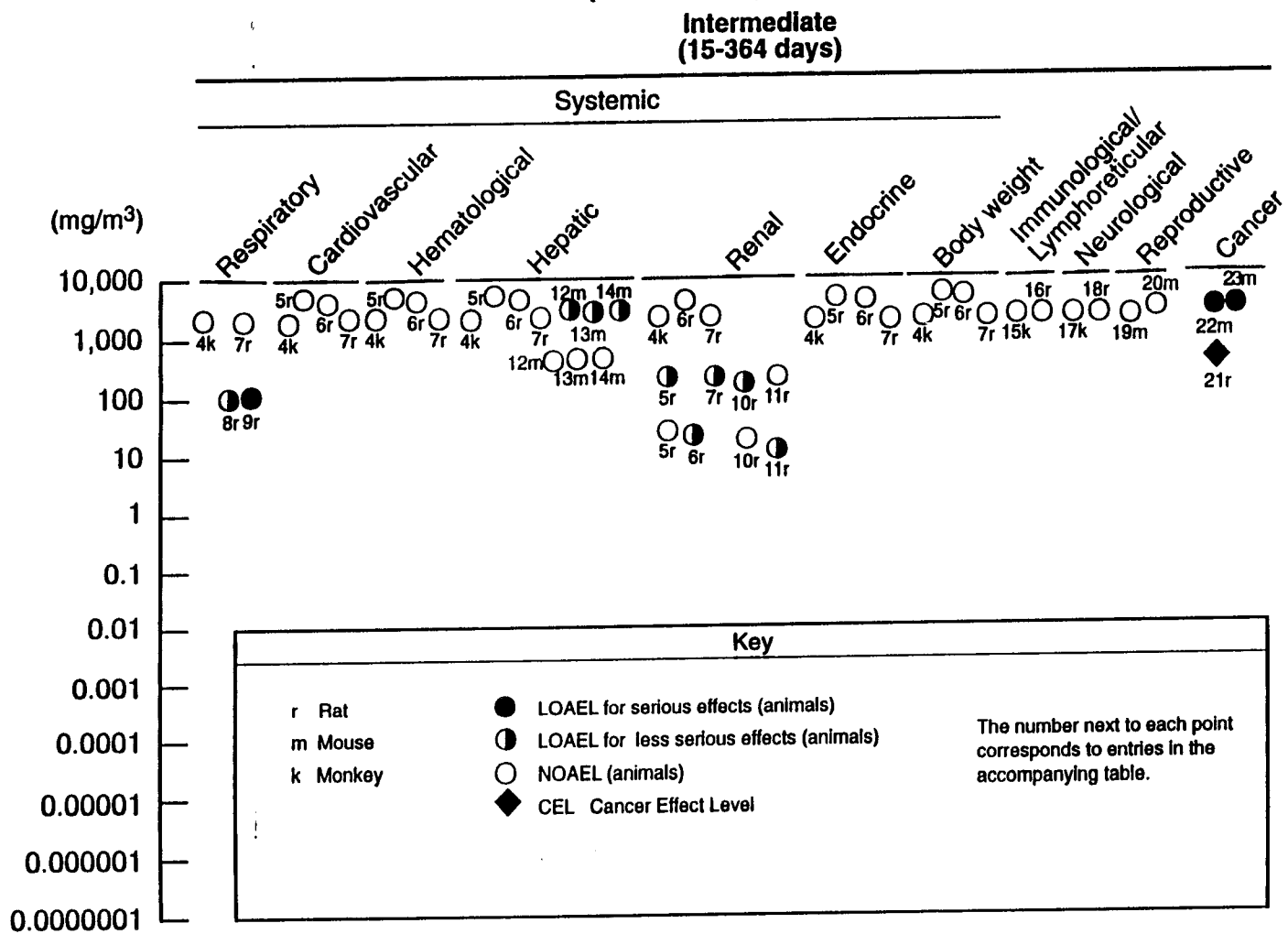
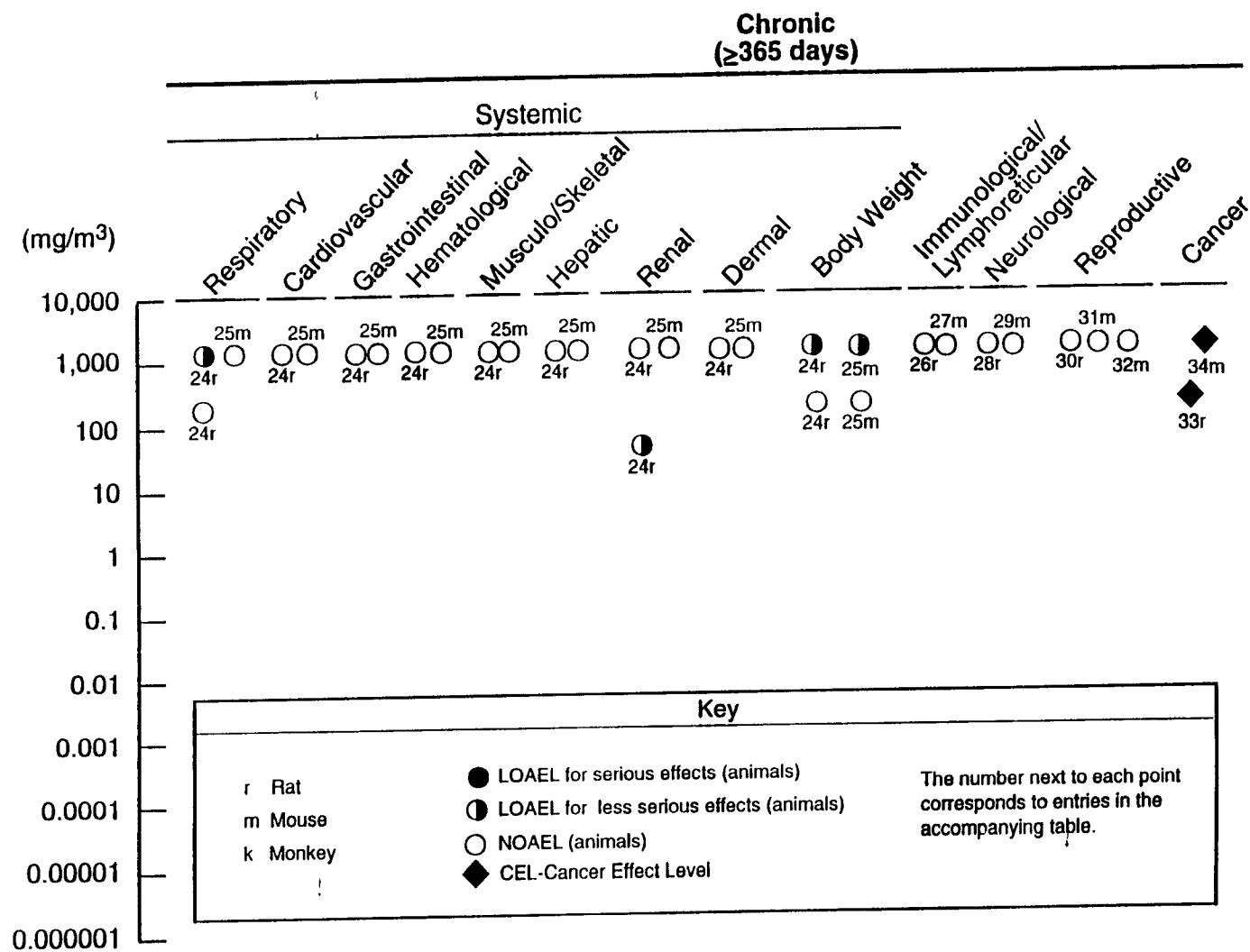


Figure 2-1. Levels of Significant Exposure to Automotive Gasoline – Inhalation (continued)



2. HEALTH EFFECTS

Intermediate-duration exposure of rats to approximately 453 ppm gasoline vapors resulted in an increase in the relative weight of the lungs in animals sacrificed after 30 days of exposure. This effect was no longer apparent in animals sacrificed after 60 days of exposure (Vyskocil et al. 1988). No biochemical, functional, or histopathological evidence of adverse respiratory effects was reported in this study, so the toxicological significance of the change in organ weight is not known. Rats and monkeys failed to exhibit any consistent adverse respiratory effects following intermediate-duration exposure to 1,552 ppm gasoline vapors (Kuna and Ulrich 1984). Although various parameters of pulmonary function were significantly altered in monkeys exposed to 1,552 ppm gasoline vapors as compared to the controls in this study, there was a lack of consistency with respect to the effects observed between the sexes, and there was a large degree of variability in the responses. Therefore, the evidence is insufficient to conclude that these changes in pulmonary function were treatment related. When the lungs of rats exposed to 100 ppm of gasoline vapors for 12 weeks were examined by electron microscopy, a progression of lesions characteristic of fibrosing alveolitis (interstitial fibrosis and alveolar collapse) was observed (Lykke et al. 1979). These lesions were not apparent at the light microscopic level. The animals began to exhibit signs of respiratory distress in this study after about 7 weeks of exposure, which is consistent with the alveolar collapse seen. Also, consistent with these findings was the observation that surfactant levels in the lung were markedly decreased in animals exposed to 100 ppm gasoline vapors for 5-15 days (Le Mesurier et al. 1979). This observation led the authors to suggest that the surfactant deficiency was probably involved in the pathogenesis of the fibrosing alveolitis observed in the Lykke et al. (1979) study. The results of these two studies indicate that gasoline-induced pulmonary changes may occur at levels previously thought to cause no effect because the tissues were not examined ultrastructurally and/or other sensitive parameters of pulmonary function were not measured.

Chronic exposure of female rats to 2,056 ppm gasoline vapors for 2 years resulted in an increase in the incidence of mild multifocal pulmonary inflammatory response (compared to respective controls) that was thought to be due to the irritant effect of gasoline (MacFarland et al. 1984). Although the incidence of the pulmonary response was slightly increased in male rats exposed to 292 or 2,056 ppm, the increase was not dose-related, and the incidence was comparable to those of female control rats. This effect was not observed in mice similarly exposed (MacFarland et al. 1984), suggesting that rats are more susceptible to the pulmonary irritating effects of gasoline.

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Cardiovascular Effects. Cardiac sensitization to circulating catecholamines leading to a fatal arrhythmia has been postulated as one possible cause of death in humans following inhalation of high concentrations of gasoline vapors (Poklis 1976). Abnormal electrocardiograms (ECGs) of a nonspecific nature have been recorded in individuals with a history of chronic leaded gasoline sniffing (Seshia et al. 1978).

A single 2-hour exposure to 70,180 ppm leaded gasoline vapors was reported to induce ECG changes and disturbances in myocardial enzyme activities and electrolyte levels in rabbits (Przybylowski 1971). The ECG readings were taken from the animals prior to exposure while they were anesthetized with evipran and again “immediately after intoxication” (elapsed time not specified). Exposure to leaded gasoline vapor resulted in a slowing of heart rate in all exposed animals and evidence of disturbed ventricular repolarization such as flattening of the T-wave (10/20), inverted T-wave (7/20), biphasic T-wave (3/20), ST depression (10/20), prolongation of the QT interval (16/20), and prolongation of the QRS complex (7/20). Decreased myocardial acid phosphatase, decreased myocardial sodium, potassium, and magnesium levels, and altered acid phosphatase and ATPase (adenosinetriphosphatase) activity in the myocardium were also observed. A decrease seen in myocardial alkaline phosphatase was not statistically significant. The author concluded that the decreased heart rate was a centrally mediated effect. He also concluded that the prolongation of the QRS complex, which is indicative of disturbed intracellular conduction, was a result of a direct effect on the myocardial electrical conduction system, and that the disturbed ventricular repolarization suggested by the ECG changes may have resulted in myocardial electrolyte disturbances (i.e., the changes in sodium, potassium, and magnesium observed). Furthermore, various enzyme activities also appear to be affected by exposure to gasoline vapor. While these conclusions appear valid, there are a number of limitations associated with this study. Only one exposure level was tested, precluding the determination of a dose-response relationship. The effects observed may have been due to oxygen deprivation because the gasoline vapor concentration was so high (approximately 7%). Therefore, a control group exposed to comparably low levels of oxygen would have been appropriate. The baseline ECGs were done on anesthetized animals, and the postexposure ECGs were done on animals that were apparently in a “narcotic sleep.” It is difficult to compare the ECGs obtained under these different conditions. Furthermore, although the authors state that the ECGs were done “immediately after exposure,” the

2. HEALTH EFFECTS

time between exposure and the ECGs was not quantified, and the animals could have been in various stages of recovery from any effects that occurred during exposure. It is possible that the cardiovascular effects may have been due to lead in the gasoline mixture since no cardiovascular effects have been observed in animals exposed to unleaded gasoline vapor (discussed in next paragraph).

No changes in heart weight or in the microscopic anatomy of the heart were observed in rats or monkeys exposed to up to 1,552 ppm unleaded gasoline vapors for 90 days (Kuna and Ulrich 1984). Similarly, rats and mice exposed to 2,056 ppm unleaded gasoline vapors for 2 years exhibited no exposure-related cardiovascular effects (MacFarland et al. 1984). A decrease in relative heart weight was observed in the rats from this chronic study, but in the absence of any biochemical, functional, or histopathological evidence of cardiovascular toxicity, the toxicological significance of a change in heart weight is not known.

Gastrointestinal Effects. No effects on the gastrointestinal system were observed in humans after inhalation exposure to gasoline (Ainsworth 1960; Carlson 1981).

One study in experimental animals was located in which the gastrointestinal tract was examined after inhalation exposure to gasoline vapors. No evidence of adverse effects was found upon histopathological evaluation of the gastrointestinal tract of rats and mice exposed to 2,056 ppm unleaded gasoline vapors for 2 years (MacFarland et al. 1984).

Hematological Effects. Several human case studies have been reported that describe the occurrence of hematological effects in individuals with known long-term exposure to gasoline vapors. However, in all of these cases, the hematological effects reported were most likely due to a constituent of gasoline rather than the gasoline mixture itself. For example, basophilic stippling, increased erythrocyte protoporphyrin, and increased δ -aminolevulinic acid dehydratase (ALAD) activity have been noted in individuals exposed to leaded gasoline vapor (Boeckx et al. 1977; Chessare and Wodarczyk 1988; Young et al. 1977). These effects are also known to occur with exposure to lead (see ATSDR toxicological profile for lead [ATSDR 1991]), and so may be due to the presence of organic

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lead compounds in the gasoline. An increased incidence of various blood dyscrasias (anemia, hypochromia, thrombocytopenia, and neutropenia) has been observed in Nigerian males with known exposure to gasoline in their occupations as motor mechanics and road-side vendors of heavy motor oil and/or gasoline as compared to controls with no known exposure to gasoline (Niazi et al. 1989). The authors attributed the increased incidence of these disorders to benzene which is present in gasoline (see ATSDR toxicological profile for benzene [ATSDR 1991]).

No exposure-related adverse effects on any hematological parameters measured or on the bone marrow have been noted in rats or monkeys exposed to 1,552 ppm unleaded gasoline vapors for 90 days (Kuna and Ulrich 1984) or in rats and mice exposed to 2,056 ppm unleaded gasoline vapors for 2 years, despite the presence of benzene (MacFarland et al. 1984).

Musculoskeletal Effects. An 18-year-old male with a history of sniffing leaded gasoline vapors was admitted to the hospital on two occasions complaining of muscle weakness and pain (Kovanen et al. 1983). He claimed to sniff 1-1.5 L at a time irregularly over the past year. Neurological examinations were normal on both hospital admissions, but his serum creatinine kinase was markedly elevated, and his urine was positive for myoglobin. Furthermore, his blood and urine lead levels were also elevated. The authors concluded that the boy suffered from acute severe myopathy associated with leaded gasoline sniffing. The mechanism by which gasoline could have induced this myopathy is not known. The authors speculated that the myopathy may have been due to individual susceptibility or that the patient may have had a subclinical, possibly metabolic, myopathy that was exacerbated by gasoline sniffing. The myopathy may also have been the result of lead toxicity (see ATSDR toxicological profile for lead [ATSDR 1991]).

No exposure-related effects were noted upon histopathologic examination of the bones in rats or mice exposed to 2,056 ppm unleaded gasoline vapors for 2 years (MacFarland et al. 1984).

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Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to gasoline.

No adverse hepatic effects were noted in rats or monkeys exposed to 1,552 ppm unleaded gasoline vapors for 90 days (Kuna and Ulrich 1984) or in rats exposed to 2,056 ppm unleaded gasoline vapors for 2 years (MacFarland et al. 1984). Hepatic hypertrophy and increased hepatic cytochrome P-450 content were observed in mice exposed to 2,039 ppm unleaded gasoline vapor for 13 weeks; however, there was no evidence of hepatic necrosis (Standeven and Goldsworthy 1993). Hepatic hypertrophy without accompanying necrosis was also noted in mice exposed to 2,056 ppm for 13 or 16 weeks (Standeven et al. 1994a; Tilbury et al. 1993). Mice chronically exposed to unleaded gasoline vapors exhibited necrosis and hemorrhage associated with liver tumors (see Section 2.2.1.8), but no other exposure-related hepatic effects were seen (MacFarland et al. 1984).

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to gasoline.

Unleaded gasoline is one of a diverse group of hydrocarbons that have been shown to induce a unique syndrome of nephropathy in male rats following subchronic or chronic inhalation exposure (Halder et al. 1984; Kuna and Ulrich 1984; MacFarland et al. 1984; Short et al. 1987, 1989a, 1989b). The components of gasoline determined to be largely responsible for the hydrocarbon-induced nephropathy in the male rat were identified as branched alkane compounds with six or more carbons. The gasoline used in the studies conducted by Halder et al. had the following composition: 45% alkanes, 12% alkenes, 43% aromatics. The mixture used by MacFarland et al. (1984) and in the studies conducted by Short et al. (1987, 1989a, 1989b) was the API PS-6 specified in the introduction to this chapter. Kuna and Ulrich (1984) used two mixtures of gasoline: "Fuel A - Unleaded EPA Reference Fuel" and "Fuel B - Leaded Commercial." Fuel A contained 30.1% aromatics, 8.2% olefins, and 61.7% saturates. Fuel A was further described as containing 0.2% benzene, 16.7% toluene, 1.0% n-butane, 5.4% isopentane, and 4.8% n-pentane. Fuel B contained 27.4% aromatics, 7.8% olefins, and 64.4% saturates with 0.4% benzene, 11.4% toluene, 0.4% n-butane, 5.5% isopentane, and 4.0% n-pentane. The lead content of Fuel B was not specified, but the concentrations of lead in the two

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exposure levels of Fuel B used in the study were 0.19 μg lead/L at the 384-ppm level and 0.72 μg lead/L at the 1,552-ppm level.

This syndrome of nephropathy is characterized by excessive accumulation of hyaline droplets containing $\alpha_{2\text{u}}$ -globulin in the P2 segment of the proximal tubule region. The accumulation of these droplets may lead to single-cell necrosis and exfoliation of P2 tubular epithelial cells, followed by tubular epithelial cellular proliferation which is often associated with tubular dilation and tubular epithelial necrosis. In addition to inducing this syndrome in young male rats, gasoline has been shown to exacerbate the rat nephropathy commonly seen in aging male rats (MacFarland et al. 1984; Short et al. 1989a). $\alpha_{2\text{u}}$ -Globulin is produced in large amounts by male rats, accounting for 26% of their total urinary protein. There is no evidence that humans produce $\alpha_{2\text{u}}$ -globulin. In addition, human urine contains relatively little protein: only 1% of the total concentration measured in male rats. Of this amount, only trace quantities are within the same protein family as $\alpha_{2\text{u}}$ -globulin (Olson et al. 1990). This suggests that humans are probably not at risk for the type of nephropathy induced by gasoline in male rats. In addition, $\alpha_{2\text{u}}$ -globulin-induced nephropathy cannot be induced in female rats (Halder et al. 1984; Kuna and Ulrich 1984; Short et al. 1989a), mice of either sex (MacFarland et al. 1984), or monkeys of either sex (Kuna and Ulrich 1984). Thus, it appears to be unique to male rats. Therefore, even though these nephrotoxic effects were seen at exposure levels that are lower than those required to induce other toxic effects, this end point was not used for the derivation of an acute, intermediate, or chronic inhalation MRL for gasoline.

Endocrine Effects. No studies were located regarding endocrine effects in humans after inhalation exposure to gasoline.

A decrease in relative adrenal weight was noted in rats following intermediate-duration exposure to gasoline vapors, but no exposure-related histopathological effects were observed in the adrenal gland (Kuna and Ulrich 1984). Therefore, the toxicological significance of this change in adrenal weight is not known.

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

No exposure-related effects on the skin were observed in rats or mice exposed to 2,056 ppm unleaded gasoline for 2 years (MacFarland et al. 1984).

Ocular Effects. Gasoline vapor at concentrations of about 200, 500, or 1,000 ppm caused eye irritation in volunteers during a 30-minute exposure period (Davis et al. 1960). Ocular irritation was also noted in subjects exposed to 500 ppm for 1 hour (Drinker et al. 1943). Both the Drinker et al. 1943 and the Davis et al. 1960 studies are limited in that the subjects were exposed to atomized gasoline vapors, which has the same composition as liquid gasoline and is not the same as the gasoline vapors that humans would be exposed to in ambient conditions.

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

Body Weight Effects. No studies were located regarding body weight effects in humans after inhalation exposure to gasoline.

Intermediate- and chronic-duration exposures to gasoline vapors have been reported to cause significant decreases in body weight gain in rats (MacFarland et al. 1984; Vyskocil et al. 1988) and mice (MacFarland et al. 1984).

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans after inhalation exposure to gasoline.

In animals, exposure to hydrocarbons has been associated with Goodpasture's syndrome (glomerulonephritis and pulmonary hemorrhage caused by the binding of circulating autoantibodies to basement membrane antigens on the glomerular and alveolar basement membranes, respectively)

2. HEALTH EFFECTS

(O'Regan and Turgeon 1986; Yamamoto and Wilson 1987). To determine whether gasoline exposure causes pulmonary alveolar damage thereby allowing autoantibodies to pass into the alveoli and bind to lung basement membrane, rats were exposed in a closed container to unleaded gasoline once or 5-7 times daily at half-hour intervals for 5-8 days (O'Regan and Turgeon 1986). The animals were then injected with sera containing anti-glomerular basement membrane (anti-GBM) antibodies, sacrificed, and the lungs were taken for light and immunofluorescence microscopy. The anti-GBM failed to bind to alveolar basement membrane (ABM) in the gasoline-exposed animals as determined by immunofluorescence. Based on these results, it does not appear that exposure to gasoline in this manner damages the alveolar endothelium to allow passage of anti-GBM to cause the pulmonary hemorrhage associated with Goodpasture's syndrome.

Rats and monkeys exposed to up to 1,552 ppm gasoline for 90 days were evaluated for the presence and deposition of IgG, a class of immunoglobulin, in the renal glomeruli and lungs (Kuna and Ulrich 1984). There was no evidence of IgG deposition in either the renal glomeruli or the lungs in the exposed animals based on immunofluorescence studies.

No evidence of adverse histopathological effects was noted in the thymus or the bone marrow of rats or mice exposed to 2,056 ppm gasoline vapors for 2 years (MacFarland et al. 1984).

The highest NOAEL values and all reliable LOAEL values for immunological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.4 Neurological Effects

Acute exposure of humans to high levels of gasoline vapors is characterized by a spectrum of neurological effects that progress in severity with increasing dose and duration and can include dizziness, headaches, giddiness, euphoria, vertigo, blurred vision, nausea, numbness, drowsiness, anesthesia, and coma (Poklis and Burkett 1977). Chronic exposure to gasoline (i.e., in those individuals who habitually sniff gasoline for its euphoric/hallucinogenic effects and in those occupationally exposed to gasoline) is associated with neurological effects as well.

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In a 2-year retrospective study, hospital records on 40 male and 10 female patients of Native American or Native Canadian origin who sniffed gasoline indicated that exposed individuals exhibited signs of jaw jerk, postural tremor, ataxia, abnormal gait, deep tendon reflexes, and affected speech (Seshia et al. 1978). A study of 51 gasoline station workers reported complaints of headaches, fatigue, sleep problems, memory loss, and general weakness (Pandya et al. 1975). The benzene content of the gasoline was high; values ranged from 10-17%. Therefore, it is difficult to determine the contribution of benzene exposure to the reported symptoms. Gasoline odors were detected periodically by office workers for several years but increased during a 9-month period in which headaches and nausea were reported by 18 individuals (Kullman and Hill 1990). Measurements (unspecified method) that were made on a day when gasoline odors were present indicated total hydrocarbon concentrations of approximately 3-22 ppm. These studies lacked adequate details on the exposure duration and concentrations. Furthermore, the investigators did not assess the contribution of other constituents of gasoline (e.g., lead, benzene) as a potential source of the neurotoxic effects.

The majority of the data on the neurological effects of gasoline have come from case reports describing patients, usually adolescents, who were chronic gasoline sniffers (Owens et al. 1985). In most instances, the exposure concentrations could not be determined and the lead content in the gasoline was not specified. Cerebellar dysfunction (e.g., ataxia, poor coordination, decreased muscle tone, broad-based gait, myoclonic movements), generalized convulsions, and hallucinations, as well as elevated blood lead levels, are typical symptoms observed in gasoline sniffers (Carroll and Abel 1973; Coulehan et al. 1983; Goldings and Stewart 1982; Goodheart and Dunne 1994; Kaelan et al. 1986; Moss and Cooper 1986; Rischbieth et al. 1987; Young et al. 1977). Some exposed individuals were also found to have abnormal electroencephalograms (EEG) and/or slowing of nerve conduction velocity (Goldings and Stewart 1982; Hall et al. 1986; Hansen and Sharp 1978; Rischbieth et al. 1987; Robinson 1978; Seshia et al. 1978). A 14 year-old male who inhaled gasoline 10-20 times a day complained of a loss of strength and paresthesia in the limbs. Motor nerve conduction velocity was slowed on his right side, and Wallerian degeneration and segmental demyelination were reported (Gallassi et al. 1980). Neuropathological changes reported in eight patients who were diagnosed as "chronic gasoline sniffers" included neuronal loss and gliosis in the cerebral cortex, cerebellum, and brainstem, including the reticular formation (Goodheart and Dunne 1994). It is difficult to discern if these effects were due to the lead in the mixture or to the long-term exposure to hydrocarbon mixtures.

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A male patient was hospitalized four times during ages 17-21 years for acute lead encephalopathy due to gasoline sniffing (Valpey et al. 1978). He experienced insomnia, anorexia, agitation, irritability, poor memory, nystagmus, and slurred speech, as well as characteristic cerebellar effects (e.g., ataxia, involuntary movements). He gradually developed permanent dementia and dysmetria and died after his fourth admission. An autopsy revealed mild congestion and atrophy of the brain, as well as a patchy loss of Purkinje cells, neuronal loss, gliosis, and early hemorrhagic pneumonia. Necrosis and demyelination of nerve cells and edema of the brain were noted in a 14-year-old boy who died having repeatedly inhaled gasoline for over 4 years (Robinson 1978). A computerized tomographic scan of a 25-year-old man exposed to gasoline for 5 years indicated cerebellar atrophy (Kaelan et al. 1986). After his death, an autopsy showed decreased brain weight, increased brain lead content, and severe atrophy in the cerebellum as well as the loss of nearly all of the Purkinje cells, some neuronal loss, and severe gliosis.

Many of the neurological changes that were observed in these subjects are related to organic and inorganic lead encephalopathy (Robinson 1978; Valpey et al. 1978). Tetraethyl lead can produce symptoms of nausea, vomiting, diarrhea, irritability, restlessness, and anxiety, progressing to the appearance of tremors, weakness, and confusion, followed by the onset of mania and convulsions (Goldings and Stewart 1982; Robinson 1978). Tetraethyl lead itself is not toxic but is converted to triethyl lead which is water soluble and becomes concentrated in the brain where it induces these neurological changes. Triethyl lead is probably degraded to inorganic lead which explains the slowed nerve conduction velocity (Robinson 1978). Chelation therapy, which increases the excretion of inorganic lead, is commonly given to reduce effects due to the lead exposure (Robinson 1978). In another case report, authors concluded that n-hexane, a component of gasoline, was the probable cause of the motor neuropathy exhibited in a 4-year-old boy who was found comatose beside a can of gasoline (Hall et al. 1986). On admission, he had elevated blood lead level and decreased nerve conduction velocity; he had reportedly demonstrated abnormal gait and imbalance 3 months earlier.

Behavioral and intellectual changes have been observed in humans exposed to gasoline (Carroll and Abel 1973; Kumar et al. 1988; Robinson 1978). Ninety exposed gasoline-pump workers had significantly affected immediate and delayed visual memory and perception ($p < 0.01$), psychomotor

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disturbances ($p < 0.05$), and visuomotor learning ability ($p < 0.05$) compared to a control group consisting of 64 subjects matched for age, economic status, education, and location (Kumar et al. 1988). The workers exposed for more than a year had a greater decrease in visual memory and intellectual capacity compared to those workers exposed to gasoline for a shorter duration, while psychomotor disturbances were similar in all workers. Psychological testing was conducted on a 13-year-old boy who sniffed gasoline daily for 6 years (Carroll and Abel 1973). The Wechsler-Bellevue Intelligence Scale indicated an intelligence quotient (IQ) of 29 (severe mental retardation), and the Bender-Gestalt test revealed severe motor incoordination. A follow-up exam 10 weeks after discharge demonstrated an IQ of 44 (moderate retardation). It was noted that his fraternal twin brother, who was not a gasoline sniffer, had an IQ of 62. Therefore, the low IQ in this case may well have preceded the gasoline abuse. Following a 6-month period of gasoline sniffing, a 15 year-old girl had an IQ of 64 with severely impaired perceptual motor skills and an abnormal EEG (Robinson 1978). It is not possible to determine if the psychological and motor impairment seen in this case was a direct result of gasoline sniffing because no information was available on these parameters before the period of gasoline sniffing. No follow-up testing of intellectual functioning was conducted after the girl stopped sniffing gasoline.

Rabbits (15-20/group) of unspecified strain and sex were exposed to 0 or 70,180 ppm leaded gasoline for 2 hours (Przybylowski 1971). All the exposed animals exhibited periods of restlessness, equilibrium disturbances, convulsions, and narcosis after 35 minutes. However, no histopathology of the brain tissue was conducted. These effects may have been partially due to the presumably low oxygen concentration in the exposure atmosphere, as discussed in Section 2.2.1.2, Cardiovascular Effects.

Rats and monkeys exposed to 1,552 ppm gasoline for 90 days exhibited no evidence of neurotoxicity, as assessed by neuropathological examination, either during exposure or at necropsy (Kuna and Ulrich 1984).

In a chronic inhalation study, Fischer-344 rats (three/sex/group) were exposed to 2,056 ppm unleaded gasoline for 7, 12, or 18 months (API 1982). The control groups for each exposure period consisted of only one male and one female rat. Pigmentation of the neuronal cytoplasm was observed in an

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unspecified number of exposed animals, and Wallerian degeneration was reported in two rats at the 7-month sacrifice. Age-related axonal degeneration and dystrophy in the distal gracile tract of the spinal cord were exhibited in the control and exposed groups with increasing severity at each exposure period. The effects were more prominent in the exposed rats compared to the controls at 18 months. No statistical analyses were conducted, and the number of animals per group was inadequate for evaluating changes.

Fischer-344 rats and B6C3F₁ mice inhaled 2,056 ppm unleaded gasoline for 107-109 weeks with interim sacrifices performed at 3, 6, 12, and 18 months (MacFarland et al. 1984). There were no treatment-related changes in the brain weight or the histopathology of the brain, spinal cord, and peripheral nerves. No other details were reported.

The highest NOAELs and all reliable LOAELs for neurological effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2-1.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to gasoline. A reproductive toxicity study in animals reported no evidence of dominant lethal effect on sperm. Inhalation exposure of male CD-1 mice to either 400 or 1,600 ppm unleaded gasoline vapor, 6 hours/day, 5 days/week, for 8 weeks, produced no significant increase in pre- or postimplantation loss of embryos in treated animals compared to controls (Litton Bionetics 1980). The composition of the gasoline used in this study was reported to be 47% paraffins, 4% olefins, 10% naphthenes, and 39% aromatics, which is similar to the mixtures used in other studies sponsored by API. The NOAEL for reproductive effects in male mice was 1,600 ppm; the LOAEL was not established.

No exposure-related histopathological effects were noted in the reproductive organs of rats or mice that were exposed to 2,056 ppm unleaded gasoline vapors for 2 years (MacFarland et al. 1984). A recent reexamination of histological sections from the McFarland et al. 1984 cancer bioassay revealed a marked decrease in the severity of uterine cystic endometrial hyperplasia (a common spontaneous

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condition) in female mice exposed to 2,056 ppm unleaded gasoline (MacGregor et al. 1993). In addition, there was an increase in the incidence and severity (primarily graded trace to mild) of uterine atrophy in aged female mice exposed to 2,056 ppm unleaded gasoline. However, the majority of the lesions were observed only at the end of the study. At terminal sacrifice, 14 of 40 female mice exhibited uterine atrophy. Uterine atrophy was not present at terminal sacrifice in control animals or in those exposed to 67 or 292 ppm. A decrease (40%) in uterine weight was observed in female mice following exposure to 2,056 ppm unleaded gasoline for 16 weeks (Standeven et al. 1994a). However, there were no significant histological changes in reproductive organs or significant effects on serum 17β -estradiol levels, uterine peroxidase activity, or uterine cytosolic estrogen receptor levels. The highest NOAEL values for reproductive effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1.

2.2.1.6 Developmental Effects

Anecdotal data have suggested a possible link between chronic gasoline vapor exposure of pregnant mothers and congenital central nervous system defects in their children. A gasoline abuse case study reported profound growth retardation and initial hypotonia of muscles progressing to hypertonia, scaphocephaly, a prominent occiput, poor postnatal head growth, and minor anomalies in two children from a small Native American community. The mothers of both children had inhaled leaded gasoline during pregnancy (Hunter et al. 1979). The results of the study are difficult to assess because of the small sample size, possibility of concomitant exposure to alcohol, lack of quantification of exposure levels, and presence of lead which may have contributed to the developmental defects in the children.

A teratogenicity study in animals exposed to gasoline vapors failed to reveal significant developmental effects. In this study, groups of 25 pregnant rats were exposed to atomized unleaded gasoline vapors at 0, 400, or 1,600 ppm for 6 hours/day from day 6 through day 15 of gestation. No adverse effects were noted in maternal animals, and there was no evidence of variation in sex ratio, embryotoxicity, reduced fetal growth, or teratogenic effects in fetuses. The results provide no evidence of developmental toxicity in rats associated with exposure to gasoline vapor at concentrations as high as

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1,600 ppm. Thus, the NOAEL for developmental effects was 1,600 ppm; the LOAEL was not established (Litton Bionetics 1978).

The highest NOAEL value for developmental effects in rats after acute inhalation exposure to gasoline is recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.7 Genotoxic Effects

One cytogenetic monitoring study of workers occupationally exposed to gasoline in Sweden was found. Peripheral lymphocytes from 15 male gasoline pump mechanics were analyzed for micronuclei induction; the results were compared to those obtained from 15 male construction workers (Högstedt et al. 1991). Seven of the exposed workers and 8 of the controls were smokers. Ages ranged from 20 to 56 and from 19 to 56 years for the exposed and control groups, respectively. Exposure concentrations, durations, and gasoline type (i.e., leaded versus unleaded) were not reported; however, the authors indicated that gasoline in Sweden may contain up to 5% benzene. Based on the findings from recent studies cited by the authors, parallel lymphocyte cultures from gasoline-exposed and control donor groups were incubated in the presence of pokeweed mitogen (PWM), which stimulates both B- and T-lymphocytes, and phytohemagglutinin (PHA), which primarily activates T-cells. The analysis showed a significant ($p < 0.02$) increase in the frequency of micronuclei in the exposure group lymphocytes stimulated by PWM but not by PHA. However, the presence of up to 5% benzene in the gasoline mixture, which is approximately 2-10 times more than the level found in typical American automotive fuels (based on a typical benzene concentration of 0.5-2.5% in American gasoline; see Chapter 3), confounds the interpretation of the results.

In a dominant lethal experiment, groups of 12 male CD-1 mice were exposed to 400 or 1,600 ppm unleaded gasoline for 6 hours per day, 5 days per week, for 8 weeks (Litton Bionetics 1980). The composition of the gasoline used in this study is discussed in Section 2.2.1.6. Two days after the final treatment, each male was housed with two untreated virgin females for 5 days. The females were replaced with two new females, and the mating sequence was continued for 2 weeks. One male in the high-dose group and two males in the low-dose group died prior to mating, thereby reducing the sample size of mated females. Fourteen days following the midweek of mating, the uteri of all

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females were examined for the numbers of live, dead, and total implants. When these results were statistically compared to the controls, no significant increases in pre- or postimplantation embryo loss were observed. Although the pregnancy rates of the treated groups were comparable to those of the untreated groups, the sample size of pregnant females was less than 20 for the majority of treatment and control groups. The results suggest that exposure of male mice to unleaded gasoline did not induce a clastogenic effect in germinal cells sampled over the spermatogenesis cycle. Nevertheless, the lack of an adequate sample size of pregnant females renders the study insufficient to support a negative conclusion.

In an unscheduled DNA synthesis (UDS) assay, Fischer-344 rats, three males and three females, were exposed to 2,000 ppm of unleaded gasoline, 6 hours per day for up to 18 consecutive days (Loury et al. 1987). Following treatment, kidneys were perfused *in situ* with a buffered salt solution containing collagenase, excised, and dispersed to release individual cells. Cultures of kidney cells were treated with a medium containing tritiated thymidine; gasoline was added directly into the cultures. Autoradiographs were prepared and the incidences of scheduled DNA synthesis (SDS) and unscheduled DNA synthesis (UDS) were determined. SDS is replicative DNA synthesis that occurs during periods of normal or tumorigenic tissue growth or replacement. UDS is a repair process that occurs when DNA has been damaged. There was no increase in UDS following 4 or 18 days of treatment. However, a marked increase in SDS was seen in the kidney cells harvested from male rats 18 days after dosing; no nephrotoxic effects were seen in females. The overall results indicate that acute- and intermediate-duration inhalation exposure to 2,000 ppm unleaded gasoline produced no genotoxic effects in the kidneys of male or female rats. Refer to Table 2-4 for a further summary of these results.

Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

A large number of epidemiological studies have been conducted on workers occupationally exposed to petroleum products and hydrocarbons. These studies all have several inherent limitations that preclude

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their use as evidence for an association between gasoline exposure and cancer. These include lack of information on levels of exposure to gasoline vapor; concurrent exposure to other potentially carcinogenic substances (i.e., service station attendants are also exposed to motor oils, diesel fuel oils, and solvents as well as automobile and truck engine exhausts); no adjustment for potential confounding factors (e.g., smoking); and no latency analyses. EPA (1987a) reviewed 55 relevant studies of unleaded gasoline-exposed populations and concluded that the evidence for drawing causal inferences between unleaded gasoline and cancer was inadequate. A few of these and other more recent studies are summarized below.

A case-control study was performed regarding exposure to petroleum-based liquids and the risk of developing cancer (Siemiatycki et al. 1987). Approximately 12.4% of the cases were exposed to gasoline as well as other chemicals. The only significant odds ratio found with regard to gasoline exposure was for stomach cancer. The odds ratio is defined as the ratio of the percentage of exposed individuals with a disease to the percentage of individuals from a control group with the same disease. When data were analyzed by exposure and job category, it was found that persons with long-term low exposures as well as persons with long-term high exposures had an increased risk of stomach cancer. The power to detect risks was only moderate for most of the associations analyzed. Using other cancer patients as controls may have decreased some of the risk estimates. No definition was provided for short, long, or substantial exposures. Auto mechanics tended to have high exposures to gasoline because they used it as a degreasing agent which may account for the excess risk seen in this group. The results of this study are based on a small number of cases in each of these groups.

A case-control study was performed regarding occupational exposure to hydrocarbons and the risk of developing renal cell carcinoma (Kadamani et al. 1989). Most of the workers exposed to hydrocarbons were either operatives or craft workers. An exposure risk index was calculated and was divided into low, medium, and high exposure categories. More cases of renal cell carcinoma occurred in males that had exposure to gasoline than in controls. The highest risk of renal cell carcinoma was among male workers exposed to moderate levels of hydrocarbons. Males <60 years of age exposed to moderate levels of hydrocarbons had the highest risk of renal cell carcinoma in comparison to the control group. Males exposed before 1930 had an increased risk at higher exposures, but males exposed after 1930 had an increased risk when exposed to moderate levels of hydrocarbons. This may

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be due to better personal protective equipment being used in the high exposure jobs. There are several limitations to this study. The exposure scores were based only on occupation. No attempt was made to determine the type of solvent exposure. The exposure index did not have sensitivity for multiple exposures and duration of exposure. The study had low power to detect differences in small groups. This would account for the inability of the study to detect an increase in females or, at certain levels of hydrocarbon exposure, in males.

A case-control study of 313 exposed males and 428 male controls who worked in petroleum refineries showed no significant risk of renal cell cancer. Women were not included in the analysis since few women work in the petroleum industry. No significant trend was found regarding increased risk of renal cancer and duration of employment (McLaughlin et al. 1985). A cohort study of 48,417 male and 12,916 female Gulf Oil Company employees revealed no significant excess deaths from kidney cancer (Wen et al. 1984). No information was provided on length or duration of employment. A cohort study of a total of 16,880 employees of the Gulf Oil Company Port Arthur refinery found no excess deaths from kidney cancer as compared to the normal population; employees were followed from January 1937 to January 1978 (Wen et al. 1984). The study included all workers who had worked at least 1 day in the plant. No trend was found for increasing risk with years of employment since duration of employment did not correlate with exposure to gasoline.

A proportionate mortality analysis (PMR) revealed an increase of leukemia deaths in gasoline station attendants and mechanics. In addition, there were four deaths due to brain cancer (Schwartz 1987). No information is provided on length or employment or exposure. The PMR does not reflect the mortality of the population because it is so easily influenced by over- and under-representation of deaths. The automobile mechanics and gasoline station attendants who died of leukemia each had different job titles. Therefore, they may not have had similar exposures. Also, several types of leukemia were found: acute myelogenous leukemia (N=2), chronic myelogenous leukemia (N=2), erythroleukemia (N=1), chronic lymphocytic leukemia (N=2), acute leukemia unspecified (N=1), and chronic leukemia undifferentiated (N=1). It is very difficult to draw any definitive conclusions from this type of analysis because several different types of leukemia were reported, and quantification of exposure is not possible in a retrospective study of this type.

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A meta-analysis (an analysis in which data from several studies are combined to obtain a single result) was performed of several cohort studies in the petroleum industry (Wong and Raabe 1989). A total of 24 studies were evaluated which encompassed a study population of 352,661; 6,405 deaths were observed in the entire cohort. The standard mortality ratio (SMR) for all cancers was reduced when the SMRs from the individual studies were combined. Most of the larger studies demonstrated a deficit for all cancers. The all cancer meta-SMR on 6,405 deaths was 85 ($p < .00001$). A British industry-wide study of refinery employees found an excess of deaths from melanoma. However, no explanation of excess was offered. The meta-SMR (SMR obtained from combining SMRs from individual studies) was not significant for skin cancer. For urinary tract cancer in Japanese refinery workers, the SMR was 205 ($p = 0.05$). British drivers had an SMR of 171 ($p = 0.05$) for kidney cancer; a significant excess was found in men aged 55-64 years (SMR=189, $p < 0.05$). A few studies showed a modest increase in lymphatic and hematopoietic cancers. A significant excess of lymphatic and hematopoietic cancers was found in Mobil Oil Company (Beaumont, Texas) refinery employees. Several studies indicated increased mortality from these cancers with increasing length of service. The meta-SMR was 103 ($p = 0.58$). An unpublished update of the study at the Gulf Oil Company Port Arthur refinery found a significant excess of leukemia among employees with 20 or more years of service. The study of Mobil Oil Company workers found an excess of leukemia in their cohort. Analysis by length of employment detected an SMR of 235 for those with 30 or more years of service. In addition, elevated leukemia mortality was found at the Shell Oil Company refineries at Wood River and Deer Park. Most of the leukemia cases in the petroleum industry were not found among those who worked on benzene units directly. Except for the Shell Oil Company refineries, most refineries reported a variety of cell types. Most of the studies did not provide a dose-response relationship. Few industrial hygiene data existed in the industry prior to the mid-1970s, whereas relevant exposure occurred earlier. This review supports the conclusion that some subgroups of the petroleum industry had an increased risk of cancer, particularly leukemia.

Results of several recent epidemiological studies have examined the possible association between gasoline exposure and increased leukemia and kidney cancer risks. In a recent follow-up study of the cohort of 34,569 British petroleum refinery and 23,306 distribution workers, an SMR of 121 for kidney cancer was reported in distribution workers (Rushton 1993). In particular, an increase in kidney cancer risk (SMR=141) was noted in tank truck drivers. For refinery workers, the SMR was

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101. In addition, excesses in leukemia mortality were found in distribution workers (SMR=121), but not refinery workers (SRM=73). For tank truck drivers, the SMR was 155. No estimate of exposure to hydrocarbons was provided in the study.

In a recent retrospective mortality study among 6,672 petroleum marketing and distribution workers from 226 locations throughout Canada, work histories were obtained, and hydrocarbon exposure frequency scores for several jobs were assigned (Schnatter et al. 1993). An increased mortality (SMR=135) for kidney cancer was found for all petroleum marketing distribution workers. The SMR was 158 for employees with “hydrocarbon” exposure in the marketing/distribution segment. When results were examined with respect to exposure frequency, the SMR for kidney cancer was 208 in employees with daily exposure. The kidney cancer SMRs for employees classified as “nonexposed” or “less than daily exposed” were 91 and 99, respectively. A kidney cancer SMR of 210 was noted for tank truck drivers employed more than 1 year. When data were evaluated on the basis of a 20-year latent period after first exposure, the SMR for kidney cancer was 181. Following the application of a Poisson regression model, a relative risk of 3.86 was calculated for employees exposed daily versus those exposed less than daily (relative risk = 0.85). The study authors concluded that although the patterns of kidney cancer risk are consistent with a possible risk due to hydrocarbon exposure, the limited number of observed and expected deaths (9 vs. 6.6) are only suggestive and do not allow a concise interpretation. A significant increase in mortality due to leukemia was noted in tank truck drivers (SMR=335).

A recent case-control study in a cohort of about 100,000 male refinery workers from five petroleum companies revealed no excess in kidney cancer in refinery workers (Poole et al. 1993) The relative risk for any exposure above refinery background levels was estimated to be 1.0. In contrast, workers involved in the distribution, transport, and movement of petroleum products (job category described as receipt, storage, and movements) showed a possible increased kidney cancer risk (relative risk = 2.49). There was no evidence for an increased kidney cancer risk in a cohort of 15,135 distribution workers with potential exposure to gasoline for at least 1 year at land-based terminals or on marine vessels between 1946 and 1985 (Wong et al. 1993). An SMR of 65.4 for kidney cancer was reported in landbased distribution workers. For marine distribution workers, the SMR was 83.7. The SMR for kidney cancer in tank truck drivers was 61. An SMR of 150 for acute myelogenous leukemia was reported

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for land-based distribution workers. However, no trend was apparent when data were analyzed by various gasoline exposure indices. The SMR for acute myelogenous leukemia was 74.2 for marine employees. In a follow-up study, the cohort mortality data were further analyzed by using a nested design (Wong et al. 1993b). This study limited analysis to the land-based workers since quantitative exposure data were available for this group. Leukemia (all cell types), acute myeloid leukemia, kidney cancer, and multiple myeloma were selected for additional analyses. Also, a more specific and homogenous job classification was developed in this nested study. Additional gasoline exposure indices consisted of length of exposure, cumulative exposure (ppm-years in terms of total hydrocarbons), and frequency of peak exposure. A time period of first exposure to gasoline (≤ 1948 vs. ≥ 1949) was also included as an exposure index. The results of the nested case-control study, along with the findings of the original study, indicated that there was no association between exposure to gasoline and leukemia (all cell types), acute myeloid leukemia, kidney cancer, or multiple myeloma. A parallel study of exposure assessment among the cohort members of the original Wong et al. 1993 study has been reported (Smith et al. 1993). In this exposure assessment, tasks and job exposures during 1975-1985 were evaluated (task-time-weight-average exposure model), and truck and marine exposures before 1975 were extrapolated on the basis of methodology to estimate historic marketing and marine distribution worker exposures to gasoline. Task exposures were highest during tank filling in trucks and marine vessels. Measured average annual, full-shift exposures during 1975-1985 ranged from 9-14 ppm of total hydrocarbon vapor for truck drivers and 2-3 ppm for marine workers on inland waterways. Extrapolated past average exposures in truck operations are highest for truck drivers before 1965 (140-220 ppm).

A recent case-control study was performed to assess the risk of renal cell cancer from occupational exposure to gasoline (Partanen et al. 1991). From a total of 672 cases, 338 eligible cases were selected and matched with 484 controls. The controls were matched to cases based on age, gender, and survival time. The odds ratio was significant when both men and women were considered together, however, this rate was unadjusted. When men were considered alone, even though the number of cases (39) remained the same, the odds ratio was not significantly increased once the rate was adjusted for obesity, smoking, and coffee consumption. The gasoline exposure was considered high for 11 cases and 2 controls, and low for 28 cases and the remaining controls. The persons exposed to gasoline had worked in various occupations such as taxis drivers and service station

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attendants. Because of possible confounding of gasoline with other fuel exposures, the odds-ratio for gasoline exposure only was calculated and found to be significantly elevated. Conditional logistic regression showed a significant risk of renal cell cancer for exposure to gasoline of 1.0-2.0 ppm, cumulative exposure of 14-102 ppm-years, and a latency of 27-33 years; duration of exposure was not significant. A ppm-year is a measure of cumulative exposure. It is the product of the mean level of exposure and the duration of exposure. The majority of the cases were deceased. Therefore, next-of-kin were contacted to fill out the questionnaire. (Next-of-kin information is unreliable because relatives may not know what other confounding factors may have been involved, such as smoking.) Subjects that were alive filled out their own questionnaires. Interviews were also conducted with personnel familiar with the workplace conditions and job exposures so that exposures could be classified with little misclassification bias. Based on the results of this study, it can be concluded that exposure to gasoline was associated with the risk of kidney cancer.

Male and female Fischer-344 rats were exposed to unleaded gasoline vapors in an initiation/promotion assay in an attempt to determine the mechanism for unleaded gasoline-induced renal tumors in male rats (Short et al. 1989b). The incidences of chronic progressive nephrosis (CPN), atypical cell foci (ACF) (believed to be the precursors to tumors), and renal cell tumors (RCT) were evaluated by light microscopy. The rats were exposed to unleaded gasoline vapors for 24 weeks or for 59-61 weeks after a 2-week exposure to the initiator, N-ethyl-N-hydroxyethylnitrosamine (EHEN) and a 4-week control period (initiation-promotion group) or a 6-week control period. There was a statistically significant linear trend for an increase in the incidence of RCT in the males initiated with EHEN but not in the rats who had not been initiated. These results show that unleaded gasoline has a promoting effect on the incidence of RCT in male, but not female, rats initiated with EHEN.

In an initiation-promotion protocol, 12-day-old female B6C3F₁ mice were administered N-nitrosodiethylamine (DEN) by the intraperitoneal route prior to exposure to gasoline (Standeven et al. 1994). At 5-7 weeks of age, mice from the DEN-initiated and control groups were exposed to 0, 292, or 2,056 ppm of wholly vaporized PS-6 blend unleaded gasoline. Exposure conditions were chosen to simulate those utilized in the previous cancer bioassay reported by MacFarland et al. (1984) (discussed below). Treatment with 2,056 ppm unleaded gasoline (but not 292 ppm) increased the size

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and number of altered hepatic foci (primarily basophilic) in DEN-initiated mice. Treatment with gasoline failed to induce altered hepatic foci in the absence of prior DEN treatment. These results show that unleaded gasoline is a liver tumor promotor in female mice. Similar results were obtained in female B6C3F₁ mice exposed to 2,039 ppm unleaded gasoline (PS-6 blend) for 13 weeks (Standeven and Goldsworthy 1993).

One chronic-duration animal study investigated the potential carcinogenicity of inhaled gasoline vapors in experimental animals (MacFarland et al. 1984). Groups of 100 Fischer-344 rats and B6C3F₁ mice per sex were intermittently exposed to gasoline vapors for 2 years with interim sacrifices at 3, 6, 12, and 18 months. A decrease in the average body weight gain at the highest exposure level (2,056 ppm) provided evidence that the maximum tolerated concentration had been achieved. The test atmosphere consisted of completely volatilized gasoline. A statistically significant concentration-related increased incidence of primary renal neoplasms (adenoma, carcinoma, and sarcoma) was observed in the male rats that died after 18 months or at terminal sacrifice (one tumor was seen in a female rat). A statistically significant increase in the incidence of hepatocellular tumors was observed in the female mice at 18 months and at study termination. Some of these tumors had metastasized to the lungs. A recent reevaluation of the liver tumor data in mice, as well as a reexamination of the slides prepared from hepatic tissue, supported the conclusion that hepatocellular tumors were increased in female mice following treatment with 2,056 ppm unleaded gasoline (Magaw et al. 1993). However, the revised incidence rates for the hepatocellular tumors in mice were approximately 20-25% lower than those reported by MacFarland et al. 1984. The MacFarland study is limited with respect to its relevance to human health risk for the following reasons. First, the animals were exposed to wholly vaporized gasoline, which has the same composition as liquid gasoline and is not the same as the gasoline vapors that humans would be exposed to in ambient conditions. Gasoline emissions normally found in the environment contain lower concentrations of hydrocarbons with very low vapor pressures (i.e., the branched-chain hydrocarbons, such as 2,2,4-trimethyl-pentane, that have been shown to induce nephrotoxicity) than those found in liquid gasoline. Secondly, the relevance of male rat kidney tumors believed to have arisen from α_{2u} -globulin accumulation to human cancer risk is questionable (see Section 2.4).

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2.2.2 Oral Exposure

2.2.2.1 Death

Accidental or intentional ingestion of large quantities of gasoline can cause death in humans (Camevale et al. 1983). The lethal ingested dose of gasoline has been estimated to be 12 ounces (350 g, or 5 g/kg for a 70-kg individual) (Anonymous 1989). The cause of death following ingestion of gasoline is either severe chemical pneumonitis resulting from the aspiration of gasoline that leads to asphyxiation, central nervous system depression leading to respiratory failure, or cardiac sensitization to circulating catecholamines resulting in the occurrence of fatal arrhythmias (EPA 1987a).

The acute oral LD₅₀ in rats for gasoline has been reported to be 14,063 mg/kg (Beck et al. 1983; Vemot et al. 1990). No treatment-related deaths were reported in a 4-week study in rats administered up to 2,000 mg/kg/day by gavage (Halder et al. 1985), but a few treatment-related deaths were seen in another study in which rats were administered 500 mg/kg/day API PS-6 by gavage (Borrison Labs 1985). The basis for this discrepancy between studies is not known. No information is available on death in experimental animals following chronic oral exposure to gasoline.

The highest NOAEL values and all reliable LOAEL and LD₅₀ values for death in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

No studies were located regarding musculoskeletal, dermal, or ocular effects in humans or animals after oral exposure to gasoline.

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

TABLE 2-2. Levels of Significant Exposure to Automotive Gasoline - Oral

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference/ Chemical form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE							
Death							
1	Rat Sprague-Dawley	once (G)				14,063 (LD ₅₀)	Beck et al. 1983; Vernet et al. 1990 NS
Systemic							
2	Human	once	Resp			6429 M (pulmonary edema)	Janssen et al. 1988 NS
			Gastro			6429 M (severe esophagitis and gastritis)	
			Hemato			6429 M (hemolysis; disseminated intravascular coagulation)	
			Hepatic		6429M (serum enzyme changes)		
			Renal			6429 M (tubular necrosis)	
3	Rat F344	2 wk 5d/wk 1x/d (G)	Renal		375M (minimal to slight regenerative tubular epithelial lesions)		Gerin et al. 1988 unleaded
4	Rat F344	9 d 1x/d (GO)	Renal	3M	30M (α ₂ μ-globulin accumulation and exfoliation of renal tubular cells)		Olson et al 1987 unleaded

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TABLE 2-2. Levels of Significant Exposure to Automotive Gasoline - Oral (continued)

Key to figure ^a	Species/ (Strain)	Exposure/ duration/ frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference/ Chemical form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
INTERMEDIATE EXPOSURE							
Death							
8	Rat F344	28 d 1x/d 7d/wk (G)				500 M (4/73 died) 500 F (2/72 died)	Borrison Labs 1985 unleaded
Systemic							
9	Rat F344	28 d 1x/d 7d/wk (G)	Renal		500M (hyaline droplets; tubular regenerative epithelium; intratubular cast formation)		Borrison Labs 1985 unleaded
			Body wt		2000 (decreased body weight)		
10	Rat F344	4 wk 1x/d 5d/wk (G)	Gastro		2000M (erythema; erosion of gastric mucosa; ulceration of gastric epithelium)		Halder et al. 1985 unleaded
			Renal		500M (hyaline droplet accumulation; tubular regenerative epithelium; intratubular cast formation)		
			Body wt		2000M (18% reduction in body weight gain)		

^aThe number corresponds to entries in Figure 2-2.

Bd wgt = body weight; d = day(s); F = female(s); (G) = gavage; Gastro = gastrointestinal; (GO) = gavage in oil; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; M = male(s); LD₅₀ = lethal dose 50% kill; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = time(s)

Figure 2-2. Levels of Significant Exposure to Automotive Gasoline – Oral

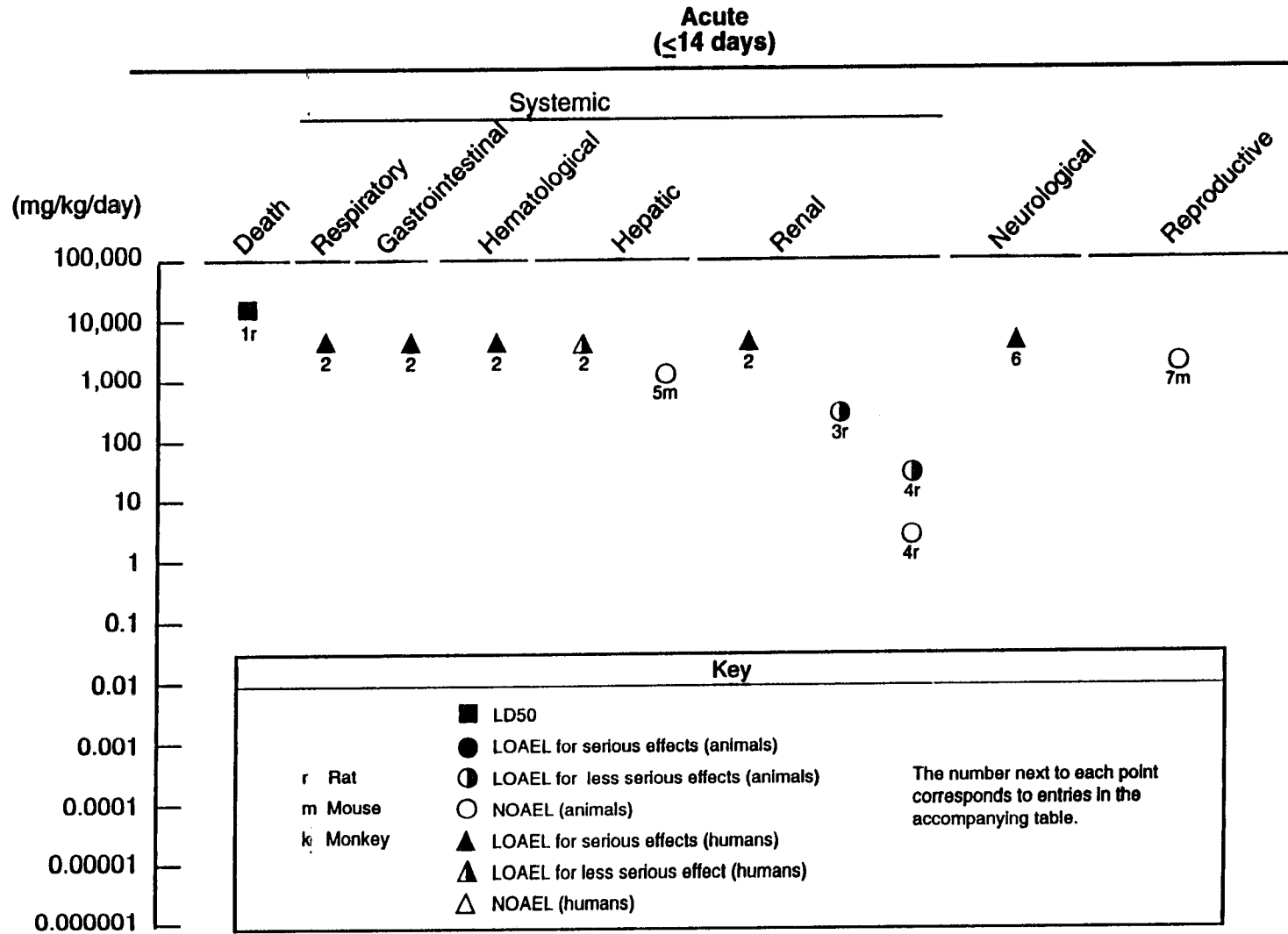
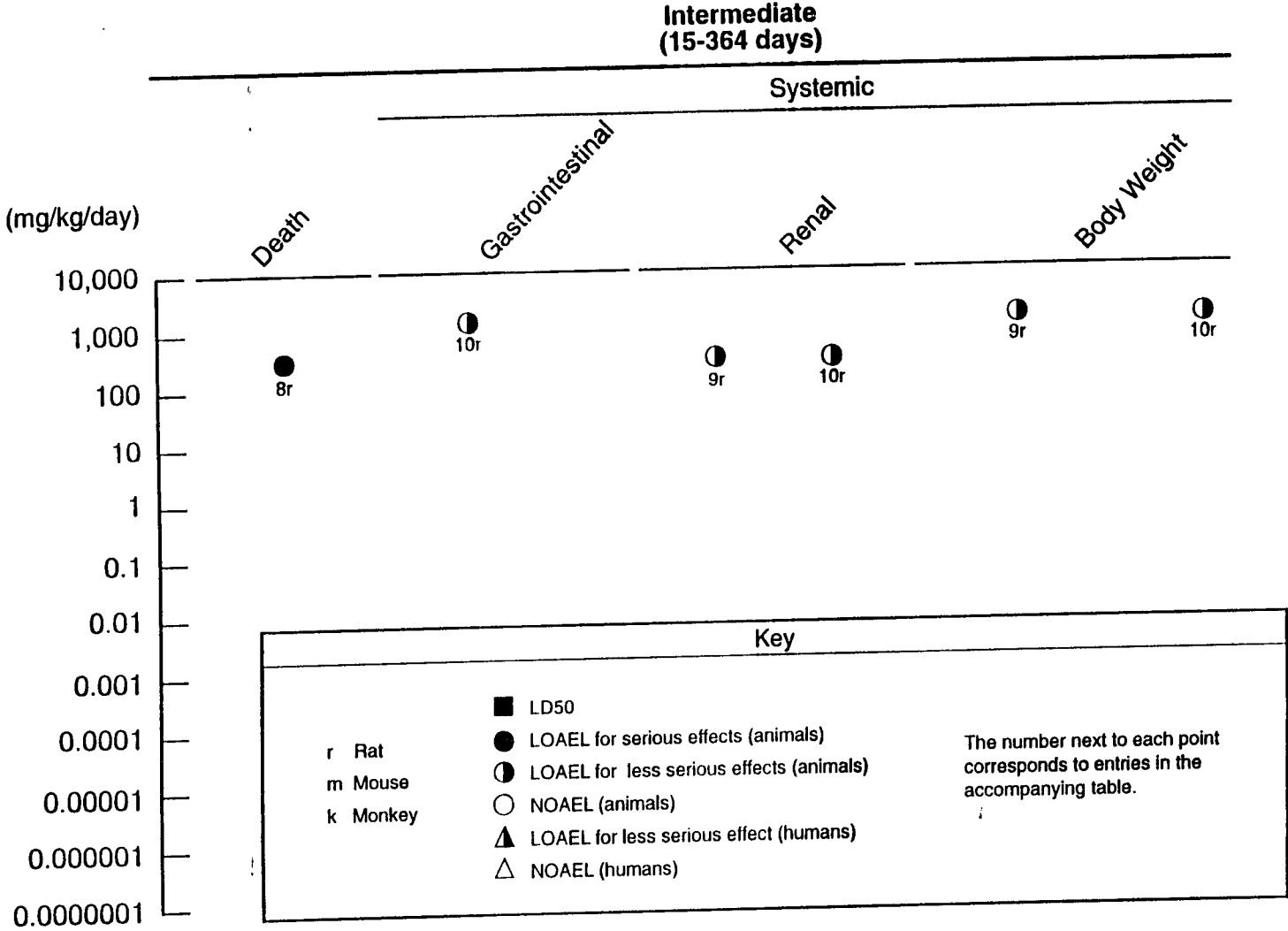


Figure 2-2. Levels of Significant Exposure to Automotive Gasoline – Oral (continued)



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Respiratory Effects. Intentional or accidental ingestion of gasoline often results in aspiration of the gasoline into the lungs because of its high volatility and low surface tension. Therefore, the most common effect associated with acute gasoline ingestion in humans is aspiration pneumonia which is often accompanied by respiratory distress, pulmonary edema, emphysema, and focal alveolar hemorrhage (Banner and Walson 1983; Beamon et al. 1976; Carnevale et al. 1983; Grufferman and Walker 1982; Janssen et al. 1988). Death from asphyxia is often the result in cases of gasoline ingestion when the aspiration pneumonia becomes severe.

No studies were located regarding respiratory effects in experimental animals after oral exposure to gasoline.

Cardiovascular Effects. The only study located regarding the cardiovascular effects of ingested gasoline in humans was reported by Banner and Walson (1983). A 15-month-old male ingested approximately 1 pint ($\approx 5,000$ mg/kg) of gasoline and was found to be hypotensive upon hospital admission. However, because the child exhibited multi-organ system toxicity (see discussions of Respiratory, Hematological, and Renal Effects in this Section 2.2.2.2) it is not possible to ascertain whether the hypotension was a direct effect of the ingested gasoline or a consequence of other adverse effects.

No studies were located regarding cardiovascular effects in experimental animals after oral exposure to gasoline.

Gastrointestinal Effects. Damage to the digestive tract (severe esophagitis, gastritis, congestive failure, degeneration of the epithelium, and mucositis of the oral cavity) has been observed in individuals who accidentally or intentionally ingested gasoline (Camevale et al. 1983; Hoffman et al. 1980; Janssen et al. 1988).

Rats that were administered 2,000 mg/kg/day unleaded gasoline by gavage for 4 weeks were found to have gastric erythema, erosion of the gastric mucosa, and ulceration of the epithelium (Halder et al.

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1985). The combined findings in humans and animals demonstrate the irritating effect of gasoline on mucosal tissue.

Hematological Effects. Hemolysis, as evidenced by a decrease in hematocrit and an increase in free urine hemoglobin, and disseminated intravascular coagulation have been observed in cases of accidental or intentional ingestion of gasoline (Banner and Walson 1983; Janssen et al. 1988). In addition, evidence of intravascular consumption of clotting factors (coagulopathy, hypofibrinogenemia, and elevated prothrombin and partial thromboplastin times) was seen in a 15-month-old male who ingested approximately 1 pint ($\approx 5,000$ mg/kg) of gasoline (Banner and Walson 1983).

No studies were located regarding the hematological effects of gasoline after oral exposure in animals.

Hepatic Effects. A transient increase in serum enzymes indicative of liver function (γ -glutamyl transferase, serum glutamic-oxaloacetic transaminase [SGOT], and serum glutamic pyruvic transaminase [SGPT]) has been noted in individuals who accidentally or intentionally ingested gasoline (Janssen et al. 1988). Mild centrilobular congestion was observed at autopsy in a death following gasoline ingestion (Carnevale et al. 1983). However, all of the visceral organs were congested in this individual, so it is not likely that gasoline had a direct toxic effect on the liver.

Mild hepatic centrilobular hypertrophy and increases in pentoxoresorufin-o-dealkylase activity, which quantitates cytochrome P-450 2B, and in the hepatocyte labeling index were observed in female B6C3F₁ mice following the administration of 1,800 mg/kg/day unleaded gasoline by gavage for 3 consecutive days (Standeven and Goldsworthy 1993). However, there was no effect on the activity of serum sorbitol dehydrogenase (SDH), nor was there evidence of hepatic necrosis.

Renal Effects. Renal injury has been reported in a number of case reports of individuals who accidentally or intentionally ingested gasoline (Banner and Walson 1983; Kuehnel and Fisher 1986; Janssen et al. 1988). A 23-year-old male developed oliguria requiring hemodialysis for 3.5 weeks after ingesting approximately 6,400 mg/kg of gasoline (Janssen et al. 1988). A biopsy taken 20 days after ingestion revealed tubular necrosis and interstitial edema. It is not known whether any

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preexisting kidney insufficiency was present in this individual prior to the gasoline ingestion. Radiologic tests (intravenous pyelography [IVP] and a computerized tomography [CT]) revealed an altered appearance in the upper poles of both kidneys of a 26-year-old man who accidentally ingested gasoline and experienced flank pain, cramps, nausea, weakness, and red-brown urine (Kuehnel and Fisher 1986). Urinalysis revealed hematuria and reduced creatinine clearance and his serum creatinine was elevated. By the 19th day after ingestion, he was asymptomatic, his urinalysis was normal, his serum creatinine decreased, and his CT scan was normal. The authors concluded that accidental acute ingestion of gasoline resulted in an acute reversible toxicity, particularly to the kidneys. Evidence of renal failure (increased urine specific gravity with elevated protein, glucose, and hemoglobin, oliguria, and elevated blood urea nitrogen [BUN]) was seen 24 hours after a 15-month-old boy ingested gasoline (Banner and Walson 1983). Serum creatinine was elevated by the 3rd post-ingestion day. Diuretic therapy did not resolve the renal failure, and peritoneal dialysis was initiated and continued for 13 days until urine output increased. The authors speculated that the renal failure was either the result of the hypotension or hemoglobinuria observed or a direct effect of gasoline.

Acute and intermediate gasoline ingestion produces the same syndrome of lesions (i.e., hyaline droplet accumulation and the deposition of γ -globulin in the kidney) in male rats as is seen after inhalation exposure (Borrison Labs 1985; Garg et al. 1988, 1989; Gerin et al. 1988; Halder et al. 1985; Murty et al. 1988; Olson et al. 1987a, 1988) (see Section 2.2.1.2, Renal Effects). The composition of the gasoline used in the studies conducted by Murty et al. and Olson et al. was reported to be (on a percent weight basis) 16.4% n-paraffins, 34.3% isoparaffins, 5.4% naphthenes, 10.0% olefins, 26.4% aromatics, and 7.5% not specified. Biochemical parameters of renal tubular function have also been observed to be affected by gasoline administration in male rats. Urinary lactate dehydrogenase (LDH) and β -N-acetyl-D-glucosaminidase (NAG) activities (indicators of tubular function) were significantly increased in male rats administered unleaded gasoline for 2 weeks, whereas BUN values. (an indicator of glomerular function) were not different from controls (Gerin et al. 1988).

As with inhalation exposure, these renal effects were not seen in female rats administered API PS-6 (Borrison Labs 1985). In addition, this syndrome could not be induced in male NCI-Black-Reiter rats administered API PS-6 (Dietrich and Swenberg 1991). The NCI-Black-Reiter rat is an inbred strain of

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rats that does not synthesize α_{2u} -globulin, which is believed to be associated with the etiology of hydrocarbon-induced nephropathy (see Section 2.4).

The effects of acute-duration oral gasoline administration on the accumulation of α_{2u} -globulin and associated nephropathy in the proximal convoluted tubules were compared in young (35-month) versus old (26-month) male rats (Murty et al. 1988). α_{2u} Globulin content was assessed by electrophoresis and radioimmunoassay (RIA). Old rats had a markedly reduced α_{2u} -globulin content in their kidneys prior to gasoline treatment as compared to the young rats, and they failed to exhibit an increase in renal α_{2u} -globulin content after administration. The young rats exhibited a 173% increase in renal α_{2u} -globulin content, and their phagolysosomes exhibited altered morphology. These results led the authors to conclude that the failure of gasoline to alter hyaline droplet accumulation and α_{2u} -globulin content in the kidneys of aged rats suggests that only young adult male rats are susceptible to hydrocarbon-induced α_{2u} -globulin-mediated nephropathy. Because α_{2u} -globulin-induced male rat nephropathy may not be relevant to humans (see Section 2.2.1.2, Renal Effects), this endpoint was not chosen as the basis for an acute or intermediate MRL for gasoline.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to gasoline.

A significant decrease in body weight gain was exhibited by rats administered unleaded gasoline (API PS-6) by gavage for 28 days as compared to the controls (Borrison Labs 1985).

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals after oral exposure to gasoline.

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2.2.2.4 Neurological Effects

There were no quantitative data on the neurological effects of gasoline following oral exposure; however, accounts of neurological effects after short-term exposure, usually by accidental ingestion, were available in case reports. A retrospective study on the hospital records of 24 children who accidentally ingested gasoline indicated central nervous system complications such as convulsions, coma, and lethargy (Beamon et al. 1976). There were no other details provided. A case study described a man who drank approximately 6,000 mg/kg of gasoline and developed seizures after gastric lavage was performed (Janssen et al. 1988). These effects were attributed to hypoxia that is secondary to chemical pneumonitis. The autopsy of a man who accidentally ingested gasoline revealed edema in the brain (Carnevale et al. 1983).

No studies were located regarding neurological effects in animals after oral exposure to gasoline.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to gasoline. Although oral administration of 3,000 mg/kg/day unleaded gasoline to female mice for 3 days resulted in a three-fold increase in estrogen metabolism in isolated hepatocytes, there were no functional antiestrogenic effects as assessed by uterotrophic assays (Standeven et al. 1994b).

2.2.2.6 Developmental Effects

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

2.2.2.7 Genotoxic Effects

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

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The oral administration of 500, 750, or 1,000 mg/kg/day unleaded gasoline (API PS-6) to groups of five male Sprague-Dawley rats for 5 consecutive days did not cause an increase in structural chromosome aberrations in bone marrow cells harvested 6 hours following the final treatment (Dooley et al. 1988). In general, animals orally exposed to gasoline did not exhibit unscheduled DNA synthesis (UDS) induction. The ability to induce UDS is a strong indication that a compound is genotoxic. One exception was a UDS assay conducted with male and female B6C3F₁ mice. The mice received 2,000 mg/kg unleaded gasoline (API PS-6) by gavage; at 2, 12, and 24 hours post-treatment, harvested hepatocytes were analyzed for UDS (Loury et al. 1986). The researchers observed slight but significant ($p < 0.01$) elevations in UDS in both sexes 12 hours after gasoline administration. No evidence of a genotoxic response was observed in the hepatocytes analyzed 2 hours after exposure. However, a marked increase in scheduled DNA synthesis (SDS) was apparent in male mice 24 hours after treatment; no hepatotoxic effects were seen in the females.

Fischer-344 rats were also gavaged with unleaded gasoline, and both liver and kidney cells were analyzed for UDS activity. To assess potential genotoxicity, hepatocytes from male rats were analyzed for UDS activity 2, 12, 24, or 48 hours after treatment with 2,000 mg/kg and 2 or 24 hours after treatment with 100 or 5,000 mg/kg. Significant UDS activity was not observed at any concentration or at any harvest time. In agreement with other in vivo rodent UDS assays, SDS was increased 24 hours and 48 hours following treatment with 2,000 mg/kg. UDS activity was not increased in kidney cells harvested from male rats 2 and 24 hours after administration of 2,000 or 5,000 mg/kg unleaded gasoline (API PS-6) (Loury et al. 1987). Similarly, increasing the exposure time of the high dose to 4 days failed to induce genotoxicity. Elevations in SDS activity were observed in both sexes following the administration of 2,000 mg/kg/day or 135 mg/kg/day unleaded gasoline for 4 or 18 days, respectively. Refer to Table 2-4 for a further summary of these results.

Other genotoxicity studies are discussed in Section 2.4.

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2.2.2.8 Cancer

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

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans following dermal exposure to gasoline.

In an acute-duration study, dermal application of up to 8.0 mL/kg (approximately 6,000 mg/kg) gasoline to rabbits resulted in no deaths (Beck et al. 1983).

2.2.3.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, or musculoskeletal effects in humans or animals after dermal exposure to gasoline.

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

Respiratory Effects. The only information located regarding the respiratory effects of gasoline following dermal exposure comes from a case report in which a 34-year-old man suffered from atelectasis, laryngeal edema, and upper airway obstruction following immersion in a pool of unleaded gasoline for approximately 8 hours after an automobile accident (Simpson and Cruse 1981). Exposure by other routes was possible.

No studies were located regarding respiratory effects in animals after dermal exposure to gasoline.

TABLE 2-3. Levels of Significant Exposure to Automotive Gasoline - Dermal

Species/ (strain)	Exposure/ duration/ frequency/	System	NOAEL	LOAEL		Reference/ Chemical form
				Less Serious	Serious	
ACUTE EXPOSURE						
Systemic						
Rabbit New Zealand	12 d 5d/wk 24hr/d	Hemato	8.0 mL/kg			Beck et al. 1983 unleaded
		Hepatic		8.0 mL/kg	(pale congested liver)	
		Renal		8.0 mL/kg	(pale congested kidney)	
		Dermal		8.0 ml/kg	(severe dermal irritation)	
Rabbit New Zealand	24 hr once	Dermal		0.5mL	(slight dermal irritant)	Vernot et al. 1990 unleaded
Rabbit New Zealand	once	Ocular	0.1mL			Vernot et al. 1990 unleaded
Immuno/Lymphoret						
Gn pig Hartley	3 wk 3d/wk 6hr/d		0.5mL M 50% solu- tion			Vernot et al. 1990 unleaded

d = day(s); Gn pig = guinea pig; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level;
NOAEL = no-observed-adverse-effect level; NS = not specified; wk = week(s); x = time(s)

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Hematological Effects. No studies were located regarding hematological effects in humans after dermal exposure to gasoline.

No adverse hematological effects were noted in rabbits that had 8.0 mL/kg applied to their shaved skin for 12 days (Beck et al. 1983).

Hepatic Effects. A transient increase in serum enzymes indicative of liver function (creatinine phosphokinase [CPK], SGOT, and SGPT) was noted in a 34-year-old male who was immersed in a pool of unleaded gasoline for approximately 8 hours (Simpson and Cruse 1981). Exposure by other routes was possible.

Pale, congested livers were observed in rabbits who had 8.0 mL/kg unleaded gasoline applied to their shaved skin for 12 days (Beck et al. 1983). No other details were provided regarding the extent of the liver toxicity, if any, in this study.

Renal Effects. Renal function tests were performed in two individuals who had been immersed in gasoline for several hours (Hansbrough et al. 1985; Simpson and Cruse 1981). There was no evidence of abnormal renal function in either case.

Pale, congested kidneys were observed in rabbits that had 8.0 mL/kg unleaded gasoline applied to their shaved skin for 12 days (Beck et al. 1983). No details regarding pathological findings were reported.

Dermal Effects. A number of case reports of individuals who were immersed in gasoline for several hours described the occurrence of either partial or full skin-thickness chemical burns in the area of contact with the gasoline (Ainsworth 1960; Hansbrough et al. 1985; Simpson and Cruse 1981).

Studies in experimental animals show that gasoline is irritating to the skin. Application of a single dose of 0.5 mL undiluted gasoline to the skin of rabbits resulted in slight dermal irritation (Vemot et al. 1990), whereas daily application of 8.0 mL/kg of undiluted gasoline to the skin of rabbits for

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12 days produced severe dermal irritation (Beck et al. 1983). Gasoline was shown not to be a dermal sensitizer in guinea pigs (Vemot et al. 1990).

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to gasoline.

Gasoline instilled into the eyes of rabbits did not cause ocular irritation (Vemot et al. 1990).

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans after dermal exposure to gasoline.

Gasoline was shown not to be a dermal sensitizer in guinea pigs (Vemot et al. 1990). The NOAEL from this study is recorded in Table 2-3.

No studies were located regarding the following effects in humans or animals after dermal exposure to gasoline:

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to gasoline. However, in many of the epidemiological studies discussed in Section 2.2.1.8, exposure probably occurred by the dermal route as well as by inhalation.

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2.3 TOXICOKINETICS

There are limited data on the toxicokinetics of gasoline in humans and animals. Information on the toxicokinetics of several components of gasoline is available (see the ATSDR toxicological profiles for benzene, toluene, and xylene [ATSDR 1991, 1989, 1990]); it should be noted, however, that the interaction of these compounds may influence their individual absorption, distribution, metabolism, and elimination characteristics.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Although there are no data on the absorption rate of gasoline, indirect evidence from case reports of gasoline sniffers indicates that it can be absorbed following inhalation exposure. The increases in blood and urinary lead levels, as well as the characteristic neurological signs, are indicators of exposure (Goldings and Stewart 1982; Robinson 1978). Because gasoline is a mixture, the pattern of absorption following inhalation varies for the individual components (NESCAUM 1989). The compounds with higher blood/gas coefficients (e.g., xylene, benzene, toluene) have a higher rate of absorption than the compounds with lower coefficients (e.g., cyclohexane, ethane, ethylene) (NESCAUM 1989).

2.3.1.2 Oral Exposure

There is no quantitative information on the absorption of gasoline following oral exposure in humans and animals. However, the absorption is believed to be relatively complete because of the high lipophilicity of the hydrocarbon compounds, the large surface area of the gastrointestinal tract, and the long resident time in the tract (NESCAUM 1989).

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2.3.1.3 Dermal Exposure

Although no studies on the dermal absorption of gasoline in humans and animals are available, the dermal absorption of hydrocarbon solvents is known to be low relative to the oral route (NESCAUM 1989). The aromatic hydrocarbons, such as benzene, are expected to have higher skin penetration than the aliphatic hydrocarbons (NESCAUM 1989).

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

Autopsies of humans who were apparently exposed to gasoline indicated elevated blood levels of hydrocarbons such as benzene, toluene, pentane, and hexane (Brugnone et al. 1986; Ikebuchi et al. 1986; Matsubara et al. 1988). An initial concentration of 247 $\mu\text{g/mL}$ gasoline was estimated from blood samples of an adult male who was found unconscious in a gasoline-vapor-filled car (Matsumoto et al. 1992). However, the patient was also exposed dermally to gasoline. The estimated half-life of the gasoline was 16.9 hours. The lead concentrations were slightly elevated in the blood of exposed gasoline station workers (Moore et al. 1976). It has been reported that triethyl lead and inorganic lead, metabolites of tetraethyl lead, may accumulate in the brain and produce encephalopathy and slowed nerve conduction (Kaelan et al. 1986; Robinson 1978). However, quantitative data on the lead content in the brain tissue were not presented in these studies.

Benzene, toluene, and xylenes were detected in the blood samples collected from Wistar rats immediately after exposure to 5,000 ppm gasoline vapor for 30 minutes (Kimura et al. 1988).

2.3.2.2 Oral Exposure

There are limited data on the distribution pattern of gasoline in humans and animals. The distribution of gasoline (gasoline concentration measured as the ratio of the concentrations of [2-methylpentane/2,2-dimethylbutane] in sample/[2-methylpentane/2,2-dimethylbutane] in standard) was determined in a male who died following accidental ingestion of gasoline (Camevale et al. 1983).

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The liver, gastric wall, and lungs had the highest gasoline concentrations at 663, 324, and 457 ppm, respectively. The brain, bile, and kidney contained 44.2, 59, and 51.5 ppm, respectively, while the concentrations in the blood from the brain, lungs, and heart were 29.4, 132, and 51.5 ppm, respectively. Autopsies of humans who were apparently exposed to gasoline indicated elevated blood levels of hydrocarbons such as benzene, toluene, pentane, and hexane (Brugnone et al. 1986; Ikebuchi et al. 1986; Matsubara et al. 1988).

2.3.2.3 Dermal Exposure

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

2.3.3 Metabolism

The metabolism of gasoline is not known, although it is expected that the interaction of the various components of gasoline may affect the metabolic products that are formed. The interaction of the components of gasoline is likely to influence the metabolizing enzymes such that the elimination rate of a compound may be altered (NESCAUM 1989). The increased metabolism of antipyrine suggested that mixed function oxygenase activity was induced after inhalation of gasoline vapors in humans (43-1,312 mg/m³) and in rats (5,000 mg/m³) (Dossing et al. 1988; Harman et al. 1981). The composition (expressed as volume percent) of the gasoline used in the Dossing et al. (1988) study was 30-40% aromatic hydrocarbons (including 3-5% benzene).

Organic tetraethyl lead was a component of gasoline (Goldings and Stewart 1982). It is converted in the liver to triethyl lead, a water-soluble metabolite that can accumulate in the brain (Robinson 1978). This compound can be further broken down to inorganic lead.

2.3.4 Excretion

Although there are no specific data on the elimination of gasoline following inhalation, oral, or dermal exposure, the elimination rate of the components of gasoline probably varies because of the

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metabolism of the gasoline components by the hepatic enzymes. Metabolites of benzene, toluene, and xylene are known to be excreted primarily in the urine (NESCAUM 1989).

Chelation therapy in individuals exposed to gasoline indicates that inorganic lead is eliminated in the urine of patients exposed to leaded gasoline (Robinson 1978). Urinary phenol, which is commonly used to indicate benzene exposure, was measured in gasoline pump workers (Pandya et al. 1975). There was an elevated amount of phenol (40 mg/L) in these subjects compared to normal values (<20 mg/L).

2.3.5 Mechanisms of Action

Several mechanisms have been proposed to account for the unique syndrome of nephropathy in male rats following exposure to certain hydrocarbons, including unleaded gasoline. Currently, the most likely mechanism is that a metabolite of gasoline or one of its constituents binds to α_{2u} -globulin; the complex is then reabsorbed in the proximal tubule and phagocytized by lysosomes within the tubule cells. Investigators at the Chemical Industry Institute of Toxicology (CIIT) have demonstrated that 2,2,4-trimethylpentane (TMP), a component of gasoline, accumulates in the renal cortex, and that 2,4,4-trimethyl-2-pentanol (TMPOH), a metabolite of TMP, binds to α_{2u} -globulin in these cells (Lock et al. 1987; Swenberg et al. 1989). This protein complex is difficult to catabolize; therefore, the TMPOH- α_{2u} -globulin complexes accumulate in the lysosomes. Eventually, the lysosomes burst, and digestive enzymes contained within the lysosomes induce cytotoxicity and cell death, which in turn leads to the accumulation of casts and the hyperplastic events described above (Swenberg et al. 1989).

The antiestrogenic effects of unleaded gasoline have been proposed as a possible underlying mechanism of female mouse liver tumor induction by this chemical (Standeven et al. 1994a). In a study utilizing an initiation-promotion protocol, female mice exposed to 2,056 ppm of PS-6 blend unleaded gasoline vapor for 6 hours/day, 5 days/week for 16 weeks exhibited increases in relative liver weight, in the number of gross hepatic neoplasms, and in the size and volume of altered hepatic foci in N-nitrosodiethylamine-initiated mice. The PS-6 blend of unleaded gasoline was derived from the same lot used in the cancer bioassay conducted by MacFarland et al. 1984. Cotreatment with ethinyl

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estradiol (EE2) (added to the diets at a concentration of 1 ppm) potentiated unleaded gasoline-induced liver tumor promotion. Treatment with 2,056 ppm unleaded gasoline also resulted in antiestrogenic effects, including decreased relative uterine weight and partial reversal of EE2-induced body weight loss, anestrus, and vaginal keratinization. Unleaded gasoline at a concentration of 292 ppm was without effect, either in the presence or absence of EE2. The conclusion that unleaded gasoline may promote liver tumors in female mice secondary to antiestrogenicity was based on findings that estrogens normally act to suppress liver tumor promotion in mice, and unleaded gasoline exhibits potential antiestrogenic properties (Standeven et al. 1994a). While available data provide strong support for an antiestrogenic effect of unleaded gasoline with respect to the pharmacological actions of exogenous estrogen, the support is weak for such an effect on endogenous estrogen (Standeven et al. 1994a). In this regard, only the effect of unleaded gasoline on uterine weight is indicative of a potential antiestrogenic effect (Standeven et al. 1994a). Subchronic exposure of mice to unleaded gasoline vapor did not affect serum 17 β -estradiol levels, uterine estrogen receptor levels, or reproductive tract histology (Standeven et al. 1994a). Although acute oral administration of unleaded gasoline to female mice resulted in an increase in estrogen metabolism in isolated hepatocytes, there were no functional antiestrogenic changes associated with the enhanced estrogen metabolism (Standeven et al. 1994b). Therefore, it is unclear whether or not the uterine effects observed in chronic toxicity studies of unleaded gasoline are due to a direct antiestrogenic effect of gasoline. Also, the potential link between possible antiestrogenic effects of unleaded gasoline and the development of hepatocellular tumors in female mice is not clear.

In female B6C3F₁ mice, unleaded gasoline vapor has been demonstrated to induce the activity of the hepatic microsomal enzyme pentoxoresorufin-o-dealkylase, an enzyme associated with CYP2B, a cytochrome P-450 isoform commonly induced by rodent liver tumor promoters (Standeven and Goldsworthy 1993). The unleaded gasoline associated with the induction of CYP2B was the PS-6 blend; mice were exposed to 2,039 ppm 6 hours/day, 5 days/week for 13 weeks. Exposure to PS-6 unleaded gasoline also increased cytochrome P-450 content and promoted hepatic preneoplastic lesions. Data have also demonstrated that the API 91-1 blend of unleaded gasoline, a blend containing a high content of saturated hydrocarbons, displays promotional effects similar to the PS-6 blend (Standeven and Goldsworthy 1993).

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2.4 RELEVANCE TO PUBLIC HEALTH

Humans living in areas surrounding hazardous waste sites may be exposed to gasoline via inhalation of gasoline vapors or ingestion of and dermal contact with contaminated water. For the majority of the general population (i.e., those not living in the vicinity of hazardous waste sites), the major route of exposure to gasoline is inhalation of gasoline vapors during automobile refueling, refueling of gasoline-powered equipment (e.g., lawn mowers), and through the use of untreated surface water or groundwater that has become contaminated with gasoline from spills or leaking underground storage tanks. For occupationally exposed individuals, the predominant route of exposure is the inhalation of gasoline vapors, but the possibility for dermal contact with gasoline also exists. Occupational exposure to gasoline can occur for workers all along the chain from gasoline production to consumer use. Workers involved in onloading and offloading gasoline at docks, bulk storage terminals, and gas stations, delivering fuel to storage terminals and gas stations, and refueling and automotive repair operations at service stations have a large potential for exposure (Runion 1988). Workers involved in the clean-up and maintenance of underground storage tanks and service station pump equipment are also exposed to higher-than-background levels of gasoline and gasoline vapor (Runion 1988). However, the majority of the general population is not likely to have significant exposures to gasoline.

Gasoline is composed of at least 150 hydrocarbons, several of which have toxic effects of their own (e.g., benzene, toluene, xylene, and ethylbenzene). Gasoline has been shown to be irritating at the portal of entry (i.e., the eyes, the lungs after inhalation, or the gastrointestinal mucosa after ingestion). One target of gasoline-induced toxicity appears to be the nervous system in both humans and animals. A whole spectrum of neurological effects can be seen following acute exposure to high levels of gasoline, either by inhalation or ingestion, that increase in severity with increasing dose. The neurotoxicity observed in humans or animals exposed to leaded gasoline may be partially attributed to the organic lead compounds present in the mixture. Inhalation of very high concentrations of gasoline vapors or ingestion of gasoline can be fatal in both humans and animals. Adverse respiratory effects (e.g., chemical pneumonitis, pneumonia, pulmonary hemorrhage, and edema) are sometimes seen in humans after ingestion of large amounts of gasoline. These effects are due to the aspiration of gasoline from the stomach following vomiting. Blood dyscrasias have been noted in humans acutely and chronically exposed to gasoline vapors, but these effects are most likely due to benzene, and the

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incidence of these findings has decreased as the benzene content in gasoline has decreased. No such effects have been observed in experimental animals. Gasoline, along with a diverse group of hydrocarbons, has been shown to induce α_{2u} -globulin-mediated nephropathy and renal tumors in male rats. These nephrotoxic and renal carcinogenic effects are believed to be unique to male rats and are most likely not relevant to humans. There is insufficient epidemiological evidence to link exposure to gasoline with cancer in humans. However, inhalation of gasoline vapors has been shown to induce an increased incidence of hepatocellular tumors in female mice. The relevance of the observed hepatocellular tumors in female mice to humans is not known.

Minimal Risk Levels for Automotive Gasoline

Inhalation

No inhalation MRLs were derived because gasoline contains many components which can vary significantly among the many compositions of gasoline. The toxicity of gasoline would depend on the specific composition.

Oral

No oral MRLs were calculated because of the variability in the composition of gasoline. Also, no quantitative information on adverse effects other than α_{2u} -globulin-mediated nephropathy in male rats was available. As discussed in Section 2.2.1.2, Renal Effects, α_{2u} -globulin-mediated nephrotoxicity is not considered an appropriate end point for the derivation of MRLs for gasoline because it is unique to male rats and, thus, not relevant to human risk assessment.

Death. Inhalation of gasoline vapors or ingestion of gasoline can be fatal to both humans and experimental animals. Several case reports of either accidental or intentional inhalation or ingestion of gasoline resulting in death have been published (Ainsworth 1960; Boeckx et al. 1977; Camevale et al. 1983; Poklis 1976; Wang and Irons 1961). Lethal concentrations of gasoline vapors have been reported to range from >5,000 ppm to 20,000 ppm in humans (Ainsworth 1960; Wang and Irons

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1961), whereas the lethal ingested dose of gasoline has been estimated to be 12 ounces (350 g, or 5 g/kg for a 70-kg individual) (Anonymous 1989). The cause of death following inhalation of gasoline vapors or ingestion of gasoline has been postulated to be either central nervous system depression (asphyxia) leading to respiratory failure or cardiac sensitization to circulating catecholamines resulting in the occurrence of a fatal arrhythmia (EPA 1987a; Poklis 1976). In addition, ingested gasoline can be aspirated leading to severe chemical pneumonitis (EPA 1987a).

Acute lethal concentrations (LC₅₀s) of airborne gasoline in experimental animals have not been reported. The acute oral LD₅₀ for gasoline in rats has been reported to be 18.8 mL/kg, or approximately 14,063 mg/kg (Beck et al. 1983; Vemot et al. 1990). This is higher than the approximate lethal dose estimated for humans cited above (12 ounces, which is equivalent to approximately 5 mL/kg, or 3,740 mg/kg). The lethal dose of gasoline following dermal exposure has not been determined in animals, but it does exceed 8.0 mL/kg, or 6,000 mg/kg, indicating that it is relatively nontoxic by the dermal route (Beck et al. 1983). Under the exposure conditions expected to be present at hazardous waste sites, it is not expected that lethal air or water concentrations of gasoline will be achieved.

Systemic Effects

Respiratory Effects. Intentional or accidental ingestion of gasoline often results in aspiration of the gasoline into the lungs because of its high volatility and low surface tension. Therefore, the most common effect associated with acute gasoline ingestion in humans is aspiration pneumonia which is often accompanied by respiratory distress, pulmonary edema, emphysema, and focal alveolar hemorrhage (Banner and Walson 1983; Beamon et al. 1976; Carnevale et al. 1983; Grufferman and Walker 1982; Janssen et al. 1988). Death from asphyxia is often the result in cases of gasoline ingestion when the aspiration pneumonia becomes severe. Atelectasis, laryngeal edema, and upper airway obstruction were observed in a 34-year-old man who had been immersed in a pool of gasoline for approximately 8 hours, suggesting that adverse respiratory effects may occur following a combination of dermal, inhalation, and oral exposure to gasoline (Simpson and Cruse 1981). No

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information is available on adverse respiratory effects in animals exposed to gasoline by oral administration.

While intermediate-duration inhalation exposure to 1,552 ppm unleaded gasoline vapors has been shown to have no effect on the lungs in rats or monkeys when examined at the light microscopic level (Kuna and Ulrich 1984), a progression of lesions indicative of fibrosing alveolitis was observed in rats exposed to 100 ppm gasoline vapors for 12 weeks (Lykke et al. 1979). In addition, a decrease in surfactant levels was reported in rats similarly exposed (Le Mesurier et al. 1979). This surfactant deficiency is probably involved in the pathogenesis of the fibrosing alveolitis observed at similar exposure levels. The results of these two studies indicate that gasoline-induced pulmonary changes may occur at levels previously thought to have no effect because the tissues were not examined ultrastructurally and/or other sensitive parameters of pulmonary function were not measured.

Gasoline vapors have been shown to be irritating to the lungs of rats, but not in mice that were similarly exposed (MacFarland et al. 1984). A mild multifocal pulmonary inflammatory response was seen in rats exposed to 2,056 ppm gasoline for 2 years, but not in mice, suggesting that rats are more susceptible to the pulmonary irritating effects of gasoline.

Cardiovascular Effects. No direct cardiovascular effects have been reported in humans after exposure to gasoline. One study in animals described ECG changes and disturbances in myocardial enzyme activities and electrolyte levels in rabbits after inhalation exposure to high levels of gasoline (Przybylowski 1971). However, limitations associated with this study preclude its use in assessing the potential cardiovascular risk to humans from exposure to gasoline. No adverse cardiovascular effects have been observed in animals exposed to levels of up to 2,056 ppm unleaded gasoline vapors for up to 2 years. The air and water concentrations of gasoline expected to be present at hazardous waste sites are unlikely to cause adverse cardiovascular effects.

Gastrointestinal Effects. Reports of human and animal ingestion of gasoline indicate that gasoline has a direct irritating effect on the gastrointestinal mucosal tissue. Damage to the digestive tract (severe esophagitis, gastritis, congestive failure, degeneration of the gastric epithelium, and mucositis of the

2. HEALTH EFFECTS

oral cavity) has been observed in individuals who accidentally or intentionally ingested gasoline (Camevale et al. 1983; Hoffman et al. 1980; Janssen et al. 1988). Similarly, rats that were administered unleaded gasoline for 4 weeks by gavage were found to have gastric erythema, erosion of the gastric mucosa, and ulceration of the gastric epithelium (Halder et al. 1985). This appears to be a direct portal-of-entry effect as inhalation exposure to gasoline does not result in any adverse gastrointestinal effects.

Hematological Effects. Several human case studies have been reported that describe the occurrence of hematological effects in individuals with known long-term exposure to gasoline vapors. However, in most of these cases, the hematological effects reported were most likely due to a constituent of gasoline. For example, basophilic stippling, increased erythrocyte protoporphyrin, and increased ALAD activity have been noted in individuals exposed to leaded gasoline vapor (Boeckx et al. 1977; Chessare and Wodarczyk 1988; Young et al. 1977). These effects are also known to occur with exposure to lead (see ATSDR toxicological profile for lead [ATSDR 1991]) and so may have been due to the presence of organic lead compounds in the gasoline. An increased incidence of various blood dyscrasias (anemia, hypochromia, thrombocytopenia, and neutropenia) has been observed in Nigerian males with known exposure to gasoline in their occupations as motor mechanics and road-side vendors of heavy motor oil and/or gasoline as compared to controls with no known exposure to gasoline (Niazi et al. 1989). The authors attributed the increased incidence of these disorders to benzene that is present in gasoline (see ATSDR toxicological profile for benzene [ATSDR 1991]).

Hemolysis and disseminated intravascular coagulation have been observed in cases of accidental or intentional acute ingestion of gasoline (Banner and Walson 1983; Janssen et al. 1988). The mechanism for these effects is not known, but they resolved within a few days after ingestion.

No adverse hematological effects have been noted in animals after inhalation exposure to up to 2,056 ppm unleaded gasoline vapors for up to 2 years (Kuna and Ulrich 1984; MacFarland et al. 1984). No information is available, however, on the hematological effects of gasoline following oral exposure in animals.

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Based on the findings reported above in humans, it appears that adverse hematological effects can occur following short-term, high-level exposure and longer-term, lower-level exposure to gasoline. These effects are most likely the result of exposure to benzene or lead, constituents of gasoline. The effects seen after acute exposure are most likely reversible, whereas the effects seen after long-term exposure may not be reversible.

Musculoskeletal Effects. One case of acute severe myopathy was reported in an 18 year-old male with a history of sniffing leaded gasoline (Kovanen et al. 1983). The mechanism by which gasoline could have induced this myopathy is not known. The authors speculated that the myopathy may have been due to individual susceptibility or that the patient may have had a subclinical, possibly metabolic, myopathy that was exacerbated by gasoline sniffing. No other reports of adverse muscular or skeletal effects in humans or animals following exposure to gasoline were found. The relevance of this one case of myopathy to humans exposed to gasoline at hazardous waste sites is not known.

Hepatic Effects. A transient increase in serum enzymes indicative of liver function (γ -glutamyl transferase, SGOT, SGPT, and CPK) has been noted in individuals who accidentally or intentionally ingested gasoline (Janssen et al. 1988) or who were immersed in gasoline (Simpson and Cruse 1981). While these enzyme changes suggest that acute exposure to gasoline caused liver toxicity, no histopathological evaluations were performed to ascertain the presence and extent of this toxicity. Given that no adverse noncancer hepatic effects have been noted in animals exposed to gasoline for 90 days or 2 years (Kuna and Ulrich 1984; MacFarland et al. 1984; Standeven and Goldsworthy 1993; Standeven et al. 1994a; Tilbury et al. 1993), the relevance of these transient enzyme changes in humans following acute exposures with regard to long-term, low-level exposure near hazardous waste sites is not known.

Renal Effects. Reversible renal injury (oliguria, tubular necrosis, interstitial edema, hematuria, and reduced creatinine clearance) has been reported in a number of case reports of individuals who accidentally or intentionally ingested gasoline (Banner and Walson 1983; Kuehnel and Fisher 1986; Janssen et al. 1988). Unleaded gasoline is one of a diverse group of hydrocarbons that have been shown to induce a unique syndrome of nephropathy in male rats that is associated with the

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accumulation of the protein, α_{2u} -globulin, following acute, subchronic, or chronic inhalation and oral exposure (Borrison Labs 1985; Garg et al. 1988, 1989; G&in et al. 1988; Halder et al. 1984, 1985; Kuna and Ulrich 1984; MacFarland et al. 1984; Murty et al. 1988; Olson et al. 1987a, 1988; Short et al. 1987, 1989a, 1989b) (see Section 2.2.1.2, Renal Effects).

The available data indicate that the nephrotoxic syndrome described above that is induced by unleaded gasoline and several other hydrocarbons is unique to male rats and not relevant to humans. The hepatic synthesis of α_{2u} -globulin is under androgenic control, and the protein is found at 100-300 times higher concentrations in male rat urine than in female rat urine (Shapiro and Sachchidananda 1982; Van Doren et al. 1983). There is no evidence that humans produce α_{2u} -globulin. Only trace quantities of proteins within the same protein family as α_{2u} -globulin have been identified in human urine (Olson et al. 1990). α_{2u} -Globulin and hyaline droplet accumulation, and the associated constellation of nephrotoxic effects that are observed in male rats, have not been observed in female rats or mice or monkeys of either sex exposed to unleaded gasoline (Kuna and Ulrich 1984; MacFarland et al. 1984). Estradiol treatment in male rats after the administration of 2 mL/kg of unleaded gasoline by gavage for 3 days reduced the content of α_{2u} -globulin in the renal cortex to 25%, 41%, and 52% on post-exposure days 3, 6, and 9, respectively, as compared to rats administered gasoline but given no hormone treatment (Garge et al. 1988). Furthermore, the removal of hyaline droplets was increased in the rats receiving estradiol treatment as compared to those receiving no hormones. In addition, this syndrome could not be induced in male NCI-Black-Reiter rats administered API PS-6 (Dietrich and Swenberg 1991). The NCI-Black-Reiter rat is an inbred strain of rats that does not synthesize α_{2u} -globulin. In their document entitled, "Alpha-2u-Globulin: Association with Chemically-Induced Renal Toxicity and Neoplasia in the Male Rat" (EPA 1991), EPA's Risk Assessment Forum concluded that in light of this evidence,

"If a compound induces α_{2u} -globulin accumulation in hyaline droplets, the associated nephropathy in male rats is not an appropriate end point to determine noncancer (systemic) effects potentially occurring in humans. Likewise, quantitative estimates of noncancer risk (e.g., reference doses and margin-of-exposure determinations) are based on other end points.

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Further,

“...if the sequence of lesions characteristic of the α_{2u} -globulin syndrome are present, the associated nephropathy in the male rat does not contribute to determinations of noncarcinogenic hazard or risk.”

Thus, it does not appear that the nephrotoxicity attributable to the α_{2u} -globulin syndrome observed in male rats after exposure to gasoline is relevant to humans exposed to gasoline at hazardous waste sites.

Endocrine Effects. No studies were located regarding endocrine effects in humans after exposure to gasoline. In rats, a decrease in relative adrenal weight was noted following intermediate-duration exposure to gasoline vapors (Kuna and Ulrich 1984). However, the toxicological significance of this change in adrenal weight is unknown since there no accompanying treatment-related histological effects.

Dermal Effects. Gasoline is irritating to the skin of both humans and animals. Partial or full skin thickness burns have been noted in individuals who were immersed in gasoline for several hours (Hansbrough et al. 1985; Simpson and Cruse 1981), and single as well as repeated applications of neat gasoline to the skin of rabbits cause slight to severe irritation (Beck et al. 1983). Gasoline is not a dermal sensitizer in guinea pigs (Vemot et al. 1990).

Ocular Effects. Ocular irritation was noted in human subjects exposed acutely to 200, 500, or 1,000 ppm atomized gasoline vapor (Davis et al. 1960; Drinker et al. 1943).

No ocular irritation was seen following the instillation of undiluted gasoline into the eyes of rabbits (Vemot et al. 1990).

Body Weight Effects. No studies were located regarding body weight effects in humans after exposure to gasoline. Intermediate- and chronic-duration exposures to gasoline vapors have been reported to cause significant decreases in body weight gain in rats and mice (MacFarland et al. 1984).

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Immunological and Lymphoreticular Effects. No studies were located regarding immunological and lymphoreticular effects in humans after exposure to gasoline.

No apparent immunological effects (as measured by IgG deposits in the kidney and lungs) were noted in rats or monkeys exposed to gasoline by inhalation for 90 days (Kuna and Ulrich 1984). Gasoline is not a dermal sensitizer in guinea pigs (Vemot et al. 1990).

Exposure to hydrocarbons has been loosely associated with Goodpasture's syndrome in humans. This syndrome is characterized by glomerulonephritis and pulmonary hemorrhage caused by the binding of circulating antibodies to basement membrane antigens on the glomerular and alveolar basement membranes, respectively (O'Regan and Turgeon 1986; Yamamoto and Wilson 1987). To determine whether gasoline exposure causes pulmonary alveolar damage, thereby allowing the passage of antibodies into the alveoli where they bind to lung basement membrane, rats were exposed by inhalation to unleaded gasoline (O'Regan and Turgeon 1986). The animals were then injected with sera containing anti-GBM, sacrificed, and the lungs were removed for light and immunofluorescence microscopy. The anti-GBM failed to bind to alveolar basement membrane in the gasoline-exposed animals as determined by immunofluorescence. Based on these results, it does not appear that exposure to gasoline in this manner damages the alveolar endothelium which would allow passage of anti-GBM and cause the pulmonary hemorrhage associated with Goodpasture's syndrome. However, in another study in which unleaded gasoline was administered to rabbits by intratracheal administration, horse anti-GBM/ABM antibodies were found bound to the ABM in a linear, but focal, fashion (Yamamoto and Wilson 1987). No deposits were found in the lungs of rabbits administered saline instead of gasoline. In addition, there was a significant increase in the uptakes of radiolabeled anti-GBM/ABM in the lungs of animals administered gasoline as compared to the animals administered saline. These results suggest that gasoline does damage the alveolar endothelium allowing the passage of antibodies into the alveoli, in contrast to the findings of O'Regan and Turgeon (1986). The reason for the discrepancy between the studies is not clear. One possible explanation is that intratracheal administration delivered a higher dose of gasoline to the lung than inhalation of gasoline vapors. The relevance of these findings to human exposure to gasoline at hazardous waste sites is not known.

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Neurological Effects. Acute exposure to gasoline vapors is characterized by a spectrum of effects that progress in severity and can include dizziness, headaches, giddiness, euphoria, vertigo, blurred vision, nausea, numbness, drowsiness, anesthesia, and coma (Poklis and Burkett 1977). Acute ingestion of large amounts of gasoline has also been reported to induce adverse neurological effects such as lethargy, convulsions, and coma (Beamon et al. 1976). Chronic exposure to gasoline (i.e., in individuals who habitually sniff gasoline for its euphoric/hallucinogenic properties) is associated with neurological effects, such as cerebellar effects including postural tremor, ataxia, abnormal gait, affected speech, fatigue, headaches, memory loss, and sleep problems (Carroll and Abel 1973; Coulehan et al. 1983; Goldings and Stewart 1982; Kaelan et al. 1986; Kullman and Hill 1990; Moss and Cooper 1986; Pandya et al. 1975; Rischbieth et al. 1987; Young et al. 1977). Behavioral and intellectual changes (effects on visual memory and perception, psychomotor disturbances, visuomotor learning ability) have been observed in individuals chronically exposed to gasoline (Carroll and Abel 1973; Kumar et al. 1988; Robinson 1978). Many of the neurological changes associated with exposure to leaded gasoline can be attributed to organic and inorganic lead encephalopathy (Robinson 1978; Valpey et al. 1978). However, the exact mechanism by which unleaded gasoline induces neurological effects is not known.

Animals acutely exposed to high levels of gasoline also exhibit neurotoxic effects, including restlessness, equilibrium disturbances, convulsions, and narcosis (Przybylowski 1971). Evidence of neuropathological effects (pigmentation of the neuronal cytoplasm, Wallerian degeneration, axonal degeneration, and axonal dystrophy) was found in rats chronically exposed to unleaded gasoline vapors (API PS-6) (API 1982). However, because of the small number of animals studied and the lack of statistical analyses, these results are of questionable value. Other chronic studies failed to note any exposure-related effects in rats or mice with respect to functional and behavioral indices or the histopathology of the brain, spinal cord, or peripheral nerves.

Based on information obtained in humans and animals, it is reasonable to expect that humans acutely exposed by inhalation to high levels of gasoline vapors or chronically exposed to low levels such as those found near hazardous waste sites will experience adverse neurological effects.

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Reproductive Effects. No studies were located regarding reproductive effects in humans after inhalation, oral, or dermal exposure to gasoline.

Only one study was available in animals in which male mice intermittently exposed to either 400 or 1,600 ppm unleaded gasoline vapors for 8 weeks showed no evidence of dominant effect on the sperm cells (Litton Bionetics 1980). The relevance of this finding with regard to adverse effects in humans is not known.

Although no exposure-related histopathological effects were noted in the reproductive organs of rats or mice exposed to 2,056 ppm unleaded gasoline vapors for 2 years (MacFarland et al. 1984), a recent reevaluation of slides from this bioassay revealed a decrease in the severity of uterine cystic endometrial hyperplasia in female mice. In addition, an increase in the incidence and severity of uterine atrophy was observed in aged female mice. It has been postulated that the uterine effects may be due to possible antiestrogenic effects of gasoline (Standeven et al. 1994a). The available data, however, provide only weak support for the antiestrogenic effect of gasoline on endogenous estrogen (Standeven et al. 1994a, 1994b). The available information is inadequate to assess the potential risk for reproductive effects in humans living in the vicinity of hazardous waste sites containing gasoline.

Developmental Effects. Anecdotal data have suggested a link between chronic gasoline vapor exposure of pregnant women and congenital defects of the central nervous system in their children. *In utero* exposure to leaded gasoline was found to cause retarded development and anomalies of head and muscles in two children (Hunter et al. 1979). Based on the limited available data, the study was considered inadequate to establish a relationship between inhalation exposure to gasoline and human developmental toxicity.

In contrast, no developmental effects were found in rats exposed to unleaded gasoline vapors at concentrations as high as 1,600 ppm during gestation (Litton Bionetics 1978). These data are insufficient to assess the developmental toxicity of gasoline in animals. No data were available for other routes of exposure in animals. Therefore, there are insufficient data to assess whether gasoline could induce developmental effects in humans exposed at hazardous waste sites.

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Genotoxic Effects. The potential genotoxicity of gasoline in humans was evaluated by measuring micronuclei induction in the peripheral lymphocytes of male gasoline pump mechanics in Sweden (Högstedt et al. 1991). In this study, the investigators compared the effects of gasoline on both B- and T-lymphocytes. The data showed that significant micronuclei induction was observed in the B-cells of the gasoline-exposed group but not in the T-cells. Since gasoline in Sweden may contain as much as 5% benzene (typical American automotive fuel contains 0.5-2.5% benzene), the study results should be interpreted with caution. This inclusion of benzene was also considered by the authors, who suggested that benzene may have been responsible for the genotoxic effects observed in this study (Högstedt et al. 1991). No other human epidemiology or case/control studies were found concerning the genotoxicity of gasoline. From this study it seems that gasoline, or at least components of gasoline (i.e., benzene), may produce some chromosomal damage in human B-lymphocytes. However, because exposure concentrations and exposure durations were not discussed and because Swedish gasoline contains higher concentrations of benzene than American fuel (see Chapter 3), it is difficult to determine the degree of exposure to American gasoline that would be harmful to humans.

In a UDS test, primary hepatocytes were recovered from three human surgery patients and were exposed to unleaded gasoline doses ranging from 0.01% to 0.1%. The results were difficult to interpret because neither the cytotoxic nor the genotoxic response was uniform. A weakly positive effect occurred in the cells from one of the three subjects and was confined to a single dose (0.01% unleaded gasoline). From these observations, the researchers concluded that human hepatocytes may not be particularly sensitive to gasoline genotoxicity (Butterworth et al. 1989). In a second UDS assay involving primary human hepatocytes, a significant increase in UDS was obtained at one dose (0.01%); exposure to higher levels (0.05%) resulted in severe cytotoxicity (Loury et al. 1986). Of additional interest was the marked increase in the percentage of cells in repair (25% in treated cells as compared to 1% in control cells).

Studies exposing whole animals to gasoline in vivo were largely negative for such genotoxic effects as chromosome aberrations in somatic cells, dominant lethal mutations in male germinal cells, and DNA damage (see Table 2-4). The oral exposure of Sprague-Dawley rats to unleaded gasoline (API PS-6) did not produce significant chromosome damage (Dooley et al. 1988). The lack of a clastogenic effect

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

Species (test system)	End Point	Results	Reference
Invertebrate animal cells: <i>Drosophila melanogaster</i> (<i>sc z w</i> ⁺)	Gene mutation	+	Nylander et al. 1978
Mammalian cells: Mouse (germinal cells)	Dominant lethal mutation	+/-	Litton Bionetics 1980
Mouse (primary hepatocytes)	Unscheduled DNA synthesis	+/-	Loury et al. 1986
Rat (primary hepatocytes)	Unscheduled DNA synthesis	-	Loury et al. 1986
Rat (kidney cells)	Unscheduled DNA synthesis	-	Loury et al. 1987
Rat (bone marrow cells)	Chromosome aberrations	-	Dooley et al. 1988
Rat (bone marrow cells)	Chromosome aberrations	-	Conaway et al. 1984
Human (peripheral lymphocytes)	Micronuclei induction	+/- ^b	Högstedt et al. 1991

^aLeaded gasoline containing approximately 0.01% 1,2-dichloroethane was used.

^bPositive result only from pokeweed mitogen induced lymphocytes; ≤ 5% benzene was present in the gasoline.

+ = positive result; +/- = inconclusive result; - = negative result; DNA = deoxyribonucleic acid; *sc z w*⁺ = transposable genetic element

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was supported by the negative findings of an additional in vivo cytogenetic assay. These results showed that neither the single intraperitoneal injection of 0.03, 0.1, or 0.3 mL per rat nor the intraperitoneal administration of 0.013, 0.04, or 0.13 ml/rat/day unleaded gasoline that contained 2% benzene and 39% aromatics for 5 days induced a clastogenic response in the bone marrow cells of male and female Sprague-Dawley rats (Conaway et al. 1984). No significant decrease in pregnancy or increase in pre- or postimplantation loss were observed in female CD-1 mice impregnated by males that inhaled unleaded gasoline prior to mating (Litton Bionetics 1980). The findings, however, are not conclusive; the sample size of pregnant females was too small to clearly establish that unleaded gasoline did not induce dominant lethal mutations. UDS was not significantly increased in the kidney cells of Fischer-344 rats exposed to unleaded gasoline (API PS-6) by inhalation or gavage (Lout-y et al. 1987), nor was UDS activity increased in the hepatocytes of male rats exposed orally to unleaded gasoline (API PS-6) (Loury et al. 1986). However, a significant rise in the number of dividing kidney cells (SDS) was observed in male rats exposed to unleaded gasoline via both oral and inhalation routes. The oral route of exposure produced the greater effect. However, cell turnover was not increased in the females (Loury et al. 1987). A weakly positive response for UDS activity was observed in hepatocytes from B6C3F₁ mice orally exposed to unleaded gasoline. In agreement with the findings in male rat kidney cells, male mice exhibited a statistically significant increase in percentage of replicating hepatocytes; no S-phase induction was seen in the females (Loury et al. 1986).

The weight of evidence from in vivo animal studies suggests that, as a mixture, unleaded gasoline is not genotoxic to rats and probably not strongly genotoxic to mice. It is possible, however, that unleaded gasoline is toxic to organs such as the kidney and liver in male rodents. The relevance of these results to humans is indeterminable at this time.

Leaded gasoline, containing approximately 0.01% 1,2-dichloroethane, was evaluated for mutagenic effects in *Drosophila melanogaster*. Larvae fed 1.0% and 2.5% gasoline showed significantly increased frequencies of somatic mutations (Nylander et al. 1978). Because 1,2-dichloroethane alone also induced a powerful mutagenic response in this study, the authors concluded that the mutagenic activity observed with gasoline was probably due to the 1,2-dichloroethane component. Although 1,2-

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dichloroethane is typically included in American unleaded gasoline as a lead scavenger, the concentration was not specified in this study. Therefore, the relevance of this finding to public health is inconclusive.

Gasoline genotoxicity was evaluated using human cells *in vitro* (see Table 2-5). Human TK6 lymphoblastoid cells were examined for mutations at the TK^{+/-} locus following treatment with 0.6% and 1.2% unleaded gasoline; higher concentrations were cytotoxic. No significant increase in incidence of mutations was observed either with or without metabolic activation (Richardson et al. 1986). The test mixture used in this study was API PS-6. Similarly, exposure to the volatile components of unleaded gasoline both with and without metabolic activation failed to induce a mutagenic effect. The same investigators reported that unleaded gasoline (API PS-6) (0.6% and 1.2% with or without activation) did not induce sister chromatid exchange in the human TK6 lymphoblastoid cell line (Richardson et al. 1986).

In vitro rodent studies produced mixed results (see Table 2-5). Mouse lymphoma L5178Y (TK^{+/-}) cells were considered negative for gene mutations because no consistent upward trend in the mutation frequency was observed (Conaway et al. 1984). In another study using mouse lymphoma cells, increases in the mutation frequency to at least twice that of the controls were observed at dose levels of API PS-6 that reduced cell growth to approximately 5% or lower (0.060 and 0.070 $\mu\text{L}/\text{mL}$ without metabolic activation, 0.150 and 0.175 $\mu\text{L}/\text{mL}$ with activation); there was, however, no dose-related effect (Dooley et al. 1988). Without evidence of a dose response, the increased mutation frequencies at severely cytotoxic levels should not be considered indicative of mutagenesis. Mouse hepatocytes were positive for UDS activity at the lowest assayed concentration (0.01% unleaded gasoline [API PS-61]); higher doses, 0.03% and 0.05%, were cytotoxic (Loury et al. 1986). Exposure of rat hepatocytes to unleaded gasoline (API PS-6) produced inconsistent results for UDS. In one study, concentrations of 0.05% and 0.1% unleaded gasoline induced reproducible and significant dose-dependent UDS responses (Loury et al. 1986). In the second study, rat hepatocytes exposed to concentrations of API PS-6 ranging from 0.0001% to 0.010% (from 0.1 to 10 $\mu\text{L}/\text{mL}$) showed no significant increase in UDS activity at any level (API 1988). It was noted, however, that cell survival at the highest assayed level (88%) was only marginally affected by treatment. It is conceivable that

TABLE 2-5. Genotoxicity of Gasoline *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
<i>Salmonella typhimurium</i> (TA1535, TA1537, TA1538, TA98, TA100) ^a	Gene mutation	-	-	Conaway et al. 1984
<i>S. typhimurium</i> (TA98, TA100) ^b	Gene mutation	-	+/-	Conaway et al. 1984
<i>S. typhimurium</i> (TA1535, TA1537, TA1538) ^b	Gene mutation	-	-	Conaway et al. 1984
Eukaryotic organisms:				
Mammalian cells:				
Mouse L5178Y lymphoma cells (TK ⁺ locus)	Gene mutation	-	-	Dooley et al. 1988
Mouse L5178Y lymphoma cells (TK ⁺ locus)	Gene mutation	-	-	Conaway et al. 1984
Mouse (primary hepatocytes)	Unscheduled DNA synthesis	+ ^c	NA	Loury et al. 1986
Rat (primary hepatocytes)	Unscheduled DNA synthesis	+	NA	Loury et al. 19986
Rat (kidney cells)	Unscheduled DNA synthesis	No data	-	Loury et al. 1987
Rat (primary hepatocytes)	Unscheduled DNA synthesis		NA	API 1988
Human TK6 lymphoblastoid cells (TK ⁺ locus)	Gene mutation	-	-	Richardson et al. 1986
Human TK lymphoblastoid cells	Sister chromatid exchange	-	-	Richardson et al. 1986

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

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Human (primary hepatocytes)	Unscheduled DNA synthesis	- ^d	NA	Butterworth et al. 1989
Human (primary hepatocytes)	Unscheduled DNA synthesis	+ ^c	NA	Loury et al. 1986

^aPlate assay

^bSuspension assay

^cLowest of three doses produced significantly positive result; higher doses were cytotoxic or lethal and prevented an accurate evaluation of unscheduled DNA synthesis activity.

^dHepatocytes were analyzed from three surgery patients; the cells from two out of three patients were negative for unscheduled DNA synthesis.

-- = negative result; +/- = inconclusive result; + = positive result; DNA = deoxyribonucleic acid; NA = not applicable; TK = thymidine kinase

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the concentrations evaluated in this second study were below the range of detection of a UDS response. Rat kidney cells were negative for UDS activity following the *in vitro* exposure to 0.005% and 0.010% unleaded gasoline (API PS-6); higher doses, 0.050% and 0.100%, were cytotoxic (Loury et al. 1986).

Ames *Salmonella* tests were negative for gene mutation both with and without metabolic activation (see Table 2-5). No mutagenic effect was seen in the Ames Salmonella/microsome plate incorporation assay conducted with unleaded gasoline containing 2% benzene and 39% aromatics at concentrations ranging from 0.001 to 5 $\mu\text{L}/\text{plate}$ (Conaway et al. 1984). When the assay was repeated using the preincubation modification of the Ames test with a dose range of 3.75-30 $\mu\text{L}/\text{mL}$, increased mutant colony counts for strains TA98 and TA100 were observed but were confined to the highest nonactivated dose (30 $\mu\text{L}/\text{mL}$). At this concentration, there was an approximate 50% reduction in cell survival. In the absence of a dose-related effect, increases in mutant colonies at cytotoxic levels cannot be considered conclusive evidence of mutagenesis.

Cancer. A number of epidemiological studies have been conducted on workers occupationally exposed to petroleum and hydrocarbons, including gasoline. These studies all have several inherent limitations that preclude their use as evidence for an association between gasoline exposure and cancer in humans. These include lack of information on levels of exposure to gasoline vapor; concurrent exposure to other potentially carcinogenic substances (i.e., service station attendants are also exposed to motor oils, diesel fuel oils, and solvents as well as automobile and truck engine exhausts); no adjustment for potential confounding factors (e.g., smoking); and no latency analyses. EPA (1987a) reviewed 55 relevant studies of unleaded gasoline-exposed populations and concluded that the evidence for drawing causal inferences between unleaded gasoline and cancer was inadequate. Some of the recent epidemiological data suggest a possible association between gasoline exposure and kidney cancer and leukemia.

An exposure-related increase in the incidence of renal tubular tumors was observed in male rats exposed to unleaded gasoline vapors for 2 years (MacFarland et al. 1984). Female rats and mice of both sexes similarly exposed in this experiment failed to exhibit renal tumors. The renal tubular

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tumors observed in the male rats are considered to be the result of a process involving the accumulation of α_{2u} -globulin that ultimately leads to cytotoxicity, tubular epithelium degeneration, hyperplastic regeneration, and tumors (MacFarland et al. 1984). The relevance of α_{2u} -globulin-mediated male rat nephropathy and carcinogenicity to humans has been questioned (see previous subsection on Renal Effects). EPA (1991) has concluded that.

“Male rat renal tubule tumors arising as a result of a process involving α_{2u} -globulin accumulation do not contribute to the qualitative weight-of-evidence that a chemical poses a human carcinogenic hazard. Such tumors are not included in dose-response extrapolations for the estimation of human carcinogenic risk.”

An exposure-related increase in the incidence of hepatocellular tumors was observed in female mice exposed to unleaded gasoline vapors for 2 years (MacFarland et al. 1984). Some of these tumors metastasized to the lungs.

The MacFarland et al. (1984) study is limited with respect to its relevance to human health risk because the animals were exposed to wholly vaporized gasoline, which has the same composition as liquid gasoline and is not the same as the gasoline vapors that humans would be exposed to in ambient conditions. Gasoline emissions normally found in the environment contain lower concentrations of hydrocarbons with very low vapor pressures (i.e., the branched-chain hydrocarbons, such as 2,2,4-trimethylpentane, that have been shown to induce nephrotoxicity) than those found in liquid gasoline. Thus, the studies in animals using wholly vaporized gasoline may not adequately reflect the carcinogenic risk to humans.

Based on the weight-of-evidence from the animal data discussed above, EPA (1987a) classified gasoline as a Group B2 (probable) carcinogen.¹

¹This classification has not been verified by EPA's Carcinogenicity Risk Assessment Verification Endeavor (CRAVE) Workgroup, is not on IRIS, and is currently undergoing review by EPA.

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Benzene, a component of gasoline, is a known human carcinogen that has been shown to cause an increased incidence of hematopoietic cancers (leukemia) in occupationally exposed workers (see toxicological profile for benzene [ATSDR 1991]). However, as discussed above and in Section 2.2.1.8, the evidence for an association between increased incidence of cancer (including leukemia) and exposure to gasoline in humans is inadequate. Furthermore, while there is sufficient evidence that benzene is carcinogenic in rats, causing an increased incidence of tumors at multiple sites including the oral and nasal cavities, Zymbal gland, and the liver, as well as myelogenous neoplasms (see toxicological profile for benzene [ATSDR 1991]), gasoline has only been shown to cause increased incidences of renal cell tumors in male rats (a finding that is not considered relevant to humans) and liver tumors in female mice. Therefore, there is no conclusive evidence to support or refute the carcinogenic potential of gasoline in humans or animals based on the carcinogenicity of one of its components, benzene.

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 (NASLNRC 1989).

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

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are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to gasoline 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 gasoline are discussed in Section 2.5.2.

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

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Gasoline

Increased blood and urine lead levels were at one time commonly used as indicators of exposure to gasoline. However, the phasing out of leaded gasoline and increased use of unleaded gasoline have decreased the effectiveness of monitoring for blood or urine lead as a biomarker for gasoline exposure. It should also be noted that elevated blood lead and urine levels are not specific for exposure to gasoline and could indicate exposure to any of the lead compounds. Elevated blood and urine lead levels have been observed in several chronic gasoline sniffers (Goldings and Stewart 1982; Robinson 1978). Gasoline vendors who had been exposed to gasoline in the workplace for anywhere from 4 months to 35 years had mean total blood lead levels of 32.9 $\mu\text{g}/100 \text{ mL}$, significantly higher than levels found in the control population (14.3 $\mu\text{g}/100 \text{ mL}$) (Moore et al. 1976).

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Increased urinary thioether output has limited use as a biomarker of exposure to gasoline. Many of the hydrocarbons in gasoline are metabolized by the mixed function oxidase system and the metabolites then undergo conjugation with glutathione, followed by urinary excretion as mercapturates (thioethers). Gasoline pump attendants and garage mechanics excreted higher than normal levels of urinary thioether at the end of the day (Stock and Priestly 1986). The differences were greater in attendant-operated outlets than in self service outlets. These results indicate that occupational exposure to gasoline induces increased urinary thioether output. However, increased urinary thioether output is not specific for exposure to gasoline and could indicate exposure to a number of chemicals. It should be noted that this study was complicated by the fact that several of the workers were smokers. Cigarette smoke is known to induce mixed function oxidase activity and thus may alter the output of metabolites that conjugate with glutathione. The influence of cigarette smoking on the urinary excretion of thioethers has been studied in workers employed in suburban petroleum retail outlets. Workers exposed to gasoline at driveway attended stations excreted a significantly greater amount of thioethers in the urine than those at self service outlets (Edwards and Priestly 1993). Urinary thioethers excretion tended to be higher in smokers than in nonsmokers. The difference between the 2 groups was not statistically significant. In addition, postwork urinary thioether concentrations were positively correlated with cigarette smoking.

Biomarkers of benzene exposure such as elevated urinary phenol levels are often used to detect exposure to gasoline. The average level of urinary phenol excreted by gasoline workers was 40 mg/L which is higher than the normal amount (<20 mg/L) (Pandya et al. 1975). It should be noted that the benzene content of the gasoline used in this study was relatively high, 10-17%, as compared to typical American gasoline which contains 0.5-2.5% benzene (see Chapter 3). For more information on the use of urinary phenol as a biomarker of benzene exposure, see the ATSDR toxicological profile for benzene (ATSDR 1991).

The hydrocarbon components of gasoline such as benzene, toluene, pentane, and hexane have been measured in the blood of gasoline-exposed humans (Brugnone et al. 1986; Kimura et al. 1988; Matsubara et al. 1988). Also, benzene, toluene, and xylenes were detected in the blood samples collected from Wistar rats immediately after exposure to 5,000 ppm gasoline vapor for 30 minutes

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(Kimura et al. 1988). Increased hydrocarbon blood levels are not specific for gasoline exposure and are not commonly used as biomarkers of exposure.

2.5.2 Biomarkers Used to Characterize Effects Caused by Gasoline

Potential biomarkers for neurological effects of gasoline are slowed motor nerve conduction velocity and indices of cerebellar dysfunction. Some chronically exposed individuals were found to have abnormal slowing of nerve conduction (Gallassi et al. 1980; Goldings and Stewart 1982; Hall et al. 1986; Hansen and Sharp 1978; Rischbieth et al. 1987; Robinson 1978; Seshia et al. 1978). Cerebellar dysfunction (e.g., ataxia, poor coordination, decreased muscle tone, broad-based gait, myoclonic movements) is a typical symptom observed in gasoline sniffers (Carroll and Abel 1973; Coulehan et al. 1983; Goldings and Stewart 1982; Kaelan et al. 1986; Moss and Cooper 1986; Rischbieth et al. 1987; Young et al. 1977). These neurological effects are not specific for gasoline exposure and could indicate exposure to lead or any other neurotoxic substance. General neurological effects such as nausea, vomiting, irritability, restlessness, and anxiety were observed in people exposed to lead and other components of gasoline. These could possibly be used as biomarkers of exposure to high levels of gasoline but, because of their nonspecificity, would only be useful when gasoline exposure is suspected.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Limited data are available on the interactions between the gasoline mixture and other substances. The metabolic interactions of benzene and gasoline vapor have been investigated in male Fischer-344 rats by utilizing a closed chamber gas-uptake exposure system to study uptake and metabolism. It was demonstrated that benzene metabolism in male rats can be decreased in the presence of gasoline vapor (Travis et al. 1992). The gasoline used in the study contained 170 ppm benzene. A physiologically based pharmacokinetic model of benzene metabolism indicated that the inhibitory effect could not be accounted for by the presence of toluene. Some information is available on the interactions between the individual components of gasoline and other substances. For example, benzene toxicity is affected by compounds that alter its metabolism such as alcohol, drugs, and industrial chemicals (Goldstein 1977; NESCAUM 1989). Also, the toxicity of benzene may be enhanced by other myelotoxic agents

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such as radiation, metals, halogenated hydrocarbons, and pesticides (Goldstein 1977; NESCAUM 1989). For more information on the interactions of the individual components of gasoline with other substances, see the appropriate ATSDR toxicological profiles on these compounds (ATSDR 1989, 1990, 1991).

The interactions among the components of gasoline should also be considered. The number of potential interactions within gasoline increases exponentially with the number of components (NESCAUM 1989). Since gasoline may contain as many as 1,000 chemical substances, the number of possible interactions is very large. It is not possible, however, to reliably predict the effects of these complex interactions (NESCAUM 1989). There are data indicating that the interactions among the components may influence their characteristic absorption, distribution, metabolism, and elimination patterns. For more information on toxicokinetics of gasoline, see Section 2.3.

The interaction between unleaded gasoline and exogenous estrogen in liver tumor promotion has been demonstrated in female mice (Standeven et al. 1994). Female mice (12 day old) were administered intraperitoneal injections of N-nitrosodiethylamine (DEN) or vehicle. The mice were exposed to wholly vaporized PS-6 blend unleaded gasoline vapor at concentrations of 0, 292, or 2,056 ppm for 6 hours/day, 5 days/week for 16 weeks. Increases in relative liver weight, the number of gross hepatic neoplasms, and the size and volume of altered hepatic foci were observed in DEN-initiated mice treated with 2,056 ppm unleaded gasoline. These effects were not observed in DEN-initiated mice treated with 292 ppm unleaded gasoline. Additionally, groups of mice were exposed to 1 ppm ethinyl estradiol (EE2) in the diet or to 1 ppm EE2 in the diet as well as to 2,056 ppm unleaded gasoline vapor for 16 weeks. Cotreatment with EE2 potentiated the unleaded gasoline-induced liver tumor promotion. Treatment with 2,056 ppm unleaded gasoline also resulted in antiestrogenic effects, including decreased relative uterine weight and partial reversal of EEZ-induced body weight loss, anestrus, and vaginal keratinization.

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2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to gasoline than will most persons exposed to the same level of gasoline in the environment. Reasons for such a response include genetic make-up, developmental stage, health and nutritional status, and chemical exposure history. These parameters may result in decreased function of the detoxification and excretory processes (mainly hepatic and renal) or may affect 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."

Limited data are available on populations that are unusually susceptible to the toxic effects of gasoline. There are limited data that gasoline may enhance sister chromatid exchange in circulating lymphocytes of cigarette smokers, possibly as a consequence of increased hepatic metabolism of gasoline to reactive metabolites (Edwards and Priestly 1993). Most of the information available on susceptible populations of gasoline toxicity pertains to the benzene component. In general, benzene exposures are likely to present a concern for those whose immune systems are not functioning optimally, such as the very young and the very old. There is some evidence to suggest that females are more susceptible to benzene toxicity (Goldstein 1977). Furthermore, pregnant women, whose hematopoietic systems are naturally under stress, may be particularly susceptible to benzene toxicity (Calabrese 1978). Benzene toxicity may be potentiated in the presence of thalassemia (abnormal hemoglobins) and malnutrition (Aksoy 1989; Calabrese 1978; Goldstein 1977). The hematotoxic effects of benzene may be enhanced by ethanol (Baarson et al. 1982, Nakajima et al. 1985). This is of particular concern for gasoline-exposed workers who consume alcohol. (Note that this is not a comprehensive discussion of populations that are susceptible to benzene toxicity. For more information on populations unusually susceptible to the toxic effects of gasoline's components, see the appropriate toxicological ATSDR profiles [ATSDR 1989, 1990, 1991]).

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2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section describes clinical practice and research concerning methods for reducing toxic effects of exposure to gasoline. 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 gasoline. 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

Supportive treatment following ingestion or inhalation of gasoline may include the following: assisted ventilation techniques, treatment for pulmonary edema and seizures, administration of oxygen, administration of antiarrhythmics and anticonvulsants, intravenous administration of dextrose in water, dialysis, and hepatic failure treatment (Bronstein and Currance 1988; Ervin and Manske 1990; Goldfrank et al. 1990; Graham 1990). In cases of chronic gasoline inhalation, it may be necessary to screen for electrolyte imbalance and acid-base disturbances and to check serum lead and free erythrocyte protoporphyrin levels (Ellenhorn and Barceloux 1988). For serious cases of aspiration secondary to gasoline ingestion, it may be necessary to follow acid-base status, fluid and electrolyte balance, renal and liver function, and serial arterial blood gases (Ellenhorn and Barceloux 1988). The use of epinephrine is not suggested because it may precipitate lethal arrhythmias in the sensitized myocardium (Bronstein and Currance 1988; Ervin and Manske 1990; Goldfrank et al. 1990). Antibiotic and steroid treatment are not usually advocated; however, it may be necessary to administer steroids in the case of “shock lung” (Ellenhorn and Barceloux 1988; Ervin and Manske 1990; Goldfrank et al. 1990).

Methods used to increase the elimination of gasoline hydrocarbons from the gastrointestinal tract following ingestion include induction of vomiting, lavage, and the administration of cathartics. Much controversy surrounds the use of emetics as a means for gastrointestinal elimination of gasoline. The traditional view is that vomiting should not be induced because of the risk of aspiration and damage to the lung (Bronstein and Currance 1988; Ervin and Manske 1990). According to another point of view, the risk of aspiration during emesis is not very great; therefore, ipecac-induced emesis is recommended

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in the alert patient who has ingested large amounts of gasoline (Ellenhorn and Barceloux 1988). In children, it is recommended that nothing be done to remove the substance from the stomach (Goldfrank et al. 1990). Since emesis causes fewer pulmonary complications than lavage, it is the preferred method for gastrointestinal decontamination (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; Ng et al. 1974). However, for those patients who are too obtunded to ingest syrup of ipecac, lavage may be necessary. Lavage with the use of an endotracheal tube to protect the airway is suggested (Ellenhorn and Barceloux 1988; Ervin and Manske 1990; Goldfrank et al. 1990). Since aspirated oils can cause lipoid pneumonia and increase absorption of gasoline, the use of oils as cathartics should be avoided (Beamon et al. 1976; Goldfrank et al. 1990). The use of saline cathartics or sorbitol has been suggested (Ervin and Manske 1990). Activated charcoal does not effectively adsorb gasoline (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990). In the case of leaded gasoline ingestion, chelation therapy may be used to lower the inorganic lead produced in the body. There is no antidote for triethyl lead intoxication (Garrettson 1990).

Following dermal exposure to gasoline, the skin should be either washed with copious amounts of soapy water or soaked in water for a prolonged period of time (Goldfrank et al. 1990; Stutz and Janusz 1988). In the case of extensive dermal injuries, early debridement might be considered especially if the gasoline contains lead additives (Hansbrough et al. 1985). If the eyes are exposed, they should be thoroughly flushed with water (Goldfrank et al. 1990; Stutz and Janusz 1988).

2.8.2 Reducing Body Burden

There are no known effective methods for reducing the body burden of gasoline. Very little is known about the toxicokinetics of gasoline. However, the elimination rate of components of gasoline, for example, benzene and toluene, probably varies because of the metabolism of the gasoline components by the hepatic enzymes. Thus it is conceivable that alteration of the activities of hepatic enzymes may affect the elimination of gasoline.

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2.8.3 Interfering With the Mechanism of Action for Toxic Effects

Although several mechanisms have been proposed for the development of α_{2u} -globulin nephropathy in the male rat following exposure to gasoline, this syndrome is unique to male rats and is not relevant to humans. The antiestrogenic effects of unleaded gasoline have been proposed as a possible underlying mechanism of the induction of hepatic tumors in female mice; however, this effect may be species and sex specific (Standeven et al. 1994a).

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 gasoline 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 gasoline.

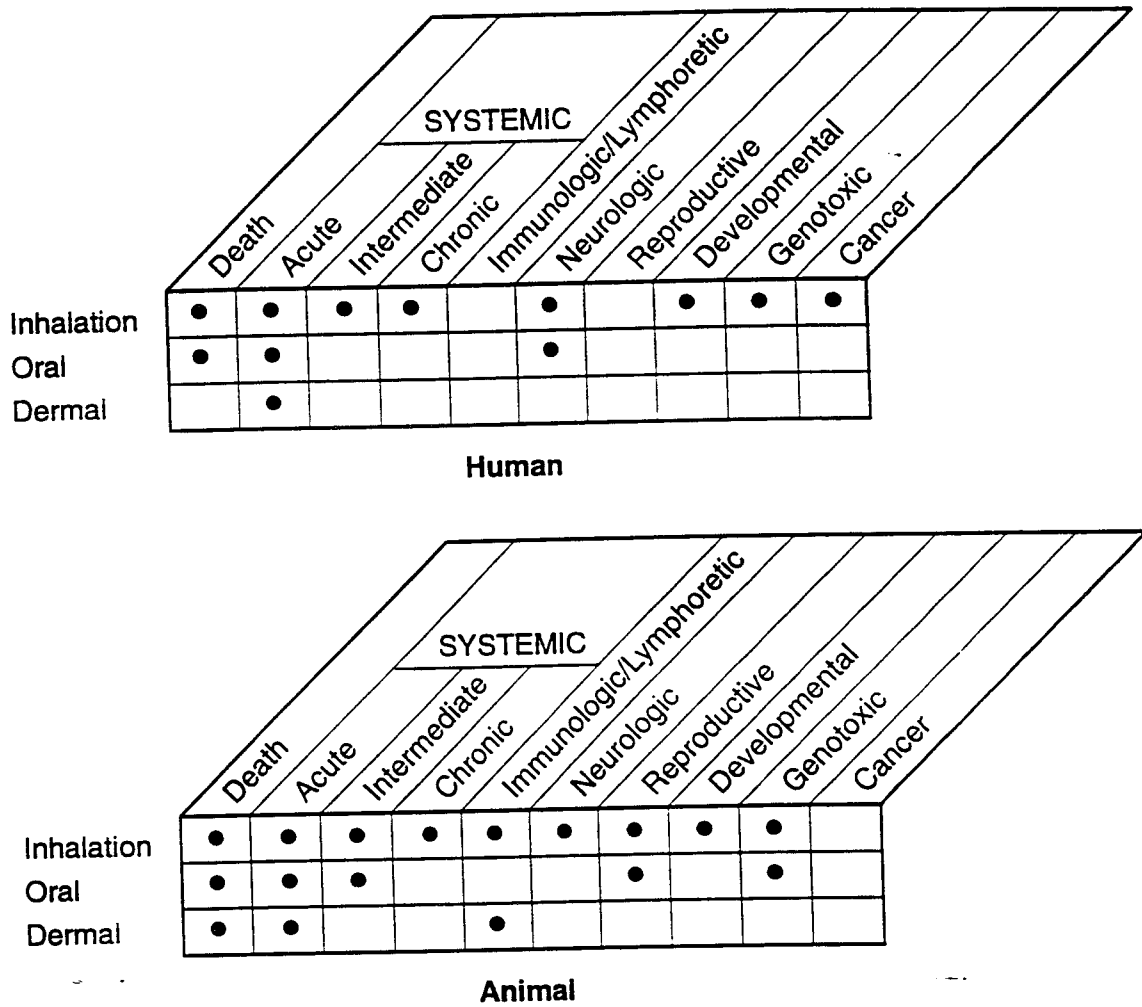
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted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

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to gasoline are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of gasoline. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply

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FIGURE 2-3. Existing Information on Health Effects of Automotive Gasoline



● Existing Studies

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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 death and acute, chronic, neurological, developmental, genotoxic, and carcinogenic effects following inhalation exposure to gasoline; death and acute and neurological effects following oral exposure to gasoline; and acute effects following dermal exposure to gasoline in humans. Animal data exist for all end points following inhalation exposure to gasoline; for death and acute, intermediate, and genotoxic effects following oral exposure to gasoline; and death and acute and immunological effects following dermal exposure to gasoline. Therefore, as can be seen in Figure 2-3, the majority of the available information is on the health effects of inhaled gasoline in humans and animals, with very little information on the effects of oral and dermal exposure.

2.9.2 Identification of Data Needs

Acute-Duration Exposure. The central nervous system appears to be a target of gasoline toxicity following acute-duration exposures in both humans and animals. Acute exposure to high levels of gasoline, either by inhalation or ingestion can result in death in both humans and animals (Ainsworth 1960; Beck et al. 1983; Boeckx et al. 1977; Carnevale et al. 1983; Poklis 1976; Vemot et al. 1990; Wang and Irons 1961). Acute inhalation exposure to gasoline is characterized by a spectrum of effects that progress in severity with exposure to increasing levels and can include eye irritation, dizziness, headaches, giddiness, euphoria, vertigo, blurred vision, nausea, numbness, drowsiness, anesthesia, and coma in humans (Poklis and Burkett 1977). Children admitted to the hospital as a result of gasoline ingestion exhibited central nervous system complications such as convulsions, coma, and lethargy (Beamon et al. 1976). Animals acutely exposed by inhalation to high levels of gasoline also exhibit neurotoxic effects, including restlessness, equilibrium disturbances, convulsions, and narcosis, but these effects may have been partially due to oxygen deprivation (Przybylowski 1971). The most common effect associated with acute ingestion of gasoline in humans is aspiration into the lungs resulting in respiratory distress, pulmonary edema, emphysema, pneumonia, and focal alveolar hemorrhage (Banner and Walson 1983; Beamon et al. 1976; Carnevale et al. 1983; Grufferman and Walker 1982; Janssen et al. 1988). Gasoline has been shown to be irritating at the portal of entry (i.e., the lungs after

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inhalation or the gastrointestinal mucosa after ingestion) in both humans and animals (Carnvale et al. 1983; Halder et al. 1985; Hoffman et al. 1980; Janssen et al. 1988). α_{2u} -Globulin-mediated nephrotoxicity has been observed in male rats orally administered gasoline (Gerin et al. 1988; Olson et al. 1987a). This lesion is not considered to be relevant to humans, although evidence of reversible renal injury has been reported in a number of cases of individuals who accidentally or intentionally ingested gasoline (Banner and Walson 1983; Janssen et al. 1988; Kuehnel and Fisher 1986). Information on the health effects of dermal exposure to gasoline are lacking, but case reports of individuals who had been immersed in gasoline indicate that toxic effects similar to those seen after inhalation or ingestion of gasoline occur (Ainsworth 1960; Hansbrough et al. 1985; Simpson and Cruse 1981). However, it is possible that these individuals were also exposed to gasoline via the inhalation and oral routes. Acute-duration dermal studies in animals report only slight to severe dermal irritation (Beck et al. 1983; Vernot et al. 1990). There are no toxicokinetic data available by the dermal route of exposure. However, given that the dermal absorption of hydrocarbon solvents is generally low relative to the oral route (NESCAUM 1989), systemic effects resulting from dermal exposure to gasoline are not as likely to occur as they would following oral or inhalation exposure. No acute MRLs have been developed because reliable exposure data are not available for end points of gasoline toxicity other than α_{2u} -globulin-mediated nephrotoxicity and because of the wide variation in the composition of gasoline. More quantitative information on the levels of exposure that elicit various neurological effects in humans and animals following inhalation or oral exposure would be helpful. In addition, there are certain populations that might be exposed to gasoline for brief periods; therefore, this information is important in assessing the risk to these populations.

Intermediate-Duration Exposure. No information is available on the effects of intermediateduration inhalation, oral, or dermal exposure to gasoline in humans. Intermediate-duration inhalation exposure to gasoline vapors has been reported to induce ultrastructural pulmonary changes in rats (fibrosing alveolitis) (Lykke et al. 1979). Ultrastructural pulmonary changes have been observed in rats exposed by inhalation to leaded gasoline (Lykke et al. 1979). These changes occur in conjunction with a reduction in the level of surfactant in the lungs of rats similarly exposed (Le Mesurier et al. 1979). This end point was not chosen as the basis for an inhalation MRL because it is considered a serious effect and because of the variability in the composition of gasoline. However, no changes of

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biological significance in pulmonary function were observed in monkeys following exposure to 1,552 ppm gasoline vapor for 90 days (Kuna and Ulrich 1984). α_2 -Globulin-mediated nephrotoxicity has been observed in male rats inhaling gasoline vapors or that have been orally administered gasoline (Borrison Labs 1985; Halder et al. 1984, 1985; Kuna and Ulrich 1984; Short et al. 1987, 1989a, 1989b). This lesion is unique to male rats and therefore, not considered to be relevant to humans. There is no information available on the health effects of gasoline following dermal exposure in either humans or animals. Intermediate oral MRLs have not been developed because quantitative information on target organs of gasoline other than male rat nephropathy has not been reported for intermediate inhalation and oral exposure. In addition, gasoline contains many components that can vary significantly among the many compositions of gasoline. The toxicity of gasoline would depend on the specific composition. More quantitative information from animal studies on the effects of intermediate-duration inhalation and oral exposure to gasoline would be useful to identify target organs other than the kidney in male rats, to verify the ultrastructural effects observed in the lungs of rats, and to establish threshold levels for any effects that may be seen following intermediate-duration exposure.

Chronic-Duration Exposure and Cancer. Chronic inhalation exposure to gasoline (i.e., in those individuals who habitually sniff gasoline for its euphoric/hallucinogenic properties) is associated with neurological effects, such as cerebellar effects including postural tremor, ataxia, abnormal gait, affected speech, fatigue, headaches, memory loss, and sleep problems (Carroll and Abel 1973; Coulehan et al. 1983; Goldings and Stewart 1982; Kaelan et al. 1986; Kullman and Hill 1990; Moss and Cooper 1986; Pandya et al. 1975; Rischbieth et al. 1987; Young et al. 1977). Behavioral and intellectual changes (effects on visual memory and perception, psychomotor disturbances, or changes in visuomotor learning ability) have been observed in individuals chronically exposed to gasoline vapors (Carroll and Abel 1973; Kumar et al. 1988; Robinson 1978). However, based on pathological examinations, chronic inhalation of gasoline vapors has not been shown to induce adverse neurological effects in animals (MacFarland et al. 1984). Chronic inhalation of gasoline vapors has been shown to be mildly irritating to the lungs of female rats, but this effect was not observed in mice in the same study and has not been reported in humans (MacFarland et al. 1984). Several human case studies have reported the occurrence of various hematological effects in individuals with known long-term exposure to gasoline vapors (Boeckx et al. 1977; Chessare and Wodarczyk 1988; Niazi et al. 1989; Young et al.

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1977). In most of these cases, the hematological effects reported were most likely due to a constituent of gasoline (i.e., lead, benzene). α_{2u} -Globulin-mediated nephrotoxicity has been observed in male rats inhaling gasoline vapors (MacFarland et al. 1984; Short et al. 1989a, 1989b). Again, because this syndrome is unique to male rats, it is not considered to be relevant to humans. No information is available on the effects of chronic oral or dermal exposure to gasoline in either humans or animals. No chronic oral MRLs have been developed because quantitative exposure data are not available for end point of chronic gasoline toxicity other than α_{2u} -globulin-mediated nephrotoxicity and because of the variability in the composition of gasoline. More quantitative information on the levels of exposure that elicit various neurological effects in humans and animals would be helpful, as would information on what the thresholds are for these effects following both inhalation and oral exposure. Information regarding the thresholds for adverse effects are important since certain populations might be exposed to gasoline for chronic durations.

An exposure-related increased incidence of renal tubular tumors was observed in male rats that were exposed to unleaded gasoline vapors for 2 years (MacFarland et al. 1984). The renal tubular tumors observed in the male rats are believed to have been the result of a process involving the accumulation of α_{2u} -globulin. The relevance of α_{2u} -globulin-mediated male rat nephropathy and carcinogenicity to humans has been questioned (EPA 1991). An exposure-related increase in the incidence of hepatocellular tumors was observed in female mice exposed to unleaded gasoline vapors for 2 years (MacFarland et al. 1984). Some of these tumors metastasized to the lungs. The MacFarland et al. (1984) study is limited with respect to its relevance to human health risk because the animals were exposed to wholly vaporized gasoline, which has the same composition as liquid gasoline and is not the same as the gasoline vapors that humans would be exposed to under ambient conditions. Gasoline emissions normally found in the environment contain lower concentrations of those hydrocarbons that have lower vapor pressures (i.e., the branched-chain hydrocarbons, such as 2,2,4-trimethylpentane, that have been shown to induce nephrotoxicity) than is found in liquid gasoline. Thus, the studies in animals using wholly vaporized gasoline may overestimate the carcinogenic risk in humans. No information is available in the literature on the carcinogenicity of gasoline in animals following chronic oral exposure. Additional inhalation bioassays using gasoline vapors of a composition similar to that which is normally found in the ambient environment and also bioassays employing the oral

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route of exposure would be helpful to more fully assess the potential carcinogenic risk of gasoline for humans exposed via inhalation or ingestion of contaminated groundwater.

Genotoxicity. Gasoline as a mixture does not appear to be strongly genotoxic to either humans or animals (see Tables 2-4 and 2-5). Although an increased incidence of micronuclei was observed in the B-lymphocytes of workers occupationally exposed to gasoline, it is probable that the lower concentration of benzene in American fuel would reduce this potential hazard (Högstedt et al. 1991). However, cytogenetic studies, specifically in human B-lymphocytes, are needed to determine the validity of this assumption. There is sufficient evidence to conclude that gasoline is not mutagenic in bacteria or mammalian cells in cultures (Conaway et al. 1984; Dooley et al. 1984; Richardson et al. 1986). The relevance of the positive findings with *Drosophila melanogaster* (Nylander et al. 1978), which appears to be associated with the 1,2-dichloroethane component, cannot be determined without further information on the concentration of 1,2-dichloroethane in American fuel. Well-conducted *in vivo* rodent cytogenetic studies showed that gasoline is not clastogenic in somatic cells (Conaway et al. 1984; Dooley et al. 1988); no conclusions can be reached for germinal cells at this time (Litton Bionetics 1980). The findings from *in vivo* and *in vitro* UDS assays with mouse, rat, and human cells produced conflicting results for genotoxicity (API 1988; Butterworth et al. 1989; Lout-y et al. 1986, 1987). The only consistent finding from the *in vivo* rodent assays was the elevation of SDS in male rat kidney cells (Loury et al. 1987) and male mouse and rat liver cells (Loury et al. 1986, 1987). Increases in SDS in female rat or mouse liver and/or kidney cells were either modest or negligible. There was, however, no correlation between SDS activity and tumor initiation in rats and mice of both sexes chronically exposed to unleaded gasoline. Overall, the findings from the *in vivo* UDS assays tend to suggest a possible nephrotoxic and/or hepatotoxic role for unleaded gasoline rather than an ability to initiate tumorigenesis (Loury et al. 1986, 1987). Therefore, it is doubtful that the performance of additional UDS/SDS studies would provide additional meaningful information.

Reproductive Toxicity. No information is available on the reproductive effects of gasoline in humans following inhalation, oral, or dermal. Only one study (a dominant lethal study that investigated toxic effects on sperm cells) was found on the reproductive effects of gasoline in animals, and the results were negative (Litton Bionetics 1980). In addition, no adverse effects on the

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reproductive organs were reported in chronic-duration inhalation studies in rats or mice (MacFarland et al. 1984). No reproductive organ toxicity data are available in the literature following oral exposure to gasoline. Pathological examination of the reproductive organs in 90-day oral studies would be useful to establish whether gasoline has the potential to induce adverse reproductive effects by this route of exposure, since chronic-duration inhalation studies failed to demonstrate any such effects.

Developmental Toxicity. Anecdotal data are available to suggest an association between chronic exposure of pregnant women to leaded gasoline vapor and congenital defects of the central nervous system in children (Hunter et al. 1979). However, these data are inadequate to assess the risk of developmental toxicity following exposure to gasoline in humans because of the small sample size, possibility of concomitant exposure to alcohol, genetic background, lack of quantification of exposure levels, and presence of lead which may have contributed to the developmental defects in the children. No developmental effects were observed in pregnant rats exposed to gasoline vapors at concentrations as high as 1,600 ppm (Litton Bionetics 1978). No information is available on the developmental toxicity of gasoline following oral or dermal exposure. Additional information on the developmental toxicity of gasoline in rats following maternal inhalation exposure would be useful to confirm the negative results obtained in the Litton Bionetics (1978) study.

Immunotoxicity. No information is available in the current literature on the immunological effects of gasoline following inhalation, oral, or dermal exposure in humans, or following oral exposure in animals. No apparent immunological effects (as measured by IgG deposits in the kidney and lungs) were noted in rats and monkeys exposed to gasoline by inhalation for 90 days (Kuna and Ulrich 1984), and no other effects were noted on lymphoid tissue or blood components in animals exposed to gasoline vapors for intermediate or chronic durations (Kuna and Ulrich 1984; MacFarland et al. 1984). Studies conducted in rats to investigate the possible contribution of gasoline to the manifestation of pulmonary hemorrhage in Goodpasture's syndrome yielded mixed results (O'Regan and Turgeon 1986; Yamamoto and Wilson 1987). The discrepancy in results between these two studies may be due to differences in route of administration and dose. Since the relationship between gasoline exposure and

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Goodpasture's syndrome is unclear and hence the possible involvement of the immune system uncertain, additional information would be useful in resolving the issue.

Neurotoxicity. The central nervous system appears to be a target of gasoline toxicity following acute-duration exposures in both humans and animals. In humans, acute inhalation exposure to gasoline is characterized by a spectrum of effects that progress in severity with increasing dose and duration and can include eye irritation, dizziness, headaches, giddiness, euphoria, vertigo, blurred vision, nausea, numbness, drowsiness, anesthesia, and coma (Poklis and Burkett 1977). Children admitted to the hospital as a result of gasoline ingestion exhibited central nervous system complications such as convulsions, coma, and lethargy (Beamon et al. 1976). Chronic intermittent exposure to high levels of gasoline (i.e., in those individuals who habitually sniff gasoline for its euphoric/hallucinogenic properties) is associated with neurological effects, such as cerebellar effects including postural tremor, ataxia, abnormal gait; affected speech; fatigue; headaches; memory loss; and sleep problems (Carroll and Abel 1973; Coulehan et al. 1983; Goldings and Stewart 1982; Kaelan et al. 1986; Kullman and Hill 1990; Moss and Cooper 1986; Pandya et al. 1975; Rischbieth et al. 1987; Young et al. 1977). Behavioral and intellectual changes (effects on visual memory and perception, psychomotor disturbances, or changes in visuomotor learning ability) have been observed in individuals chronically exposed to gasoline vapors (Carroll and Abel 1973; Kumar et al. 1988; Robinson 1978). Animals acutely exposed by inhalation to high levels of gasoline also exhibit neurotoxic effects, including restlessness, equilibrium disturbances, convulsions, and narcosis, but these effects may have been partially due to oxygen deprivation (Przybylowski 1971). However, chronic inhalation of gasoline vapors has not been shown to induce adverse neurological effects in animals as indicated by pathological examinations (MacFarland et al. 1984). More quantitative information on the levels of exposure that elicit various neurological effects, including changes in learning and behavior, as well as additional studies that examine sensitive neuropathological end points via inhalation and oral routes would be useful.

2. HEALTH EFFECTS

Epidemiological and Human Dosimetry Studies. A number of epidemiological studies have been conducted on workers occupationally exposed to petroleum products and hydrocarbons (e.g., Kadamani et al. 1989; McLaughlin et al. 1985; Partanen et al. 1991; Poole et al. 1993; Schnatter et al. 1993; Schwartz 1987; Siemiatycki et al. 1987; Wong et al. 1993). These studies all have several inherent limitations that preclude their use as evidence for an association between gasoline exposure and cancer in humans. These limitations include lack of information on levels of exposure to gasoline hydrocarbons; concurrent exposure to other potentially carcinogenic substances (i.e., service station attendants are also exposed to used motor oils, diesel fuel, and solvents as well as automobile and truck engine exhausts); no adjustment for potential confounding factors (e.g., smoking); and no latency analyses. EPA (1987a) reviewed 55 relevant studies of unleaded gasoline exposed populations and concluded that the evidence for drawing causal inferences between unleaded gasoline and cancer was inadequate. Since occupational exposure to gasoline invariably occurs in workers who are also exposed to a number of other toxic and potentially carcinogenic substances, additional epidemiological studies in occupationally exposed populations that identify these variables would be difficult to conduct and are thus not likely to yield any more useful data with respect to adverse health effects specific to gasoline. Exposure to low levels of gasoline is extremely common in the general population, and it would be difficult to conduct meaningful epidemiological studies in any subset of the population. If populations exposed primarily to automotive gasoline can be identified, monitoring gasoline exposure and gathering information regarding neurological, developmental, and cancer effects would be useful for establishing cause/effect relationships.

Biomarkers of Exposure and Effect. Increased blood and urine lead levels, urinary thioether, urinary phenol, and blood benzene, toluene, pentane, and hexane levels can all be used as biomarkers of exposure to short-term exposure to gasoline (Brugnone et al. 1986; Goldings and Stewart 1982; Kimura et al. 1988; Matsubara et al. 1988; Pandya et al. 1975; Robinson 1978; Stock and Priestly 1986). However, none of these biomarkers are specific for gasoline, and there do not appear to be any biomarkers of effect that would be useful for monitoring either intermediate or long-term exposure to gasoline. Development of additional, more sensitive biomarkers that are specific for gasoline exposure would be useful in monitoring populations at risk.

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Potential biomarkers of effect for intermediate and long-term gasoline exposure include slowed motor nerve conduction velocity and indices of cerebellar dysfunction (Carroll and Abel 1973; Coulehan et al. 1983; Gallassi et al. 1980; Goldings and Stewart 1982; Hall et al. 1986; Hansen and Sharp 1978; Kaelen et al. 1986; Moss and Cooper 1986; Rischbieth et al. 1987; Robinson 1978; Seshia et al. 1978; Young et al. 1977). However, these effects are not specific for gasoline exposure. Biomarkers of effect for short-term exposure to gasoline include nausea, vomiting, diarrhea, irritability, restlessness, and anxiety. These are also nonspecific for gasoline. Development of additional, more sensitive biomarkers that are specific for gasoline effects would be useful in monitoring populations at high risk. However, there are no adverse health effects known at this time that are specific for gasoline.

Absorption, Distribution, Metabolism, and Excretion. There are no quantitative data available on the rates and extent of absorption, distribution, metabolism, or excretion of gasoline in humans or animals following inhalation, oral, or dermal exposure. Although data are available on these parameters for many of the individual components of gasoline (i.e., benzene, toluene, xylene) that may be used to predict the toxicokinetics of gasoline, it is possible that interactions between these components may influence the toxicokinetics of the mixture as a whole. Quantitative data on the toxicokinetics of gasoline following inhalation, oral, and dermal exposure would be useful to predict the behavior of this mixture in the body.

Comparative Toxicokinetics. There is relatively little quantitative information on the toxicokinetics of gasoline in any species, including humans. However, the toxicity data available on gasoline indicate that, with the exception of α_{2u} -globulin-mediated nephrotoxicity in male rats, the target organs/systems are similar in humans and animals (Beamon et al. 19761; Poklis and Burkett 1977; Przybylowski 1971).

Methods for Reducing Toxic Effects. All of the treatment modalities currently available for use in cases of gasoline ingestion, inhalation, or skin contact are supportive in nature and/or involve hastening the elimination of gasoline from the body. The mechanisms of gasoline toxicity are not known, so there are currently no methods geared towards mitigating the effects of gasoline by

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interfering with its mechanism of action. Development of further methods to mitigate the effects of gasoline would rely on characterizing its mechanism of action.

2.9.3 On-going Studies

W.L. Backes at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, is studying the toxicological significance of the metabolism in rats and rabbits of alkylbenzenes (including toluene, xylenes, ethylbenzene, and n-propylbenzene), which are major constituents of gasoline. Specifically, the identification of changes in the metabolic fate of the alkylbenzenes due to their prior administration, the effects of age, sex, and strain differences, the effects of exposure time and exposure to hydrocarbon mixtures, and the effect of hydrocarbon induction of cytochrome P-450 on the association of the alkylbenzenes with the enzyme will be studied. The objective of these studies is to provide information that will aid in the identification of conditions under which individuals might be susceptible to alkylbenzene-induced toxicity.

R.W. Wood at the National Institutes of Health, National Institute on Drug Abuse in Rockville, Maryland, is studying drug self-administration by inhalation of several compounds including alkylbenzenes in the primate. In conjunction with models of learned and unlearned behavior, self administration models will be developed that will provide a method to assess abuse potential, assist in setting workplace exposure limit values to prevent substance abuse and performance impairment, determine whether inhalants maintain “drug-seeking” behavior as strongly as other abused drugs, measure the severity of dependence, withdrawal, and toxicity syndromes, assess irritancy and its consequences, and characterize direct behavioral effects of solvents.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Gasoline is a refined product of petroleum consisting of a mixture of hydrocarbons, additives, and blending agents. The composition of gasolines varies widely, depending on the crude oils used, the refinery processes available, the overall balance of product demand, and the product specifications. The typical composition of gasoline hydrocarbons (% volume) is as follows: 4-8% alkanes; 2-5% alkenes; 25-40% isoalkanes; 3-7% cycloalkanes; 1-4% cycloalkenes; and 20-50% total aromatics (0.5-2.5% benzene) (IARC 1989). Additives and blending agents are added to the hydrocarbon mixture to improve the performance and stability of gasoline (IARC 1989; Lane 1980). These compounds include anti-knock agents, anti-oxidants, metal deactivators, lead scavengers, anti-rust agents, anti-icing agents, upper-cylinder lubricants, detergents, and dyes (IARC 1989; Lane 1980). At the end of the production process, finished gasoline typically contains more than 150 separate compounds although as many as 1,000 compounds have been identified in some blends (Domask 1984; Mehlman 1990). Information regarding the chemical identity of gasoline is located in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties for the gasoline mixture is located in Table 3-2. In cases where data are not available for gasoline, ranges are given to indicate the different values for the individual components.

CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of Gasoline

Characteristic	Information	Reference
Chemical name	Gasoline	RTECS 1990
Synonyms	Casing head gasoline; motor fuel; motor spirit; natural gasoline; petrol	HSDB 1993
Registered trade name(s)	No data ^a	
Chemical formula	No data ^a	
Chemical structure	No data ^a	
Identification numbers:		
CAS registry	8006-61-9	RTECS 1990; Sax and Lewis 1989
NIOSH RTECS	LX3300000	RTECS 1990; SANSS 1986; Sax and Lewis 1989
EPA hazardous waste OHM/TADS	No data 7217073	OHM/TADS 1991; SANSS 1986
DOT/UN/NA/IMCO shipping	UN1203, UN1257	RTECS 1990
HSDB	No data	
NCI	No data	

^aGasoline is a mixed compound consisting of hydrocarbons, blending agents, and additives.

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemicals Substances; SANSS = Structure and Nomenclature Search System

CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-2. Physical and Chemical Properties of Gasoline

Property	Information	Reference
Molecular weight	108 ^a	Anonymous 1989
Color	Colorless to pale brown or pink	Sax and Lewis 1989; Weiss 1986
Physical state	Liquid	Sax and Lewis 1989
Melting point	No data	
Boiling point	Initially, 39°C After 10% distilled, 60°C After 50% distilled, 110°C After 90% distilled, 170°C Final boiling point, 204°C	Budavari et al. 1989; OHM/TADS 1991; Sax and Lewis 1989
Density	0.7-0.8 g/cm ^{3,b}	IARC 1989
Odor	Gasoline odor	Weiss 1986
Odor threshold	0.025 ppm ^c	Weiss 1986
Solubility: Water at 20°C	Insoluble	OHM/TADS 1991; Sax and Lewis 1989
Organic solvent(s)	Absolute alcohol, ether, chloroform, benzene	Budavari et al. 1989; Sax and Lewis 1989
Partition coefficients: Log K _{ow}	2.13-4.87 ^d	Air Force 1989
Log K _{oc}	1.81-4.56 ^d	Air Force 1989
Vapor pressure ^e at 60°C	465 mmHg	ASTM 1989
at 56°C	518 mmHg	
at 51°C	593 mmHg	
at 47°C	698 mmHg	
at 41°C	773 mmHg	
Henry's law constant: at 20°C	4.8x10 ⁻⁴ -3.3 m ³ /mol ^d	Air Force 1989
Autoignition temperature	280-486°C	NEPA 1986; Sax and Lewis 1989; Weiss 1986
Flashpoint	-46°C	Sax and Lewis 1989
Flammability limits	1.4-7.4%	Weiss 1986

TABLE 3-2. Physical and Chemical Properties of Gasoline (*continued*)

Property	Information	Reference
Conversion factors	No data	
Explosive limits	1.3-6.0%	Budavari et al. 1989; Sax and Lewis 1989

^aAverage molecular weight

^bTemperature not specified

^cNot specified whether data for air or water

^dSince data are not available for gasoline, ranges are given indicating different values for the individual components.

^eThe American Society for Testing and Materials (ASTM) has established guidelines on compositions of gasoline that will permit satisfactory performance under varying conditions. These guidelines define five volatility classes that vary by seasonal climatic changes. The values given for vapor pressure at the given temperatures are based on these volatility classes.

CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-3. Major Components of Gasoline^a

Component	Percentage Composition ^b	Component
<i>n</i> -alkanes		<u>Other possible components</u>
C ₅	3.0	octane enhancers
C ₆	11.6	methyl t-butyl ether (MTBE)
C ₇	1.2	t-butyl alcohol (TBA)
C ₉	0.7	ethanol
C ₁₀ -C ₁₃	0.8	methanol
total of <i>n</i> -alkanes	17.3	antioxidants
branched alkanes		<i>N,N'</i> -dialkylphenylenediamines
C ₄	2.2	2,6-dialkyl and 2,4,6-trialkylphenols
C ₅	15.1	butylated methyl, ethyl and dimethyl phenols
C ₆	8.0	triethylene tetramine di(monononylphenolate)
C ₇	1.9	metal deactivators
C ₈	1.8	<i>N,N'</i> -disalicylidene-1,2-ethanediamine
C ₉	2.1	<i>N,N'</i> -disalicylidene-propanediamine
C ₁₀ -C ₁₃	1.0	<i>N,N'</i> -disalicylidene-cyclohexanediamine
total of branched	32.0	disalicylidene- <i>N</i> -methyl-dipropylene-triamine
cycloalkanes		ignition controllers
C ₆	3.0	tri- <i>o</i> -cresylphosphate (TOCP)
C ₇	1.4	icing inhibitors
C ₈	0.6	isopropyl alcohol
total of cycloalkanes	5.0	detergents/dispersants
olefins		alkylamine phosphates
C ₆	1.8	poly-isobutene amines
total of olefins	1.8	long chain alkyl phenols
aromatics		long chain alcohols
benzene	3.2	long chain carboxylic acids
toluene	4.8	long chain amines
xylenes	6.6	corrosion inhibitors
ethylbenzene	1.4	carboxylic acids
C ₃ -benzenes	4.2	phosphoric acids
C ₄ -benzenes	7.6	sulfonic acids
others	2.7	
total aromatics	30.5	

^aAdapted from Air Force 1989^bPercent by weight

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Originally, “straight-run” gasoline was produced by simple distillation of crude oil without the use of chemical conversion processes (Lane 1980; Sax and Lewis 1987). Shortly after 1900, motor vehicles began to appear in growing numbers, and gasoline began to have a marketable value as a refinery product. Around 1912, distillation of crude oil alone could not satisfy the rapidly growing demand for gasoline. At this time, gasoline-range hydrocarbons were recovered from “wet” natural gas. However, only a limited amount of natural gasoline could be included in finished gasoline because of its high volatility and its relatively low anti-knock quality (Lane 1980). Since then, petroleum refineries have developed several processes to contribute to the production of gasoline.

In general, gasolines are blended from several petroleum refinery process streams that are derived by the following methods: direct distillation of crude oil, catalytic and thermal cracking, hydrocracking, catalytic reforming, alkylation, and polymerization. Modern petroleum refining begins with the distillation of crude oil into the following fractions: light naphtha (used as a component of finished gasoline without additional refining), heavy naphtha (catalytically reformed to a higher-octane blending stock), kerosene and light gas-oil (used in the production of kerosene, jet fuel, diesel fuel, and furnace oils), heavy gas-oil (used in heavy diesel fuel, industrial fuel oil, and bunker oil), and reduced crude. The heavy gas-oil and other heavy oils recovered from the reduced crude can be cracked into gasolines (Lane 1980). The use of cracking to produce gasoline began in 1913. Cracking breaks down higher-boiling hydrocarbons into lower-boiling ones. The two general types of cracking used are catalytic and thermal. Catalysts may consist of naturally occurring clays or synthetic compounds. Catalytic cracking produces blending components for high-octane gasoline. Therefore, in addition to serving as a gasoline-production process, catalytic cracking also serves to improve octane (Hood 1973; Lane 1980). Hydrocracking, which consists of cracking in the presence of added hydrogen, permits wide variations in yields of gasoline and furnace oils to meet seasonal demand changes and can effectively process hard-to-crack stocks. However, since hydrocracked stocks lack the high-octane olefins present

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

in catalytically cracked stocks, they must be reformed (Lane 1980). Reforming processes convert lowoctane gasoline-range hydrocarbons into higher-octane ones. Thermal reforming has been almost completely replaced by catalytic reforming. Most reforming catalysts are bimetallic catalysts consisting of platinum with another promoting metal, such as rhenium (Hood 1973; Lane 1980). Alkylation converts refinery gases into gasoline-range liquids of exceptionally high anti-knock quality. However, the process is costly and is not commonly used in gasoline production (Domask 1984; Lane 1980). Polymerization combines two or more low molecular weight olefin gases into higher molecular weight olefin liquids suitable for gasoline blending or for use as chemical feed stocks. However, because olefinic liquids have low anti-knock quality and the reactants, olefin gases, are valuable chemical feeds, the polymerization process is no longer widely used to produce gasoline blend streams (Domask 1984; Lane 1980).

After the various gasoline streams have been blended, foul-smelling, corrosive, sulfur compounds are removed by hydrogenation (Lane 1980). Additives and blending agents are added to improve the performance and stability of gasoline. These compounds include anti-knock agents, anti-oxidants, metal deactivators, lead scavengers, anti-rust agents, anti-icing agents, upper-cylinder lubricants, detergents, and dyes (IARC 1989; Lane 1980). At the end of the refining process, finished gasoline typically contains more than 150 separate compounds although as many as 1,000 compounds have been identified in some blends (Domask 1984; Mehlman 1990). At present, the only commercial source of gasoline is petroleum, but it has been produced from shale oil, Athabasca tar sands, and by hydrogenation or gasification of coal (Hood 1973; Sax and Lewis 1987).

Gasoline is available in the United States in leaded and unleaded grades. In the past, organic lead compounds were widely used as anti-knock agents in gasoline; however, methyl-tertiary-butyl ether has almost completely replaced tetraethyllead as an anti-knock agent and is now widely used in the production of unleaded gasoline (Sax and Lewis 1987). Now, EPA regulations do not permit intentional addition of lead or phosphorous to unleaded gasoline and limits their maximum concentrations to 0.013 g lead/L and 0.0013 g phosphorus/l. Leaded gasoline is produced in much smaller quantities for use in engines not equipped with catalytic converters. According to EPA regulations, leaded gasoline can contain any lead additive at a concentration higher than 0.013 g lead/L but no more than 1.1 g lead/L. The two common grades of both leaded and unleaded gasoline,

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

premium and regular, differ in their anti-knock quality. Better anti-knock quality is indicated by a higher octane number (IARC 1989). Gasoline is marketed as several products and, within each product line, in various grades (IARC 1989).

The U.S. production volume of motor gasoline has steadily increased between 1983 and 1989 from 277.2 million gallons/day to 306.6 million gallons/day (DOE 1989a). During the month of January 1989, U.S. production of unleaded gasoline was nearly six times as high as U.S. production of leaded gasoline (DOE 1989b). The states leading production of unleaded gasoline were Texas, California, and New Jersey and the states leading production of leaded gasoline were Texas, California, and Illinois (DOE 1989b). In 1989, the 10 U.S. companies leading gasoline sales were the following (in descending order of sales): Shell, Amoco, Exxon, Mobil, Chevron, Texaco, Unocal, BP America, Sun, and Phillips (API 1991).

Since gasoline releases are not required to be reported under SARA Section 313, there are no data on gasoline in the Toxics Release Inventory (TR188 1990).

4.2 IMPORT/EXPORT

Between 1988 and 1989, net U.S. imports of gasoline declined by 14% to an average of 13.0 million gallons/day. By 1990, imports were up to an average of 14.3 million gallons/day (DOE 1990). Typically net U.S. imports of gasoline account for 4-5% of demand (DOE 1989a). During the month of January 1989, the primary countries exporting gasoline to the United States were (in order of decreasing volume) Saudi Arabia, Venezuela, Brazil, Canada, France, Spain, and the United Kingdom (DOE 1989b).

Between 1988 and 1989, U.S. exports of finished motor gasoline increased from 924,000 gallons/day to 1.6 million gallons/day. Exports reached the highest point ever in 1989 at 2.4 million gallons/day (DOE 1990). During the month of January 1989, the United States exported primarily to Guatemala, Japan, and Mexico (DOE 1989b).

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.3 USE

Gasoline is used almost exclusively to fuel internal combustion engines (IARC 1989). Consumption of gasoline decreased slightly in 1982 and then again in 1989. In 1989, 306.6 million gallons of gasoline were consumed in the United States. During 1989, the use of unleaded gasoline continued to rise, accounting for 88.8% of the total gasoline demand in that year (DOE 1989a).

4.4 DISPOSAL

Most gasoline is burned in internal combustion engines. Limited data are available on the disposal of gasoline. A suggested method is to spray it into an incinerator (OHM/TADS 1991).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

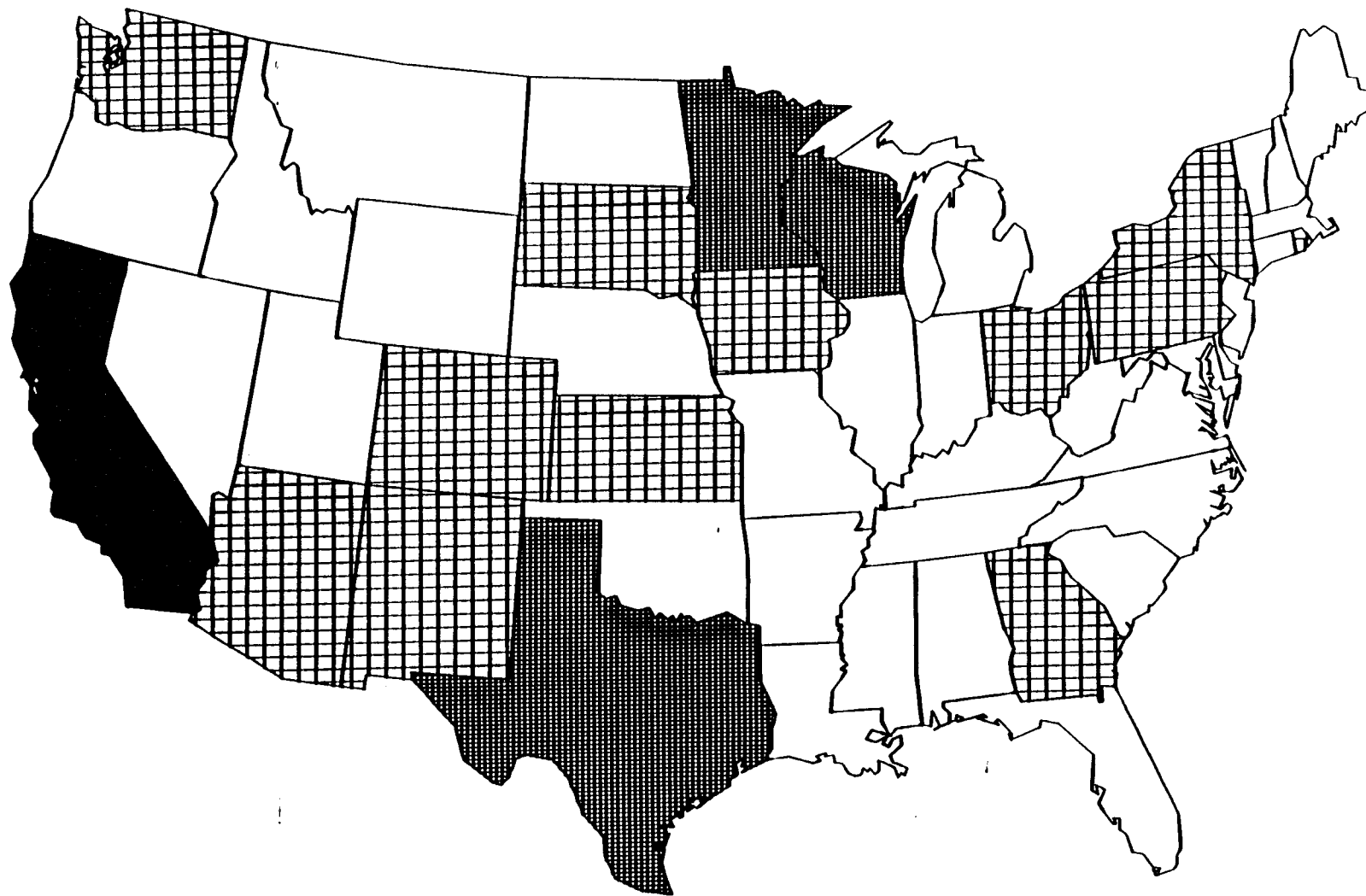
Gasoline is a mixture of relatively volatile hydrocarbons, including alkanes, cycloalkanes, alkenes, and aromatics. Individual hydrocarbon components differentially partition to environmental media on the basis of their physical/chemical properties. Gasoline is released to the atmosphere as hydrocarbon vapors from processing and use as a fuel, and to surface water, groundwater, and soil through spills and leaks in aboveground and underground storage tanks and pipelines. Gasoline has been identified in 23 of the 1,397 NPL hazardous waste sites that have been proposed for inclusion on the NPL (HAZDAT 1992). The frequency of these sites within the United States can be seen in Figure 5-1.

The volatile hydrocarbon fraction of gasoline, which consists primarily of short-chain (C_4 - C_5) alkanes and alkenes and some aromatics, partitions to the atmosphere where photochemical oxidation is the main removal process. Much of what is released to surface waters and surface soils is lost by volatilization to the atmosphere. Releases to subsurface soils may leach through the unsaturated zone and contaminate groundwater. Aromatics constitute most of the water soluble fraction of gasoline. Biodegradation of gasoline hydrocarbons by a diverse group of microorganisms is an important removal process in surface waters, soil, and groundwater. Bioconcentration and sorption of gasoline hydrocarbons to soils and sediments may be important only for higher molecular weight hydrocarbons that are resistant to biodegradation.

Exposure of the general population to gasoline occurs primarily through inhalation of very small quantities of the volatile fraction of the mixture during automobile refueling. Another important source of exposure is ingestion, dermal, and inhalation exposure for certain populations through the use of gasoline-contaminated surface water or groundwater in domestic potable water applications. Inhalation also appears to be the main route of occupational exposure for individuals employed in the petroleum and automotive industries. Populations with potential exposures to gasoline hydrocarbons

FIGURE 5-1. FREQUENCY OF NPL SITES WITH GASOLINE CONTAMINATION *

GASOLINE



5. POTENTIAL FOR HUMAN EXPOSURE

FREQUENCY



1 SITE
5 SITES



2 SITES

*Derived from HazDat 1994

5. POTENTIAL FOR HUMAN EXPOSURE

include individuals living in the vicinity of gasoline service stations or tank farms or near leaking underground storage tanks.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

Gasoline vapors are released to the air during refueling of gasoline-powered vehicles (Kearney and Dunham 1986; McDermott and Vos 1979; Shiller 1987), bulk transfer of gasoline at distribution terminals (Irving and Grumbles 1979; Kawai et al. 1991; Phillips and Jones 1978), leaks from storage containers and loading equipment (Dell'Acqua et al. 1976; Phillips and Jones 1978), and during removal and maintenance of underground storage tanks (Kramer 1989; Shamsky and Samimi 1987). Volatile hydrocarbons in gasoline spilled on soil or surface water will rapidly evaporate, contributing to air contamination (Kramer 1989; Phillips and Jones 1978; Van Gelder-Ottway 1976).

Releases of small amounts of gasoline vapors have been shown to occur at service stations during refueling of vehicles. Most of the release comes from displacement of hydrocarbon vapors during filling of the vehicle or the underground storage tank. Some release will also occur from spills and line leaks. Gasoline vapor levels measured in the air (personal air samples) at a high-volume service station in Pennsylvania during 1 week in May ranged from 0.9 to 116.3 mg/m³. The highest levels generally were found within the immediate vicinity of the fuel nozzle during refueling operations and levels decreased with distance from the pump, indicating that considerable release occurs during vehicle refueling (Keamey and Dunham 1986).

Releases of gasoline vapors during bulk transfer operations occur primarily via displacement of hydrocarbon vapors from the tanker by the liquid gasoline (Irving and Grumbles 1979; Phillips and Jones 1978). Other sources of release include leaks in fill lines and spills. The amount released during transfer operations will vary with the method used. Loading operations employing vapor recovery systems do not release as much vapor as those not utilizing them. Measurements taken at five plants located in the south, southwest, midwest, and west coast area during May and June showed lowest releases in top or bottom loading operations with vapor recovery systems (Phillips and Jones

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1978). Samples taken during top-loading had levels of 25 ppm or less in 98% of the samples while levels of 110 ppm or less were found in 90% of the samples taken during bottom-loading. In contrast, loadings without vapor recovery systems were considerably higher. Ninety percent of the samples from both the top- and bottom-loaded samples with no vapor recovery had levels of 225 ppm or less. Measurements of benzene (used as an indicator of gasoline vapor release) taken at plants in the east, southeastern, and southwestern United States confirm that releases occur during bulk transfers (Irving and Grumbles 1979). Ninety-five percent of samples from top-loading facilities without vapor recovery systems had benzene levels below 8.5 ppm. At bottom-loading facilities without vapor recovery, 95% of the samples were below 3.5 ppm. At bottom-loading facilities with vapor recovery, 95% were below 1.8 ppm. Release from underground storage tanks during removal and maintenance procedures has been documented by personal monitoring and area sampling (Kramer 1989; Shamsky and Samimi 1987). Measurements of total hydrocarbons in the vicinity of tank excavation and maintenance operations have ranged from 0.64 ppm upwind from the removal site to 860 ppm during inerting (addition of dry ice to the tank to remove hydrocarbon vapors and lower the oxygen content) (Shamsky and Samimi 1987). An area sample taken during transfer of gasoline from the storage tank to a tank truck contained 11 ppm of total hydrocarbons (Kramer 1989). Release of vapors occurs during all phases of the operation including transfer of gasoline from the storage tank, washing of the interior and removal of vapors, excavation, and examination and maintenance (Kramer 1989; Shamsky and Samimi 1987). Gasoline vapors will also be released from soil at the site contaminated by spillage of gasoline (Kramer 1989). Gasoline is not listed on the Toxics Release Inventory; however, several of the component hydrocarbons are listed. Refer to the ATSDR toxicological profiles for benzene, toluene, xylene, and ethylbenzene (ATSDR 1989, 1990, 1991) for information on these individual hydrocarbon components of gasoline.

5.2.2 Water

Gasoline can migrate to groundwater from the soil surrounding leaking underground storage tanks and pipelines. By one estimate, as many as 75,000-100,000 tanks leak millions of gallons of gasoline to groundwater each year (Feliciano 1984; Tanglely 1984). This estimate does not include leakage from abandoned tanks. One leak reported in a Michigan 1997-1979 survey resulted in the release of over 60,000 gallons of gasoline to groundwater (Feliciano 1984). The state of Maine estimates that leaking

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underground storage tanks are responsible for the release to groundwater of about 11 million gallons of gasoline yearly (Feliciano 1984). Gasoline in underground drainage water and sump water from a basement have been traced to leaking underground storage tanks at service stations (Dell'Acqua et al. 1976). Gasoline from an unidentified source was found floating on the water table in Hampden Township, Pennsylvania (McKee et al. 1972). A leak from a pipeline or underground storage tank contaminated groundwater in the north Los Angeles area of California with an estimated 100,000-250,000 gallons of gasoline (McKee et al. 1972). Although the total amount of gasoline released by leaking underground tanks throughout California is unknown, it has been estimated that the majority of reported leaky tanks (11,000) contained gasoline (Hadley and Armstrong 1991).

Release of gasoline to seawater may occur when barges or tankers carrying the chemical ground on reefs. Grounding of a barge in Block Island Sound, Rhode Island, resulted in release of 1,900 metric tons of gasoline into the water (Dimock et al. 1980). Based on the U.S. Coast Guard National Response Center database, an estimated 48,816 gallons of gasoline were accidentally discharged to New Jersey's Newark Bay and associated major tributaries from 1982 to 1991 (Gunster et al. 1993). Gasoline is not listed in the Contract Laboratory Program Statistical Database (CLPSD) of chemicals found in groundwater or surface water at hazardous waste sites.

5.2.3 Soil

Release of gasoline to soil from leaking underground storage tanks and pipelines has been reported (Tangley 1984). Most releases from storage tanks and pipelines are reported as releases to groundwater because this is where evidence of a leak first appears. However, the release is actually to surrounding soil with a migration to groundwater due to gravity and water wash down. Most estimates of the amounts of the releases are based on levels found in groundwater and have been reported in Section 5.2.2. An estimated 75,000-100,000 leaking tanks release millions of gallons of gasoline per year to the surrounding soil (Feliciano 1984; Tangley 1984). This estimate does not include abandoned tanks that may be leaking. Excavation around a tank suspected of leaking showed that gasoline was seeping into the soil from the tank (Dell'Acqua et al. 1976). Gasoline is also spilled on soil during the removal and maintenance of underground storage tanks (Kramer 1989). Soil in the business section of Rockaway Beach in Queens County, Long Island, was contaminated with gasoline

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from an identified source (McKee et al. 1972). Gasoline leaking into a department store basement in Harlan, Kentucky, was traced to the city-owned service station (McKee et al. 1972).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Gasoline is a mixture of relatively volatile hydrocarbons, including normal and branched chain alkanes, cycloalkanes, alkenes, and aromatics, that vary widely in their physical and chemical properties. Liquid gasoline generally contains alkanes, aromatics, and alkenes (IARC 1989). Gasoline is formulated to meet certain product performance specifications. Each batch of gasoline is likely to have a unique chemical composition as a result of the variable composition of the petroleum starting materials and the specific types of processing methods used in the formulation of different seasonal and performance grades of the product (Cline et al. 1991; CRCS 1985; Ghassemi et al. 1984). Upon release to the environment, gasoline is not transported as a mixture; rather, the various components of the mixture selectively partition to the atmosphere, soil, or water according to their individual physical/chemical properties. Therefore, gasoline itself is unlikely to be found in different environmental media.

The volatile fractions of gasoline are released to the atmosphere during every phase of the product formulation, handling, and marketing chain, including purchase by the consumer during refueling of gasoline-powered vehicles. These fractions generally consist of short-chain aliphatic hydrocarbons, alkenes, and aromatics (Air Force 1989; CRCS 1985; NESCAUM 1989). For example, more than 75% of airborne gasoline vapors have been reported to consist of C₁-C₁₀ and lighter hydrocarbons (McDermott and Killiany 1978). In the atmosphere, the components are subject to transport, dilution, dispersion, and photochemical reaction (see Section 5.3.2.1). The more water soluble of these fractions (e.g., aromatics) may also be washed out of the atmosphere in precipitation and reenter surface waters and soils. This partitioning is particularly likely for the breakdown products of atmospheric oxidation, which are more water soluble than the parent hydrocarbons (Air Force 1981; FAO 1977; Svoma and Hauzim 1984).

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Gasoline released to surface soils will differentially partition by volatilization, dissolution, or adsorption of individual constituents according to their physical/chemical properties. Gasoline exists in soil in four states: (1) as a free-moving liquid; (2) adsorbed to soil particulates; (3) dissolved in groundwater; and (4) as a vapor (NESCAUM 1989; Svoma and Hauzim 1984). Short-chain (C_4 - C_8) alkanes and alkenes with high vapor pressures and low water solubilities will volatilize to the atmosphere. Results of field experiments indicate that the volatility of gasoline from contaminated soils can be enhanced by the addition of water to the soil (Donaldson et al. 1992). Evaporation may be limited by infiltration and vertical movement of the liquid product into the soil, the extent of which depends on soil porosity (Bossert and Bartha 1984). Releases of liquid gasoline to subsurface soils will also limit volatilization losses of the lower molecular weight alkanes, which may be transported to groundwater (Air Force 1989). Higher molecular weight alkanes, alkenes, cycloalkanes, and aromatics may sorb to some extent to soil particulates (Air Force 1981, 1989). Potential sorption is greatest for alkenes, followed by aromatics, cycloalkanes, and least for alkanes (Hathaway and Andrews 1990).

Components of gasoline that are not volatilized or sorbed to soil particulates will migrate downward through the unsaturated zone by gravity or leaching to the water table (DOI 1984; Yaniga 1984). Liquid gasoline, as a result of its lower kinematic viscosity, is expected to move through the unsaturated zone of the soil at a velocity 2-3 times that of water (Bouchard et al. 1990). The amount of liquid product that reaches the water table is dependent upon the amount of product released and site-specific soil and hydrogeological conditions (Yaniga 1984). For example, if the amount of gasoline hydrocarbons is small relative to the distance to the groundwater through the unsaturated zone, the hydrocarbons will probably be retained in the soil pore spaces. However, if the amount released is large relative to the distance to the groundwater, soil pore space capacity may be exceeded and bulk fluid transport to the groundwater may occur (Bouchard et al. 1990). Hydrocarbons immobilized in the unsaturated zone may be solubilized by downward moving soil water or fluctuating elevations of groundwater, and this residual material may serve as a source of contamination through leaching of solubilized components for long periods of time (DOI 1984). Water-soluble components, which consist predominantly (87-95%) of aromatics (Coleman et al. 1984), will dissolve in groundwater, whereas insoluble components will float as a separate phase on top of the water table. Water-soluble compounds, such as benzene, toluene, and xylene, show a greater potential for transport in groundwater aquifer than insoluble forms (Uchirin and Katz 1991). Gasoline-contaminated

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groundwater may serve as a source of surface water contamination in areas where groundwater discharges to surface waters (Air Force 1989).

Liquid gasoline released to surface water spreads horizontally over the surface, presenting a large surface area from which the volatile components will rapidly partition to the atmosphere (Bossert and Bartha 1984; CRCS 1985). For example, following oil spills in marine environments, hydrocarbons of carbon chain lengths up to C₁₃ have been found to be lost by volatilization within the first few days after the spill. Hydrocarbons of up to C₂₀ volatilize after a few weeks (FAO 1977). Lateral spreading also increases dissolution of the water soluble components. Spills of gasoline in high winds and heavy seas may produce emulsions which limit evaporative losses (CRCS 1985). Components not lost to the atmosphere by evaporation probably remain near the surface where they may be degraded (see Section 5.3.2.2). Higher molecular weight components (e.g., naphthalene and substituted naphthalenes) may partition to sediments (Air Force 1981).

The bioaccumulation potentials of the major components of gasoline range from low to high. Some higher molecular weight components (e.g., naphthalene and substituted naphthalenes) may be taken up by fish and domestic animals and bioconcentrated if they persist in environmental media (Air Force 1989). Alkenes have low log octanol/water partition coefficients (K_{ow}) of about 1 and estimated bioconcentration factors (BCF) of about 10; aromatics have intermediate values (log K_{ow} values of 2-3 and BCF values of 20-200), while C₅ and greater alkanes have fairly high values (log K_{ow} values of about 3-4.5 and BCF values of 100-1,500) (NESCAUM 1989).

5.3.2 Transformation and Degradation

5.3.2.1 Air

Gasoline hydrocarbons volatilized to the atmosphere quickly undergo photochemical oxidation. The hydrocarbons are oxidized by reaction with molecular oxygen (which attacks the ring structure of aromatics), ozone (which reacts rapidly with alkenes but slowly with aromatics), and hydroxyl and nitrate radicals (which initiate side-chain oxidation reactions) (Stephens 1973). Alkanes, isoalkanes, and cycloalkanes have half-lives on the order of 1-10 days, whereas alkenes, cycloalkenes, and

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substituted benzenes have half-lives of less than 1 day (EPA 1979a). Photochemical oxidation products include aldehydes, hydroxy compounds, nitro compounds, and peroxyacyl nitrates (Cupitt 1980; EPA 1979a; Stephens 1973).

5.3.2.2 Water

Of the hydrocarbon components of gasoline, only xylenes, trisubstituted benzenes, and naphthalenes have been reported to undergo photolysis and photooxidation in aqueous solution. Alkanes, benzenes, and monosubstituted benzenes have been found to be resistant to photolytic breakdown in aqueous systems. The rate of reaction of trisubstituted benzenes and naphthalenes is competitive with that of volatilization from surface waters (Air Force 1981).

Many of the hydrocarbon components of gasoline have been found to undergo biodegradation in surface waters and sediment (Atlas 1981; Walker et al. 1975b). Microorganisms in marine and estuarine environments, including bacteria, yeasts, and filamentous fungi, are capable of degrading petroleum and petroleum products, including gasoline. Microbial activity becomes important about 1 week after the spill or release, after initial hydrocarbon losses have occurred through volatilization and photooxidation. Alkanes are attacked more rapidly and by a greater number of species than aromatics or naphthenics, with removal in the time frame of days-to-weeks; *n*-alkanes are more easily degraded than branched chain alkanes (FAO 1977). Degradation of gasoline hydrocarbons in surface waters is expected to be rapid under conditions favorable to microbial activity; however, it may be slow or limited under unfavorable conditions, such as low pH, low temperature, low oxygen levels, or high salinity, or where populations of degrading microbes are low (Air Force 1989).

Organic pollutants have also been found to undergo biodegradation by microorganisms isolated from groundwater (Wilson and McNabb 1983). For example, a mixed population of 32 cultures of microbes isolated from groundwater contaminated with gasoline were able to degrade gasoline hydrocarbons. *Nocardia* cultures were found to metabolize most of the alkanes, whereas *Pseudomonas* cultures were responsible for degradation of most of the aromatics (Jamison et al. 1976).

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Biodegradation of gasoline in groundwater can occur under denitrifying conditions (Carroquine et al. 1992).

5.3.2.3 Soil

After volatilization, biodegradation and photooxidation are the most important removal mechanisms for gasoline hydrocarbons released to surface soils (Air Force 1989). Photooxidation in surface soils is less important than in surface water environments since infiltration of the liquid product into the soil will limit exposure to solar radiation (Bossert and Bartha 1984).

Biodegradation of gasoline hydrocarbons in soil by a diverse group of microorganisms has been reported by numerous investigators (Atlas 1981; Bossert and Bartha 1984; Haines and Alexander 1974; Mann and Gresham 1990; Thomas et al. 1990). Bacteria and fungi appear to be the most important hydrocarbon-utilizing microbes in soils (Atlas 1981). n-Alkanes, n-alkylaromatics, and aromatics of carbon chain length C₁₀-C₂₂ are the most readily degradable hydrocarbons. n-Alkanes, alkylaromatics, and aromatics above C₂₂ are generally not available for metabolism by soil microbes because of their limited water solubility and solid physical state. Higher molecular weight hydrocarbons sorbed to soil particulates are also generally unavailable for metabolism by microorganisms. Hydrocarbons in the C₅-C₉ range are biodegradable only at low concentrations since at higher concentrations they exhibit membrane-solvent toxicity to soil microbes and are generally removed by volatilization. Hydrocarbons with condensed ring structures, such as polycyclic aromatic hydrocarbons (PAHs), and cycloalkanes are relatively resistant to biodegradation (Atlas 1981; Bossert and Bartha 1984). Isoalkanes and 1,3,5-trimethylbenzene have also been reported to be resistant to biodegradation (Mann and Gresham 1990). Some of the intermediate products of metabolism (e.g., alcohols, aldehydes, and monocarboxylic acids) are more water soluble or strongly sorbed than the parent hydrocarbons (Atlas 1981; Bossert and Bartha 1984; Carlson 1981). The rate of biodegradation is highly dependent upon the amount of the hydrocarbon substrate and a number of site-specific environmental factors, including temperature, oxygen content, moisture content, nutrient content, salinity, and pH (Atlas 1981; Bossert and Bartha 1984). Degradation of hydrocarbons by soil microbes appears to be almost exclusively an aerobic

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process. The initial steps in microbial metabolism require oxygen; reference to biodegradation under anaerobic conditions is limited (Atlas 1981; Bossert and Bartha 1984; Corapcioglu and Hossain 1990).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Several variables can influence the measured concentrations of gasoline vapor and component hydrocarbons in air. Among these are wind direction and velocity, distance from the source of the vapors, ambient temperature, duration of sampling time, the presence of vapor recovery equipment, and composition of the gasoline (McDermott and Vos 1979; Shiller 1987).

Levels of gasoline vapor have been measured in air at service stations in several areas of the country. Area air samples taken in the vicinity of a high-volume service station in Pennsylvania during 1 week in May showed concentrations of gasoline vapor ranging from not detected (detection limit of 0.4 mg/m^3 , assuming a desorption volume of 1 mL solvent) to 28 mg/m^3 (Keamey and Dunham 1986). Air levels of gasoline vapor measured at seven different service stations in the United States (Houston, Texas; Manhattan Beach, California; New Britain, Connecticut; New Orleans, Louisiana; Plantation, Florida; Stickney, Illinois; and Walnut Creek, California) from March to June ranged from 1.81 to 99.2 ppm (McDermott and Vos 1979). Corresponding concentrations of benzene ranged from <0.01 to 1.21 ppm.

Monitoring of the storage tank removal and maintenance operation indicated relatively high levels of gasoline vapor can be found near the site of the activities (Kramer 1989; Shamsky and Samimi 1987). Area sampling at the bottom of the excavation, directly above the excavation at ground level, upwind and downwind of the site, and at the site location during inerting (i.e., flushing with carbon dioxide) indicated the highest concentrations are found in the location of the site during the inerting process when no controlled venting of the vapors is performed. The total hydrocarbon level (a measure of gasoline vapor) at the site when no vents were used was 860 ppm. With the use of vents the total hydrocarbons measured 21.8 ppm. Total hydrocarbons were also high at the bottom of the excavation site, measuring 395 ppm compared to 16.7 ppm just above the site at ground level. As expected,

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mean upwind concentrations were lower than downwind concentrations (0.64 and 3.86 ppm total hydrocarbons, respectively) and were considerably lower than concentrations at the excavation site. Levels of 0.08 ppm benzene and 4 ppm total hydrocarbons were measured in air during on-site monitoring of an underground storage tank excavation (Kramer 1989). Levels of 1.0 ppm benzene and 11 ppm total hydrocarbons were measured during the transfer of gasoline from a tank excavated for cleaning to a tanker truck (Kramer 1989). During purging of the tank, the average atmospheric concentration of benzene near the tank was 6.7 ppm (Kramer 1989). Although venting was not used in this excavation procedure, the measured levels were considerably below previous measurements (Shamsky and Samimi 1987). The reason for the discrepancy in results could not be determined. Gasoline is not listed in the CLPSD of chemicals found in soil at NPL sites only (CLPSD 1989).

5.4.2 Water

One day following the accidental release of 1,900 metric tons of gasoline into the water at Block Island Sound, Rhode Island, total levels of C₈-C₁₂ hydrocarbons at three sites close to the spill ranged from 5 to 20 µg/L at a depth of 3.5 meters in the water column (Dimock et al. 1980). These concentrations exceeded the background levels found at sites distant from the spill. Although gasoline is known to migrate to groundwater following its release from leaking underground storage tanks and pipelines (see Section 5.2.2), no information on levels in groundwater was located.

5.4.3 Soil

Although methods for the detection of gasoline hydrocarbons in soil exist (see Chapter 6), no specific data on levels in soil were located. Gasoline is known to be present in soil in areas where it has been spilled and in soil surrounding leaking underground storage tanks or pipelines (Dell'Acqua et al. 1976; Kramer 1989; McKee et al. 1972). Discriminant analysis, a multivariate statistical technique, has been applied to differentiate between gasoline contaminated soils resulting from leaking underground storage tanks and those of background origin (Saentz and Pingitore 1991).

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5.4.4 Other Environmental Media

Data on the concentration of hydrocarbons from gasoline contamination in media other than air, water, and soil are very limited. This is due, at least in part, to the difficulty in tracing the source of hydrocarbon contamination in other environmental media such as food, fish and shellfish, and terrestrial plants and animals. Samples of bivalve mollusks collected 2 days following an accidental spill of gasoline into Block Island Sound, Rhode Island, contained low levels of gasoline compounds (Dimock et al. 1980). However, there were no adequate control samples by which to confirm background levels of these compounds in the shellfish, so it is not certain that the contamination resulted from the spill.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population may be exposed to gasoline or gasoline vapors during automobile refueling procedures, refueling of gasoline-powered equipment (e.g., lawn mowers), and through the use of gasoline-contaminated surface water or groundwater. However, no specific data on exposure of the general population were located.

Possible occupational exposure to gasoline and gasoline vapors exists for workers all along the chain of gasoline production to consumer use. Workers involved in onloading and offloading gasoline at docks and bulk storage terminals; loading, driving, and delivering fuel to storage terminals and gas stations; and refueling and automotive repair operations at service stations have a large potential for exposure (Runion 1988). Workers involved in the cleanup and maintenance of underground storage tanks and service station pump equipment are also exposed to higher-than-background levels of gasoline and gasoline vapor (Runion 1988).

Several monitoring surveys of service station employees have been conducted. Personal air sample measurements of employees at a high-volume service station in Pennsylvania for 1 week in May showed geometric mean total gasoline vapor time-weighted average (TWA) exposures of employees ranged from 2.9 to 5.2 mg/m³ (Keamey and Dunham 1986). Geometric mean personal short-term exposures to gasoline vapor ranged from 12.7 to 24.7 mg/m³. Actual exposure concentrations during

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refueling ranged from not detected (detection limit of 10 mg/L extraction solvent) to 116.3 mg/m³. Component analysis of personal long-term samples showed that 2-methyl butane and pentane were the most prevalent hydrocarbons and were detected in all 18 samples at concentrations ranging from 0.1 to 1.7 ppm. Another survey of service station employees conducted from March to June at seven service stations located throughout the United States (Houston, Texas, Manhattan Beach, California, New Britain, Connecticut, New Orleans, Louisiana, Plantation, Florida, Stickney, Illinois, and Walnut Creek, California) showed that mean TWA attendant exposures ranged from 3.63 to 22.3 ppm for gasoline vapor and 0.02-0.24 ppm for benzene (McDermott and Vos 1979). The high values were found at the New Britain, Connecticut service station and appeared to be due to hydrocarbon exposure from a source other than gasoline in one sample. Excluding the Connecticut results, the range of 3.63-9.26 ppm gasoline vapor was a more representative estimate of service station employee exposure. Monitoring of service station personnel responsible for refueling operations at two service stations located near a major expressway, revealed a geometric mean 8-hour TWA of 4.0 mg/m³ (range of 1.1-130.3 mg/m³) (Halder et al. 1986a). Closer monitoring of these workers showed no detectable hydrocarbon exposure levels for refueling operations totaling 22 minutes or less (limit of detection = 30 µg/sample). However, for total refueling times of 27 and 354 minutes, TWA 8-hour total hydrocarbon levels ranged from 0.7 to 1.4 and from 2.1 to 4.8 mg/m³, respectively. Most of these were lighter weight (5 or less carbon atoms) hydrocarbons.

Analysis of air samples for benzene at a service station and alveolar air levels of benzene in the attendants showed that benzene levels in the breath samples taken during refueling operations were considerably higher than during times when refueling was not occurring (Brugnone et al. 1986). Alveolar concentrations ranged from 210 to 458 ng/L during refueling and from 52 to 191 ng/L when refueling was not being done. Corresponding air levels taken in the breathing zone ranged from 63 to 611 ng/L and from 20 to 77 ng/L during periods of refueling and no refueling, respectively. The higher concentrations of benzene in alveolar air in most samples may indicate that the eliminated benzene was previously absorbed and stored.

Biological monitoring of service station workers in India revealed substantially higher levels of urinary phenol when these workers were compared to persons with no known exposure to either gasoline or benzene (Pandya et al. 1975; Rao et al. 1977). Excretion of phenol in the urine can be evidence of

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benzene exposure. Since benzene is a component of gasoline and gasoline vapor, presence of excess phenol in the urine of these workers may be associated with their exposure to gasoline vapor. Of the 51 service station workers monitored, 88% had urinary phenol levels of >20 mg/L and 47% had levels >40 mg/L. Average urinary phenol excretion in unexposed subjects was reported to be 8.6 mg/L (range of 3.3-15 mg/L). Since no measurements of gasoline or benzene in the breathing zones of these subjects were taken, the excess phenol cannot be unequivocally attributed to gasoline exposure.

Monitoring surveys of workers occupationally exposed to gasoline indicate that exposure results in higher blood and urinary concentrations of lead in these workers. A group of 26 workmen employed in a petrol company in Poland were assessed for blood and urinary levels of lead associated with their exposure to gasoline (Turlakiewicz and Chmielnicka 1985). The mean blood lead levels of these workers was 25.6 µg/dL and the mean urinary lead concentration was 7.4 µg/dL. Corresponding levels in the control group were 10.6 and 2.5 µg/dL for blood and urinary levels, respectively. Mean 8-hour TWA concentrations of lead in the workplace air ranged from 0.015 to 0.205 mg/m³ depending on the specific job. A similar survey of 47 service station workers in Tasmania also indicated that blood lead levels were higher in subjects occupationally exposed to gasoline (Moore et al. 1976). The mean blood lead level of the service station workers was 32.9 µg/dL compared to a mean level of 14.3 µg/dL in the control population.

A survey of workers employed at five bulk-transfer facilities, two marine loading facilities, and two service stations located near a major expressway was conducted (Halder et al. 1986a). Personal monitoring of breathing zone levels of hydrocarbons with 6 or more carbon atoms showed 8-hour TWA geometric mean exposure concentrations of 5.7 mg/m³ (range of 0.8-120.8 mg/m³) for terminal workers and 4.0 mg/m³ (range of 1.1-130.3 mg/m³) for service station workers. Geometric mean 8-hour TWA exposures to hydrocarbons with four carbons or more were 31.2 mg/m³ (range of 1.3-237.6 mg/m³) and 89.4 mg/m³ (range of 9.1-1,580.4 mg/m³) for terminal workers and marine loading facility workers, respectively. The bulk of the hydrocarbon exposure at bulk terminals and marine loading facilities (61.3-67.4%) was to lighter hydrocarbons containing four or five carbon atoms, and of these, n-butane, isobutane, n-pentane, and isopentane were responsible for most of the

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exposure. Measured geometric mean TWA levels of benzene ranged from 0.5-0.8 mg/m³ for the three worker categories.

Workers involved in the removal and maintenance of underground storage tanks are exposed to both gasoline and gasoline vapor. Monitoring of workers involved in these operations showed that exposure occurred during tank draining, tank removal, cutting and cleaning, and tank testing (Kramer 1989; Shamsky and Samimi 1987). Levels of exposure during these operations were measured for personnel involved in the procedures. Highest exposure occurred during tank removal, cutting and cleaning, with levels of total hydrocarbons in the breathing zone ranging from 9 ppm over a 6-hour exposure period for an observer to 459 ppm for a 30 minute exposure period for a laborer (Kramer 1989). Levels of benzene ranging from 0.19 ppm over 5.5 hours for an observer to 4.57 ppm over 30 minutes for a laborer were also observed. Exposures to gasoline vapors were lower for workers involved in gasoline transfer and tank-testing operations. Levels in these workers ranged from 4 to 5 ppm total hydrocarbons in the breathing zone (for exposure periods of 30 minutes to 6 hours in personnel involved in gasoline transfer) to 7-12 ppm (for periods of 3.25 to 4.75 hours in the breathing zone of workers involved in tank testing). For all procedures, laborers generally had the highest exposure to gasoline vapor and observers were exposed to the lowest amounts. Exposure to gasoline was not quantified, but dermal exposure was stated to be common during the maintenance operations. Results from a similar study of tank maintenance personnel found mean breathing zone levels of total hydrocarbons of 2.3 ppm for 18-35 minutes exposure of observers and 106 ppm for 15-110 minutes exposure of laborers. Mean benzene exposure levels were 0.1 and 6.8 ppm for observers and laborers, respectively. Potential exposures for personnel upwind and downwind of the excavation site, at the bottom of the site, directly above the site at ground level, and at the site during inerting with and without vents were also determined. Highest levels were measured during inerting without vents (mean total hydrocarbons = 860 ppm) and at the bottom of the excavation (mean total hydrocarbons = 395 ppm). Data on specific hydrocarbons in the gasoline vapor suggested that exposures exceeding the TLVs could occur for pentane, n-hexane, benzene, toluene, xylene, and total hydrocarbons if workers were exposed for 8-hour periods to concentrations found at the bottom of the excavation and during inerting of tanks without vents. However, these workers would not normally encounter 8-hour continuous exposure work days.

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Breathing zone samples collected at bulk loading terminals where driver/salesmen load their own trucks showed that highest exposure occurred during loading of tanker trucks when no vapor recovery system was used (Phillips and Jones 1978). Approximately 90% of the samples had levels of hydrocarbons of 225 ppm or less. Exposure was substantially reduced when a vapor recovery system was used, with 90% of the samples having levels of 110 ppm or less during a bottom-loading operation and 98% of samples having levels of 25 ppm or less during a top-loading operation. During unloading at service stations, 98% of the samples had levels hydrocarbons of 50 ppm or less. Results from another survey where benzene was used to monitor workers at a bulk transfer facility for exposure to gasoline vapor support the reduced exposure associated with vapor recovery systems (Irving and Grumbles 1979). Ninety-five percent of samples from top-loading facilities without vapor recovery systems had benzene levels below 8.5 ppm. At bottom-loading facilities without vapor recovery, 95% of the samples were below 3.5 ppm and at bottom-loading facilities with vapor recovery, 95% were below 1.8 ppm. These data also suggest reduced exposure levels are associated with bottom-loading of tankers.

According to the National Occupational Exposure Survey conducted from 1981 to 1983 by NIOSH, 70 employees (including 7 females) in seven plants producing petroleum and coal products were potentially exposed to natural gasoline or products containing natural gasoline (NOES 1991). Most of these (63 workers) were categorized as miscellaneous machine operators and the remainder were operators of separating, filtering, and clarifying machinery. These data are based only on actual observations of the use of gasoline or of products containing gasoline in 4,490 business establishments in the United States. In view of the information on exposure presented above, these data are believed to substantially underestimate the potential occupational exposure to gasoline.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Results from surveys of service station personnel strongly indicate that general population exposure to gasoline vapor can be expected at service stations. People who refuel their own vehicles are at risk of higher exposure than those who let attendants service their vehicles. These people are also at greater risk of contacting gasoline released from leaking pump lines and overfilled tanks. Populations living in the vicinity of a service station or bulk loading terminal are expected to have higher exposure to

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volatile gasoline-related hydrocarbons than those far removed from these businesses. Higher exposure to both gasoline and its vapor is also expected during filling of tanks on machines that operate on gasoline such as gasoline-powered lawn mowers.

Populations located near underground storage tanks or pipelines are at risk of exposure to high levels of gasoline-associated hydrocarbons through ingestion of contaminated drinking water. Additional inhalation and dermal exposure would come from other water uses such as washing dishes and showering. These populations may also be exposed to higher than background levels of gasoline vapor that may seep into basements.

Workers employed in occupations in which gasoline is transferred between various storage containers, such as those employed at bulk transfer facilities or marine loading facilities, tanker truck drivers, and service station employees, are exposed daily to higher levels of gasoline and gasoline vapor. Workers employed in occupations responsible for location of leaks, remediation of spills and leaks, and removal and maintenance of underground storage tanks are also potentially exposed to high levels of gasoline and gasoline vapor.

5.7 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 gasoline is available. Where adequate information is not available, ATSDR, in conjunction with 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 gasoline.

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

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identified data needs will be evaluated and prioritized, and a substance-specific research agenda may be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of gasoline and its primary component chemicals are well defined (Air Force 1989; ASTM 1989; OHM/TADS 1991; Sax and Lewis 1989) and can be used to estimate the fate of gasoline following release to the environment. Data needs associated with specific compounds that are components of the gasoline mixture (e.g., benzene, toluene, xylene, and other hydrocarbons and lead) are presented in the ATSDR toxicological profiles for these chemicals (ATSDR 1989, 1990, 1991). Therefore, no additional studies are needed at this time.

Production, Import/Export, Use, and Release and Disposal. Production, import/export, use, and release of gasoline are thoroughly described in the literature (see Chapter 4). Gasoline is used almost exclusively to fuel internal combustion engines (IARC 1989). The data indicate that the potential for human exposure is considerable and is most likely to occur from contact with contaminated air and/or groundwater. Production of gasoline has steadily increased between 1983 and 1989 from 277.2 million gallons/day to 306.6 million gallons/day (DOE 1989a). No data are available regarding predicted production volume of gasoline. Only limited information on one method of disposal (by spraying gasoline into an incinerator) was located (OHM/TADS 1991). No information regarding rules and regulations governing disposal of gasoline was located. More information on where and how gasoline is usually disposed of would aid in determining the potential risk of exposure to gasoline that has been improperly discarded.

Environmental Fate. Gasoline partitions to the different environmental compartments according to the physical/chemical properties of its individual components. The most important fate process is volatilization, especially for the short-chain alkanes (Air Force 1989; NESCAUM 1989). These compounds are transformed photochemically in the atmosphere (Cupitt 1980; Hendry and Kenley 1979; Stephens 1973). Migration to groundwater is also an important fate process for the soluble

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aromatics (Bouchard et al. 1990; DOI 1984; Yaniga 1984). The higher molecular weight hydrocarbons may sorb to soil (Air Force 1989; Hathaway and Andrews 1990). Gasoline-related hydrocarbons released to surface waters and soil are broken down by photooxidation and microbial degradation (Air Force 1989; Atlas 1981; Bossert and Bartha 1984; Thomas et al. 1990; Walker et al. 1975b). Biodegradation also occurs in groundwater (Wilson and McNabb 1983). The behavior of the gasoline mixture following release to the environment is well characterized. The fate of several of the most important component chemicals has also been studied (see ATSDR toxicological profiles for these chemicals [ATSDR 1989, 1990, 1991]). Data needs for specific hydrocarbons making up the gasoline mixture have been discussed in the ATSDR toxicological profiles for these chemicals (ATSDR 1989, 1990, 1991).

Bioavailability from Environmental Media. The various chemicals making up the gasoline mixture are known to be absorbed by inhalation, oral, and/or dermal routes. The extent of absorption by these routes will depend on the volatility, solubility, lipophilicity, and other properties of the specific components. Several of these component compounds have been discussed in detail in their individual ATSDR toxicological profiles (e.g., benzene, toluene, xylene, and lead), which should be consulted for further information (ATSDR 1989, 1990, 1991). More information linking exposure levels of gasoline and gasoline vapor with biological levels of component chemicals would be useful in determining which chemicals in the mixture are most likely to be absorbed and by which routes. This information would aid in determining daily human exposure levels and more accurately assessing the risk associated with gasoline exposure.

Food Chain Bioaccumulation. Gasoline, as a mixture of hydrocarbons, does not bioaccumulate in the food chain per se. However, the individual components making up the mixture may bioaccumulate depending on their individual properties (Air Force 1989; NESCAUM 1989). In general, the alkenes (e.g., pentene, butene, hexene) will not tend to bioaccumulate, the aromatics have a moderate tendency to bioaccumulate, and the higher molecular weight alkanes will tend to bioaccumulate (Air Force 1989). The need for further research on biomagnification of the components of gasoline has been presented in the individual ATSDR toxicological profiles on these chemicals (ATSDR 1989, 1990, 1991). Research on the biomagnification of the gasoline mixture would not be useful since gasoline is

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not available to the food chain as a mixture because it partitions into its different constituent components as soon as it enters the environment. Individual components of the mixture may be bioconcentrated. Bioconcentration studies should be conducted on the individual components that are persistent and for which this information is lacking.

Exposure Levels in Environmental Media. There is a substantial amount of exposure data on air levels of gasoline vapors surrounding service stations and bulk loading terminals, and some data on air levels resulting from excavation and maintenance of underground storage tanks (ATSDR 1989, 1990, 1991). Reliable monitoring data for the levels of gasoline in contaminated media at hazardous waste sites would be useful so that the information obtained on levels of gasoline in the environment can be used, in combination with the known biomarkers used to identify exposure to gasoline, to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Measurements of exposure levels have been taken for workers employed at service stations, bulk transfer facilities, and marine loading docks and those involved in storage tank excavation and maintenance (Halder et al. 1986a; Kearney and Dunham 1986; Kramer 1989; Shamsky and Samimi 1987). In addition, increased urinary excretion of phenol (20-40 mg/L) and lead (73.8 µg /L) and increased blood lead levels (256.3 µg /L) have been measured in workers occupationally exposed to gasoline (Moore et al. 1976; Rao et al. 1977; Turlakiewicz and Chmielnicka 1985), and increased levels of benzene have been measured in the expired air of service station workers (Brugnone et al. 1986). These increased levels are believed to result from the increased levels of lead and benzene absorbed when gasoline vapors are inhaled. However, because these and other chemicals in gasoline are frequently found in the environment, it is difficult to associate the increased levels of these chemicals specifically with exposure to gasoline. Methods more specific for gasoline exposure would aid in determining which markers would be most useful in determining exposure levels in humans. This information is necessary for assessing the need to conduct health studies on these populations.

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Exposure Registries. Service station workers, workers at bulk loading terminals and marine loading docks, and workers responsible for excavation and maintenance of gasoline storage tanks are known to have increased exposure to gasoline and its vapors. However, no registry exists for exposure to gasoline.

No exposure registries for gasoline were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this substance.

5.7.2 On-going Studies

A laboratory study on the effect of soil heterogeneity on the movement of light nonaqueous phase liquids is being conducted at the Colorado State University. The study, which is funded by the National Science Foundation, will utilize a dual energy gamma attenuation system to examine the movement of water, air, and light hydrocarbons through soils placed in a laboratory flume. Results of this research are expected to be useful for testing and validating models that predict the behavior of light hydrocarbons leaked from underground storage tanks to the water table.

Field and laboratory investigations being conducted by the U.S. Geological Survey of the Department of Interior are examining the anaerobic biodegradation of petroleum and gasoline hydrocarbons, including benzene and alkylbenzenes. A separate study is attempting to model the transport and biodegradation of organic mixtures, including gasoline.

At the University of Nevada, a study is underway that is attempting to: (1) establish improved methods for analyses of soils for gasoline constituents; and (2) determine the utility of using volatilization as a method for decontaminating soils containing gasoline. This field experiment will be conducted under conditions similar to those used in landfarming. The purpose is to demonstrate the relative rates of

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loss of various petroleum hydrocarbons, with identification of a treatment method that optimizes loss at lowest cost.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring gasoline in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify gasoline. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect gasoline in environmental samples are the methods approved by federal organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

Gasoline is a complex mixture of hydrocarbons and additives. The major hydrocarbon component categories in gasoline include alkanes, isoalkanes, cycloalkanes, alkenes, and aromatics (MacFarland et al. 1984). The methods most commonly used to detect the major hydrocarbon components in gasoline in biological materials include gas chromatography (GC) and high resolution gas chromatography (HRGC) combined with flame ionization detection (FID). GC combined with mass spectrometry (MS) has been used for both identification and quantification of the hydrocarbon components in gasoline and increases the reliability of the technique. GC or HRGC combined with atomic absorption spectrometry (AAS) are the most commonly used methods for detecting lead or alkyllead compounds. Highperformance liquid chromatography (HPLC) combined with electron capture detector (ECD) has also been used to detect alkyllead compounds. See Table 6-1 for a summary of the analytical methods most commonly used to determine gasoline in biological materials. For more analytical methods information, see the ATSDR toxicological profiles on some of the individual components of gasolines (e.g., benzene, toluene, xylene, cyclohexane, ethane, ethylene, and lead) (ATSDR 1989, 1990, 1991).

TABLE 6-1. Analytical Methods for Determining Gasoline in Biological Materials

Sample Matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Alveolar air (benzene)	Expire into glass tube; transfer headspace gas to cryogenic trap; desorb by heating	HRGC/FID HRGC/MS	NR	NR	Brugnone et al. 1986
Lung gas (isopentane, <i>n</i> -pentane, 2-methyl-2-butene, 2-methyl-pentane, 3-methyl-pentane, <i>n</i> -hexane)	Collect sample in vial; heat in water bath; inject headspace gas	GC/FID GC/MS	NR	NR	Ikebuchi et al. 1986
Blood (benzene)	Collect venous blood sample into glass tube; transfer headspace gas to cryogenic trap; desorb by heating	HRGC/FID HRGC/MS	NR	NR	Brugnone et al. 1986
Blood (isopentane, <i>n</i> -pentane, 2-methyl-pentane, benzene, 2-methylhexane, 3-methylhexane, toluene)	Add internal standard to blood; heat; inject headspace gas	GC/FID GC/MS	NR	81-125%	Matsubara et al. 1988

TABLE 6-1. Analytical Methods for Determining Gasoline in Biological Materials (continued)

Sample Matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood (aromatic and aliphatic hydrocarbons)	Add internal standard to blood; heat; inject headspace gas	GC/MS	0.01 µg	NR	Kimura et al. 1988
Blood (tetramethyl lead)	Hemolyze blood samples by freezing; extract alkyllead compound with <i>n</i> -heptane in ultrasonic bath	HRGC/AAS	0.01 µg/mL	90-95%	Andersson et al. 1984
Blood, urine (lead)	Add ²¹⁰ Pb to sample and digest with acid; coprecipitate lead by adding barium nitrate, followed by electro-deposition on platinum wire	IDMS	NR	98-99%	Manton and Cook 1984
Urine (benzene)	Steam distill urine specimens in sulphuric acid	Spectrophotometry	NR	NR	Pandya et al. 1975; Buchwald 1966
Urine (benzene metabolites)	Hydrolyze sample with perchloric acid; extract phenol and cresol with diisopropyl ether	GC/FID	NR	NR	NIOSH 1974

TABLE 6-1. Analytical Methods for Determining Gasoline in Biological Materials (continued)

Sample Matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine (benzene metabolites)	Digest sample enzymatically and with acid; extract phenol, phenyl sulfate, and phenyl glucuronide with ethyl ether	GC/FID	1 mg/L	92-98%	Bochet 1988 (IARC Method 6)
Urine (benzene metabolites)	Centrifuge sample; analyze supernatant; elute with potassium phosphate-acetonitrile	HPLC/UV	4-5 mg/L	100-102%	Ogata and Taguchi 1987
Urine (toluene metabolite)	React sample with benzenesulfonyl chloride to form colored hippuric acid product	Spectrophotometry	2 mg/L	NR	NIOSH 1984a
Urine (toluene metabolite)	Extract sample with ethyl acetate; evaporate; redissolve in water (hippuric acid)	HPLC/UV	30 mg/L	NR	NIOSH 1984b
Urine (lead)	Wet ash sample with acid mixture; dissolve in diluted perchloric acid	ASV	4 µg/L	90-110%	NIOSH 1977 (Method P&CAM 200)

TABLE 6-1. Analytical Methods for Determining Gasoline in Biological Materials (continued)

Sample Matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Tissues (blood, brain, and lung)	Place tissue samples in water bath; heat; inject headspace gas	HRGC/FID	NR	NR	Shankles et al. 1982

AAS = atomic absorption spectrometry; ASV = anodic stripping voltammetry; FID = flame ionization detector; GC = gas chromatography; HPLC = high-performance liquid chromatography; HRGC = high resolution gas chromatography; IDMS = isotopedilution mass spectrometry; MS = mass spectrometry; NR = not reported; UV = ultraviolet detection

6. ANALYTICAL METHODS

GC/FID, HRGC/FID, GC/MS, and HRGC/MS have been used for quantification and identification of the hydrocarbon components of gasoline (aromatics, isoalkanes, alkanes, and alkenes) in alveolar air and lung gas (Brugnone et al. 1986; Ikebuchi et al. 1986). Since many of the components are volatile, analysis of the headspace gas is the most commonly used technique. Although the limit of detection for each component was not reported, sensitivity for the method, based on data reported, is in the ppb to sub-ppm range. Precision was very good (3.9-7% coefficient of variation [CV]) for measuring the components in lung gas (Ikebuchi et al. 1986). Precision data were not reported for alveolar air. Recovery data were not reported for either alveolar air or lung gas.

HRGC/FID, HRGC/MS, GC/FID and GC/MS have been used for quantification and identification of the hydrocarbon components of gasoline (aromatics, isoalkanes, alkanes, alkenes) in blood (Brugnone et al. 1986; Matsubara et al. 1988; Kimura et al. 1988). The hydrocarbon components were measured by analyzing headspace gas (Brugnone et al. 1986; Kimura et al. 1988; Matsubara et al. 1988). The headspace technique combined with GC/MS is rapid and makes for reliable qualitative and quantitative estimations of small amounts of volatile fuel components (Kimura et al. 1988). The limit of detection for GC/MS was 0.01 μg (Kimura et al. 1988). GC/FID is also a rapid and simple method for determining gasoline in blood (Matsubara et al. 1988). Accuracy is generally good (81-125% recovery) and precision (4.8-24% CV) is adequate (Matsubara et al. 1988). Although the limit of detection for various components was not reported, the sensitivity of the method, based on data reported, is in the ppm-range (Matsubara et al. 1988).

GC and HRGC combined with AAS have been used to measure lead and alkyllead compounds of gasoline, such as tetramethyl lead, in blood and urine (Andersson et al. 1984; Harman et al. 1981; Moore et al. 1976). AAS is the most common detector used to measure lead or alkyllead compounds in blood and urine since AAS is a lead-specific detector (Andersson et al. 1984; Harms et al. 1981; Moore et al. 1976). The alkyllead compounds are solvent extracted (Andersson et al. 1984; Harman et al. 1981). For blood samples, recovery was excellent (>90%) and precision was adequate (<10% relative standard deviation [RSD]) (Andersson et al. 1984). The detection limit was in the ppm-range (Andersson et al. 1984). No recovery, precision, or sensitivity data were reported for measuring lead in urine (Harman et al. 1981; Moore et al. 1976). Another method for determining alkyllead compounds (tetraethyl lead and tetramethyl lead) in gasoline (no matrix reported) has been investigated

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(Bond and McLachlan 1986). This method includes HPLC coupled with ECD at both solid and mercury electrodes (Bond and McLachlan 1986). This method is more specific for alkyllead compounds in gasoline than atomic absorption spectrometric detection since the mercury electrode acts as a very specific detector for alkyllead compounds (Bond and McLachlan 1986). The limit of detection is in the low ppm range (≈ 2 mg/L) for both tetramethyllead and tetraethyllead (Bond and McLachlan 1986). Precision is excellent ($\pm 3\%$ CV) (Bond and McLachlan 1986). Spectrophotometric detection of phenol in urine has been used for determining benzene (a component of gasoline) in urine (Pandya et al. 1975; Buchwald 1966). No details were given regarding recovery, precision, or detection limits.

A single method of analyzing the hydrocarbon components of gasoline in tissue samples was located (Shankles et al. 1982). This method utilized HRGCFID and involved injection of headspace gas. The limit of detection, accuracy, and precision of this method were not reported.

6.2 ENVIRONMENTAL SAMPLES

The methods most commonly used to detect the major hydrocarbon components of gasoline in environmental samples include GC/FID, GC/MS, HRGC/FID, HRGCMS, and HRGC/photoionization detector (PID)/FID. GC combined with photoionization-ion mobility spectrometry (PI-IMS) has been used and is selective to aromatic hydrocarbons. See Table 6-2 for a summary of the analytical methods used to determine gasoline in environmental samples. Several of the gasoline components have been discussed in detail in their individual toxicological profiles (e.g., benzene, toluene, xylene, cyclohexane, ethane, ethylene, and lead), which should be constituted for more information on analytical methods.

GC/FID, HRGC/FID and HRGC/MS are the most commonly used methods to selectively detect and identify the hydrocarbon components of gasoline in air (Berglund and Petersson 1990; Brown 1988; Brugnone et al. 1986; Esposito and Jacobs 1977; Russo et al. 1987). Air samples are usually collected on an adsorbent tube, examples of which include charcoal, Tenax[®], and Chromosorb[®]. Analytes are then extracted by heat or liquid solvent and analyzed. Collection efficiency ($>90\%$ recovery) was very good using charcoal tubes (Esposito and Jacobs 1977; Russo et al. 1987). No recovery data were

TABLE 6-2. Analytical Methods for Determining Gasoline in Environmental Samples

Sample Matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (benzene)	Collect air sample from breathing zone of individual; transfer headspace gas to cryogenic trap; desorb by heating	HRGC/FID HRGC/MS	NR	NR	Brugnone et al. 1986
Air (benzene)	Collect sample in Tedlar bag; inject	GC/PID	50 ppb	NR	NIOSH 1987 (Method 3700)
Air (toluene)	Collect sample on activated carbon; extract with carbondisulfide	GC/FID	0.01 mg	NR	NIOSH 1987
Air (benzene, ethylbenzene)	Collect sample on charcoal sorbent; desorb with carbon disulfide	GC/FID	10-100 ppb	NR	NIOSH 1984c (Methods 1500 and 1501)
Air (aliphatic and aromatic components)	Collect air sample onto Chromosorb®-106 and charcoal tubes; desorb by heat	HRGC/FID	NR	NR	Brown 1988
Air (hydrocarbons)	Collect air sample onto adsorbent tube, Tenax®-GC; desorb by heat	HRGC/FID	NR	NR	Berglund and Petersson 1990

TABLE 6-2. Analytical Methods for Determining Gasoline in Environmental Samples (continued)

Sample Matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (isobutane, <i>n</i> -butane, isopentane, <i>n</i> -hexane)	Collect air onto two charcoal tubes; desorb with carbon disulfide	GC/FID	NR	>90%	Russo et al. 1987
Air (aromatics)	Collect air samples on charcoal tube; extract aromatics with carbon disulfide and H ₂ SO ₄	GC/FID	NR	92-100%	Esposito and Jacobs 1977
Water (volatile hydrocarbons)	Sparge (purge and trap) water sample; collect volatile analytes on glass tube containing Tenax®/Ambersorb®/charcoal; thermally desorb; concentrate	HRGC/FID	NR	95-104%	Belkin and Hable 1988
Groundwater (hydrocarbons)	Collect water sample; acidify; extract with hexadecane	GC/FID	NR	NR	Dell'Acqua et al. 1976

TABLE 6-2. Analytical Methods for Determining Gasoline in Environmental Samples (continued)

Sample Matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Groundwater (BTEX)	Collect sample in glass vial; add mercuric chloride to prevent biodegradation; place in water bath; manually withdraw headspace gas with syringe; inject gas	HRGC/PID/FID	NR	NR	Roe et al. 1989
Sea water (hydrocarbons)	Extract sample with methylene chloride; column cleanup; concentrate; solvent exchange to hexane	HRGC/MS	NR	≈60%	Dimock et al. 1980
Soil (volatile aromatics)	Analyze headspace gas vapors of soil sample	GC/PI-IMS	0.18 mg/Kg	NR	Eiceman et al. 1987
Soil (BTEX)	Collect soil sample in glass vial; extract with distilled water; add mercuric chloride to sample to prevent biodegradation; place in water bath; manually withdraw headspace gas with syringe	HRGC/PID/FID	NR	NR	Roe et al. 1989

TABLE 6-2. Analytical Methods for Determining Gasoline in Environmental Samples (continued)

Sample Matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Bivalve mollusks (hydrocarbons)	Digest tissue; extract with methylene chloride; column cleanup; solvent exchange to hexane	HRGC/MS	NR	≈60%	Dimock et al. 1980

BTEX = benzene, toluene, ethylbenzene, and three xylene isomers; FID = flame ionization detection; GC = gas chromatography; H₂SO₄ = sulfuric acid; HRGC = high-resolution gas chromatography; MS = mass spectrometry; NR = not reported; PID = photoionization detection; PI-IMS = photoionization-ion mobility spectrometry

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reported for other types of adsorption tubes for comparison purposes. Both GC and HRGC combined with FID have adequate reproducibility (precision ranging from 5-12% CV) (Brown 1988; Russo et al. 1987). Although detection limits were not reported for these methods, based on data reported, sensitivity is in the low- to sub-ppm range.

GC/FID, HRGC/FID, HRGU/PID/FID, and HRG/MS have been used to measure the hydrocarbon components of gasoline in water, groundwater, and sea water (Belkin and Hable 1988; Dell'Acqua et al. 1976; Dimock et al. 1980; Kanai et al. 1991; Roe et al. 1989). Sample preparation methods include solvent extraction, purge-and-trap (dynamic headspace), and static headspace techniques. With the purge-and-trap technique, the multicomponent tube (Tenax[®]/Ambersorb[®]/charcoal) was effective in the collection and adsorption of a wide range of compounds found in gasoline (Belkin and Hable 1988). A disadvantage associated with the use of the purge-and-trap method is that it is subject to the inherent problems associated with the use of adsorbents, such as overloading, carryover, and breakdown with repeated heating and purging cycles (Roe et al. 1989). The static headspace method, however, is an attractive method due to its rapid turn around times and its simplicity, i.e., no sample workup is required outside the vial (Roe et al. 1989). The static headspace method is less expensive than the purge-and-trap because of the lack of expensive purging equipment (Roe et al. 1989). With the headspace method, multiple runs can be performed on a single sample vial, whereas the purge-and-trap method is essentially destructive; the sample may only be purged and analyzed once (Roe et al. 1989). Poor extraction efficiency ($\approx 60\%$ recovery) was obtained using a solvent extraction technique (Dimock et al. 1980). Good recovery (95-104%) and adequate precision (9.4-10.6% CV) were obtained using the purge-and-trap technique with HRGUFID (Belkin and Hable 1988). No recovery data were reported using the static headspace preparation method with HRGC/PID/FID; however, precision was good (2-8% RSD) (Roe et al. 1989). The use of serial detectors (PID/FID) with HRGC enhanced selectivity by providing an additional means of discrimination for the complex-gasoline mixture. Although detection limits were not reported for any method, based on data reported, sensitivity is in the ppm-to-ppb range.

HRGC/PID/FID and GC/PI-IMS are methods that have been used to measure the volatile aromatic components of gasoline in soil (Eiceman et al. 1987; Roe et al. 1989). Sample preparation is simple because the static headspace method is used. The use of serial detectors (PID/FID) with HRGC

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enhanced selectivity. No recovery data or detection limits were reported for HRGC/PID/FID; however, precision was good (2-8% RSD) (Roe et al. 1989). PID has a high selectivity to aromatic hydrocarbons (Eiceman et al. 1987). The combination of PI with IMS (PI-IMS) provided a second basis for resolution of chemical information and thus enhanced selectivity (Eiceman et al. 1987). Reproducibility for the GCM-IMS method ranged from 10 to 60% with a detection limit of 18 mg/kg (Eiceman et al. 1987).

Limited data were located regarding methods for detecting the hydrocarbon components of gasoline in biota (bivalve mollusks) (Dimock et al. 1980). The methods used were GC (detector not reported) and GUMS. Sample preparation included tissue digestion, extraction and clean-up, and solvent exchange to hexane. Recovery was poor ($\approx 60\%$). Sensitivity and precision were not reported.

6.3 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 gasoline is available. Where adequate information is not available, ATSDR, in conjunction with 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 gasoline.

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 will be proposed.

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6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Methods exist to measure lead (organic and inorganic) levels in blood and urine (Andersson et al. 1984; Bond and McLachlan 1986; Harman et al. 1981; Moore et al. 1976). Elevated urinary and blood lead levels may be indicators of exposure to leaded gasoline, but are not specific for gasoline. Methods also exist for measuring the hydrocarbon components of gasoline in alveolar air and lung gas (Brugnone et al. 1986; Ikebuchi et al. 1986), blood (Brugnone et al. 1986; Kimura et al. 1988; Matsubara et al. 1988), and urine (Buchwald 1966; Pandya et al. 1975) as biomarkers of exposure to gasoline, but again, are not specific for gasoline. The existing methods are sensitive enough to measure background levels in the population and levels at which biological effects occur. Recovery, precision, and accuracy data are needed for measuring urinary lead levels. Recovery and detection limit data are needed for measuring the hydrocarbon components in alveolar air, lung gas, blood, and urine. These data will help to improve the reliability and reproducibility of the methods and will be useful in monitoring populations exposed to gasoline.

There do not appear to be any biomarkers of effect that are specific for gasoline.

Methods for Determining Parent Compounds and Degradation Products in

Environmental Media. Methods exist to detect the major hydrocarbon components of gasoline in air (Berglund and Petersson 1990; Brown 1988; Brugnone et al. 1986; Esposito and Jacobs 1977; Russo et al. 1987), water (Belkin and Hable 1988; Dell'Acqua et al. 1976; Dimock et al. 1980; Kanai et al. 1991; Roe et al. 1989), and soil (Eiceman et al. 1987; Roe et al. 1989). The most commonly used methods are GC/FID, HRGC/FID, GC/MS, HRGC/MS, HRGC/PID/FID, and GC/PI-IMS. These methods are relatively sensitive, selective, and reliable and can be used to detect the levels of the gasoline components found in the environment and levels at which health effects occur. Recovery data and detection limits are needed for measuring components found in all media. Recovery data will help to assess and improve reproducibility of the methods. Detection limit data will aid in comparison of sensitivity between methods and indicate where improvements in sensitivity are needed. This information will be useful in monitoring gasoline contamination in the environment.

6. ANALYTICAL METHODS

6.3.2 On-going Studies

No on-going analytical methods studies were located.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding gasoline in air, water, and other media are summarized in Table 7-1. Regulations and guidelines pertaining specifically to gasoline emissions are not included in Table 7-1. Regulations and guidelines for which it has not been explicitly stated if they apply to gasoline vapor and/or emissions have been included in Table 7-1. There is no EPA reference dose (RfD) or reference concentration (RfC) for gasoline. EPA has established many regulations on gasoline to control air pollution (EPA 1990a, 1990b, 1990c). Many states have adopted additional, more stringent regulations (CELDS 1991). Under the Hazardous Material Transportation Act, gasoline is designated as a hazardous substance subject to special requirements for packaging, labeling, and transportation (DOT 1989a, 1989b).

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Gasoline

Agency	Description	Information	References
<u>NATIONAL</u>			
Regulations:			
a. Air:			
EPA OAQPS	Backing of lead usage right allowed in connection with regulations significantly reducing allowable gasoline lead content Lead content limit in gasoline	Yes	EPA 1985a (40 CFR 80); EPA 1985b
OSHA	PEL TWA	0.10 grams/ gallon 900 mg/m ³ (300 ppm)	EPA 1985a (40 CFR 80); EPA 1985c OSHA 1989a (29 CFR 1910.1000); OSHA 1989B
	STEL (15-minute average)	1,500 mg/m ³ (550 ppm)	OSHA 1989a (29 CFR 1910.1000); OSHA 1989b
b. Other			
DOT	Hazardous Material Transportation Act: Designated as a hazardous substance subject to requirement for packaging, labeling, and transportation	Yes	DOT 1989a (49 CFR 172.101, Appendix A); DOT 1989b
Guidelines:			
a. Air:			
ACGIH	TLV TWA	890 mg/m ³ (300 ppm)	ACGIH 1990
	STEL (15-minute average)	1,480 mg/m ³ (500 ppm)	ACGIH 1990
NIOSH	Carcinogen: lowest feasible concentration		NIOSH 1988
<u>STATE</u>			
Regulations and Guidelines:			
a. Air			
	Acceptable Ambient Air Concentration		NATICH 1991
Connecticut	(8 hours)	1.8 ug/m ³	
Florida-Fort Lauderdale	(8 hours)	9.0 ug/m ³	
Florida-Pinellas	(8 hours)	9.0 ug/m ³	
Florida-Pinellas	(24 hours)	2.16 ug/m ³	
Kansas	(1 year)	1.33 ug/m ³	
Kansas-Kansas City	(Annual)	1.33 ug/m ³	
Maryland		0.00	
Nevada	(8 hours)	2.14x10 ¹ mg/m ³	
North Dakota	(1 hour)	1.48x10 ¹ mg/m ³	
North Dakota	(8 hours)	8.90 mg/m ³	
Oklahoma	(24 hours)	8.90x10 ⁴ ug/m ³	
Texas	(30 minutes)	8.9x10 ³ ug/m ³	
	In addition to federal regulations many states has adopted additional rules and regulations on gasoline. These regulations vary from state to state.		CELDS 1991
Alabama	Emissions from leaks from gasoline terminals, gasoline dispensing facilities, and petroleum refinery sources	Yes	
	Emissions from leaks from gasoline tank trucks and vapor collection systems	Yes	
	Organic emissions	Yes	
Arizona	VOC emissions from petroleum storage and petroleum refineries	Yes	
California	Leaking underground fuel tanks	Yes	

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Gasoline (continued)

Agency	Description	Information	References
State (Cont.)			
Colorado	Hazardous materials transportation	Yes	
Connecticut	Visible emissions	Yes	
Florida	Ozone emission standards for existing petroleum liquid storage, bulk gasoline plants and terminals, and gasoline service stations	Yes	
Illinois	Gasoline distribution	Yes	
Kansas	Leaks from gasoline delivery vessels and vapor collection systems	Yes	
	VOC emissions from gasoline dispensing facilities	Yes	
Kentucky	VOC emissions from service stations	Yes	
	Hydrocarbon emissions from bulk gasoline plants and new terminal loading facilities	Yes	
Louisiana	Bulk gasoline terminals	Yes	
Maine	Open burning	Yes	
	VOC emission from bulk gasoline terminals and transfer operations	Yes	
Maryland	Special wastes	Yes	
	VOC emissions from large storage tanks	Yes	
	Gasoline leaks from tank trucks and vapor control	Yes	
Massachusetts	Transportation of hazardous materials	Yes	
	Transportation of hazardous liquids	Yes	
	Motor vehicle fuel tank trucks, vapor recovery	Yes	
Michigan	Vehicle exhaust emissions	Yes	
	VOC emissions at loading and dispensing facilities	Yes	
Missouri	Petroleum liquid storage, loading and transfer	Yes	
New Jersey	Air pollution from toxic substances	Yes	
New York	Petroleum liquid storage facilities	Yes	
North Carolina	Bulk gasoline plants and terminals, gasoline service stations	Yes	
North Dakota	Performance from bulk gasoline terminals	Yes	
Ohio	VOC emissions from bulk gasoline terminals and gasoline tank trucks	Yes	
Pennsylvania	VOC emissions from bulk gasoline terminals and storage tanks during transfer operations	Yes	
Rhode Island	Oil pollution	Yes	
South Carolina	Bulk gasoline terminals and vapor collection	Yes	
Tennessee	Bulk gasoline terminals	Yes	
Texas	Reports required for gasoline	Yes	
	VOC emissions from loading and unloading facilities	Yes	
Washington, DC	Gasoline storage vessels	Yes	
	Organic compounds	Yes	
Wisconsin	VOC emissions in transfer operations	Yes	
	Performance of bulk gasoline terminals	Yes	
Virginia	Emission standards for petroleum liquid and transfer operations	Yes	

ACGIH = American Conference of Governmental Industrial Hygienists; DOT = Department of Transportation; EPA = Environmental Protection Agency; NIOSH = National Institute for Occupational Safety and Health; OAQPS = Office of Air Quality Planning and Standards; OSHA = Occupational Safety and Health Administration; PEL = Permissible Exposure Limit; STEL = Short Term Exposure Limit; TLV = Threshold Limit Value; TWA = Time-Weighted Average; VOC = Volatile Organic Compound

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc}) The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

9. GLOSSARY

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo -- Occurring within the living organism.

Lethal Concentration_(LO)(LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration₍₅₀₎(LC₅₀) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose_(LO)(LD_{LO}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose₍₅₀₎(LD₅₀) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎(LT₅₀) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

9. GLOSSARY

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1^* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu\text{g/L}$ for water, mg/kg/day for food, and $\mu\text{g/m}^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up- to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

9. GLOSSARY

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD₅₀) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

Chapter 1

Public Health Statement.

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer endpoints, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

- (1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

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- (2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the “System” column of the LSE table (see key number 18).
- (4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 “18r” data points in Figure 2-1).
- (5) Species The test species, whether animal or human, are identified in this column. Section 2.4, “Relevance to Public Health,” covers the relevance of animal data to human toxicity and Section 2.3, “Toxicokinetics,” contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to toxaphene via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.
- (7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. “Other” refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.
- (8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote “b”).
- (9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into “Less Serious” and “Serious” effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.
- (10) Reference The complete reference citation is given in chapter 8 of the profile.

- (11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.
- (12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote “b” indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

- (13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.
- (14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.
- (15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale “y” axis. Inhalation exposure is reported in mg/m³ or ppm and oral exposure is reported in mg/kg/day .
- (16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote “b” in the LSE table).
- (17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.
- (18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk-levels are derived from the EPA’s Human Health Assessment Group’s upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q₁*).
- (19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 →

TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

Key to figure ^a	Species	Exposure frequency/duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
INTERMEDIATE EXPOSURE							
2 →	5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5d/wk 6hr/d	Resp	3 ^b	10 (hyperplasia)	Nitschke et al. 1981

CHRONIC EXPOSURE							
						11	
						↓	
	Cancer						
38	Rat	18 mo 5d/wk 7hr/d				20	(CEL, multiple organs) Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d				10	(CEL, lung tumors, nasal tumors) NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d				10	(CEL, lung tumors, hemangiosarcomas) NTP 1982

12 →

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

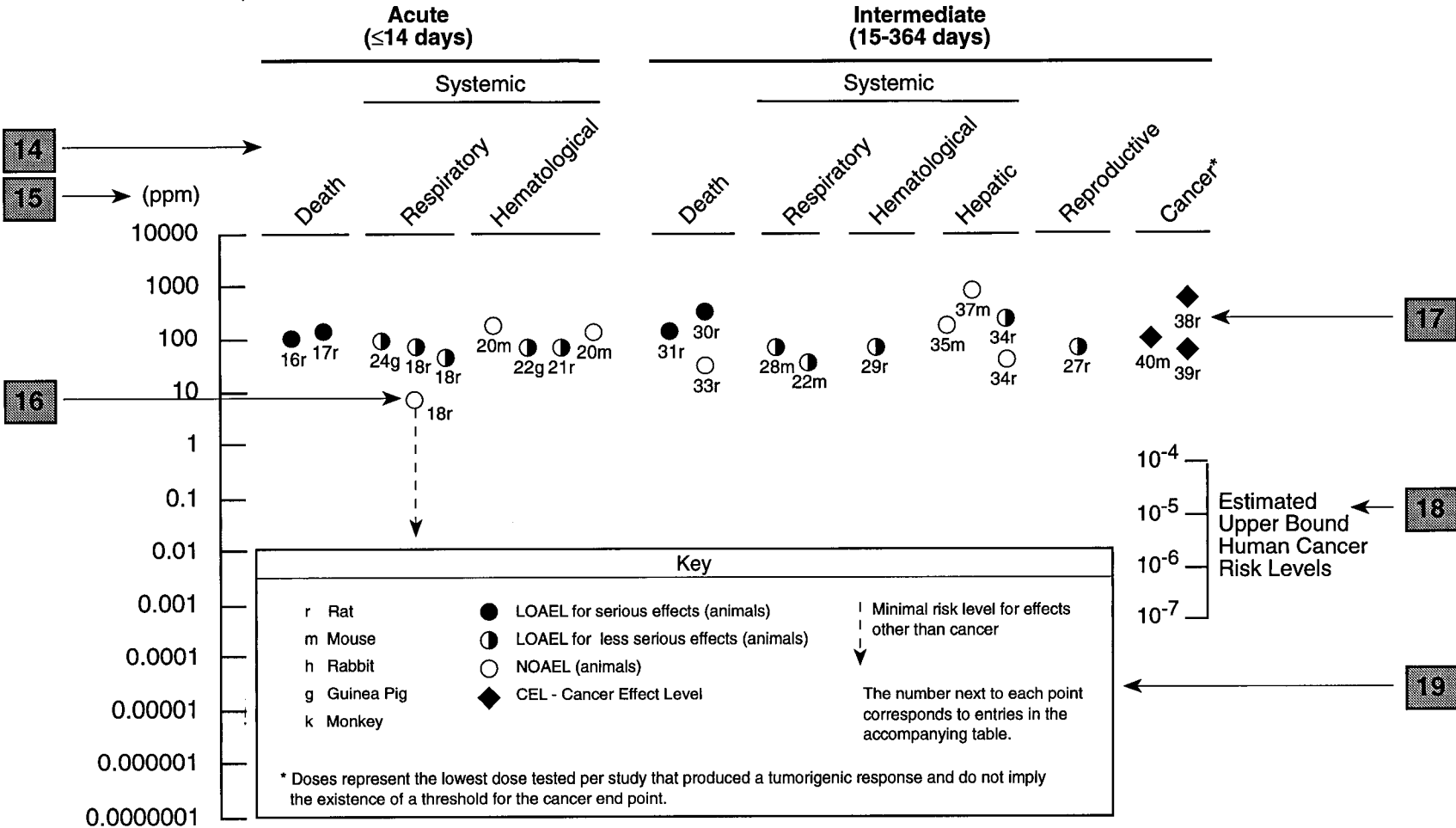
^b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

13

Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation



APPENDIX A

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions.

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers endpoints in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer endpoints (if derived) and the endpoints from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Substances," and 2.7, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
dL	Deciliter
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F ₁	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
K _d	adsorption ratio
kg	kilogram
kkg	metric ton
K _{oc}	organic carbon partition coefficient
K _{ow}	octanol-water partition coefficient

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L	liter
LC	liquid chromatography
LC _{Lo}	lethal concentration, low
LC ₅₀	lethal concentration, 50% kill
LD _{Lo}	lethal dose, low
LD ₅₀	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification

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SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram