TOXICOLOGICAL PROFILE FOR HEXACHLOROETHANE

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

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UPDATE STATEMENT

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:

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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). 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 described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is 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.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where 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 of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance 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; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may 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.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel 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 toxicological profiles are developed in response to the Super-fund 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 Super-fund). 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).

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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 end points.

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.

PEER REVIEW

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

1. Mr. Bruce Jacobs, General Physics Corporation, Edgewood, MD
2. Mr. Lyman Skory, Private Consultant, Midland, Michigan
3. Dr. Peter Van Voris, Senior Program Manager, Richland, Washington

These experts collectively have knowledge of hexachloroethane'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(1)(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 hexachloroethane and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,416 hazardous waste sites as the most serious in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. Hexachloroethane has been found in at least 45 of the sites on the NPL. However, the number of NPL sites evaluated for hexachloroethane is not known. As EPA evaluates more sites, the number of sites at which hexachloroethane is found may increase. This information is important because exposure to hexachloroethane may cause harmful health effects and because these sites are potential or actual sources of human exposure to hexachloroethane.

When a substance 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. This release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking substances containing it or by touching it.

If you are exposed to a substance such as hexachloroethane, many 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 HEXACHLOROETHANE?

Hexachloroethane is a colorless solid that gradually evaporates when it is exposed to air. This compound is also called perchloroethane, carbon hexachloride, and HCE. It is sold under the trade names Avlothane, Distokal, Distopan, and Distopin. In the United States, about half of the hexachloroethane is used by the military for smoke-producing devices. It is also sold as degassing pellets that are used to remove the air bubbles in melted aluminum. Hexachloroethane may be present as an ingredient in some fungicides, insecticides, lubricants, plastics, and cellulose. At one time, hexachloroethane was prescribed for deworming animals.

Hexachloroethane does not occur naturally in the environment. It is made by adding chlorine to tetrachloroethylene. Hexachloroethane is no longer made in the United States, but it is formed as a by-product in the production of some chemicals. For example, it is a by-product in the high temperature synthesis of tetrachloroethylene from carbon tetrachloride. Some hexachloroethane can be formed by incinerators when materials containing chlorinated hydrocarbons are burned.

Hexachloroethane itself does not easily catch fire. Some hexachloroethane can also be formed when chlorine reacts with carbon compounds in drinking water.
Hexachloroethane vapors smell like camphor. You can begin to smell hexachloroethane in air when there are 150 parts present in a billion parts of air (ppb). You can smell it in water at 10 ppb. Neither a description of the taste nor the amount of hexachloroethane that gives a taste to water were found.
For more information on the properties and uses of hexachloroethane, see Chapters 3,4, and 5.

1.2 WHAT HAPPENS TO HEXACHLOROETHANE WHEN IT ENTERS THE ENVIRONMENT?

Hexachloroethane is released to the air during military operations and training exercises when smoke-producing devices containing it are used. In a smoke pot or grenade, most of it is used up

1. PUBLIC HEALTH STATEMENT

by the smoke-producing reaction. Only small amounts (5% or less) remain after the smoke has formed. However, these small amounts can collect in the atmosphere and in the soil. At one military training site, about 14,700 pounds of hexachloroethane were released to the air over a 2-year period.

Hexachloroethane also enters the environment as part of the waste from companies that make or use it. Vapors can be released to the air during production, use, or transport. Solid wastes containing it are buried in landfills or burned. In landfills, it can dissolve in underground water because it does not bind strongly to soil. Once dissolved, it can reach rivers, lakes, streams, or well water.

Hexachloroethane in the air does not break down to other compounds. It gradually escapes into the upper atmosphere. Some hexachloroethane that is in lakes or streams and surface soils will evaporate into the air. Some will be broken down by microscopic organisms. Microbes can break down hexachloroethane more easily without oxygen than with oxygen. That is why hexachloroethane will break down more quickly when it is buried in the soil or trapped in underground water than when it is near the surface. In one study, it took only 4 days for 99% of the hexachloroethane in soil to break down when oxygen was not present. It took 4 weeks when oxygen was present.

Hexachloroethane does not appear to collect in plants or animals used for food. It has a slight tendency to build up in fish, but the fish break it down quickly, so the amount found in fish from polluted waters is very low. Rainbow trout from Lake Ontario had only 0.03 parts hexachloroethane per trillion (ppt) parts of fish.

More information on what happens to hexachloroethane in the environment is in Chapters 4 and 5.

1. PUBLIC HEALTH STATEMENT

1.3 HOW MIGHT I BE EXPOSED TO HEXACHLOROETHANE?

You can be exposed to hexachloroethane from the air. Background levels in air range from 5 to 7 ppt. Larger amounts may be found near military installations where smoke pots and grenades that contain hexachloroethane are used during training. When a smoke pot or grenade is used, the heat will cause other chemicals to be formed, including tetrachloroethylene, carbon tetrachloride, phosgene, and hexachlorobenzene. These chemicals can also be toxic. Higher than average amounts can occur near aluminum smelters that use hexachloroethane as a degassing agent. Incinerators that burn industrial wastes containing chlorine can release hexachloroethane to the air.

If you live near a hazardous waste site, you might be exposed to hexachloroethane by breathing or by drinking contaminated water. Private wells within one mile of a hazardous waste site contained 4.6 ppb hexachloroethane. Children who play in soil near a waste site that contains hexachloroethane could be exposed if they put soil or soiled fingers into their mouths.

You are not likely to be exposed to hexachloroethane from your food. However, you might be exposed if you use insecticides, fungicides, or plastics that contain this chemical. You may also be exposed to small amounts of this chemical from your drinking water if chlorine is used to kill germs. Hexachloroethane has occasionally been reported in drinking water at concentrations of 0.03-4.3 ppb in some locations in the United States.

If you work in an industry that uses hexachloroethane, such as aluminum smelting, or a chemical plant, you could be exposed by breathing it or touching it. About 8,500 people in the United States are exposed to hexachloroethane at work.

People who work with smoke-producing devices that contain hexachloroethane are exposed to it in the smoke. They can contact it through smoke particles on plants and in the soil.

More information on how you can be exposed to hexachloroethane is in Chapter 5.

1. PUBLIC HEALTH STATEMENT

1.4 HOW CAN HEXACHLOROETHANE ENTER AND LEAVE MY BODY?

Hexachloroethane can enter your body through your lungs if you breathe its vapors. Of the amount that enters your lungs, only a small fraction of the hexachloroethane will enter your bloodstream and ultimately your body tissues. It can enter your body if you eat or drink something contaminated with it. Based on studies in animals, about half of the hexachloroethane you eat will get into your bloodstream. Very little will enter your body if you get it on your skin.

The hexachloroethane that enters your bloodstream will go to your liver where it is turned into other compounds. Some of these compounds are harmful and will affect your health in almost the same way hexachloroethane does. If you are exposed to carbon tetrachloride, your liver can make hexachloroethane from it.

When hexachloroethane gets into your body, some is temporarily stored in your body fat. Most of it leaves your body in 1 or 2 days in the air you breathe out, in your urine, and in your feces.

More information on how hexachloroethane enters and leaves your body is in Chapter 2.

1.5 HOW CAN HEXACHLOROETHANE AFFECT MY HEALTH?

Mild skin irritation has been reported by workers at a munitions factory who were exposed to low levels of hexachloroethane. The workers were wearing protective clothing that greatly reduced exposure. No other information is available concerning health effects in people exposed to hexachloroethane. However, results of animal studies can be used to show how it can affect your health. Based on the animal data, hexachloroethane in the air can irritate your nose and lungs and cause some buildup of mucus in your nose, much like an allergy. It can also irritate your eyes and make them tear.

If you are in an area that has a lot of hexachloroethane vapor, your facial muscles may twitch or you may have difficulty moving. These effects have been observed in animals during exposure

at levels far greater than those found in industrial use of hexachloroethane or those which would be expected in areas near a hazardous waste site.

Hexachloroethane is not a highly toxic substance. If you are exposed to a large amount for a long time, some of your liver cells could be destroyed and fat could build up in your liver. There is also a slight chance that your kidneys could be damaged.

No results from animal studies suggest that hexachloroethane would make it hard for you to become pregnant or that it would hurt your baby while you are pregnant. However, animal studies that have looked at the effects of hexachloroethane during pregnancy are limited.

Liver tumors developed in mice that were orally exposed to hexachloroethane for their whole lifetime. Tumors of this kind are common in mice. Hexachloroethane will not necessarily have the same effect on people. Male rats that were exposed to hexachloroethane for their lifetime developed kidney tumors. This type of tumor is not found in people, so it is unlikely that exposure to hexachloroethane would cause you to develop cancer of the kidney. The Department of Health and Human Services has determined that hexachloroethane may reasonably be anticipated to be a carcinogen (can cause cancer). The International Agency for Research on Cancer (IARC) has determined that hexachloroethane is not classifiable as to its carcinogenicity in people. EPA has determined that hexachloroethane is a possible human carcinogen.

More information on the health effects from hexachloroethane exposure is in Chapter 2.

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

Samples of your blood, urine, or feces can be tested to see if you were exposed to hexachloroethane. The tests are not routinely available at most doctors' offices, but your doctor can collect blood, urine, or fecal samples and send them to a special laboratory for testing. These tests are useful only if you were exposed 24-48 hours before you saw the doctor. Your body changes hexachloroethane into the same compounds that it makes from other chemicals like

tetrachloroethylene or pentachloroethane. Your body can also make hexachloroethane from carbon tetrachloride. Therefore, if a laboratory finds hexachloroethane in your body blood or excretions, your doctor will ask you if you were exposed to carbon tetrachloride. More information on medical tests that can be used to determine if you have been exposed to hexachloroethane is in Chapters 2 and 6.

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

The federal government is concerned about the amount of hexachloroethane that you are exposed to in the environment. The government has established standards and guidelines to prevent you from being overexposed. The Occupational Safety and Health Administration (OSHA) has set a limit of 1 part per million (ppm) for the hexachloroethane in workplace air over an &hour workday. The National Institute for Occupational Safety and Health (NIOSH) considers hexachloroethane as a potential occupational carcinogen (can cause cancer) and recommends 1 ppm in air as a tolerance value.

The EPA recommends that children not drink water with more than 5 ppm hexachloroethane for more than 10 days or more than 100 ppb for any longer than 7 years. Adults should not drink water with more than 450 ppb any longer than 7 years. EPA suggests that water consumed over a lifetime contain no more than 1 ppb hexachloroethane.

Industrial releases of more than 100 pounds of hexachloroethane into the environment must be reported to EPA.

More information on government regulations for hexachloroethane is in Chapter 7.

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
(404) 639-6000

This agency can also provide you with information on the location of occupational and environmental health clinics. These clinics specialize in the recognition, evaluation, and treatment of illness 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 hexachloroethane. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observedadverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be

2. HEALTH EFFECTS

important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of hexachloroethane are indicated in Table 2-2 and Figure 2-2. Because cancer effects could occur at lower exposure levels, Figure 2-2 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 ($10m^{-4}$ to 10^{-7}), as developed by EPA.

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

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

2. HEALTH EFFECTS

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

2.2.1 Inhalation Exposure

Hexachloroethane is a solid that sublimes at ambient air temperatures. At 20°C the saturated vapor concentration is 670-700 ppm (Weeks et al. 1979); thus, there is a limitation on the vapor concentration that can be used in studies using the inhalation route of exposure. In circumstances where the saturation threshold is exceeded, microcrystalline hexachloroethane forms in the atmosphere and is inhaled by the exposed animals along with the volatilized hexachloroethane.

2.2.1 .l Death

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

Rats were exposed to vapor concentrations of either 260 or 5,900 ppm hexachloroethane for 8 hours (Weeks et al. 1979). The 5,900 ppm vapor concentration was generated at 50°C and crystallized as it entered the exposure chamber. At the higher concentration the exposed animals showed signs of distress (staggering gait) during exposure, and 2 of 6 were dead at the end of 8 hours. No animals died at the lower exposure concentration.

Following 6 weeks of inhalation exposure to 15-260 ppm, no deaths in quail were reported; however, 2 of 50 rats, 4 of 10 guinea pigs, and 1 of 4 dogs died at the 260 ppm concentration (Weeks et al. 1979). Based on clinical signs, the dogs seemed to be particularly sensitive to hexachloroethane exposure. The animals developed tremors and ataxia and closed their eyes. The one dog that died experienced convulsions before death. The rats and guinea pigs that succumbed to exposure died during weeks 4 or 5 and, thus, appear to be less sensitive. The quail were the most resistant to death following hexachloroethane exposure.

All identified LOAEL values for lethality in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1. These values indicate that hexachloroethane is lethal to animals exposed intermittently to 260 ppm for 6 weeks; however, no deaths occurred in animals acutely exposed for 8 hours to the same concentration. Concentrations of 48 ppm and lower were not lethal in rats, guinea pigs, dogs, or quail.

TABLE 2-1. Levels of Significant Exposure to Hexachloroethane - Inhalation

Key [a] to figure	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)		LOAEL (effect) Less serious (ppm)		LOAEL (effect) Serious (ppm)	Reference
	ACUTE EXPOSURE								
	Death								
1	Rat (Sprague-Dawley)	8 hr						5900 M (2/6 rats died)	Weeks et al. 1979
	Systemic								
2	Rat (Sprague-Dawley)	8 hr	Resp	260	M	5900	M (interstitial pneumonitis in 2/4 survivors)		Weeks et al. 1979
			Cardio	5900	M				
			Gastro	5900	M				
			Musc/skel	5900	M				
			Hepatic	5900	M				
			Renal	5900	M				
			Endocr	5900	M				
			Derm	5900	M				
			Bd Wt	260	M	5900	M (reduced body weight gain, quantitative data not provided)		
	Neurological								
3	Rat (Sprague-Dawley)	6 hr		260	M			5900 M (staggered gait in 1/6 rats)	Weeks et al. 1979
4	Rat (Sprague-Dawley)	11 d Gd 6-16 6hr/d		48 [b]	F			260 F (tremors)	Weeks et al. 1979

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

Key[a] to figure	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
	Reproductive						
5	Rat (Sprague-Dawley)	11 d Gd 6-16 6hr/d		260 F			Weeks et al. 1979
	Developmental						
6	Rat (Sprague-Dawley)	11 d Gd 6-16 6hr/d		260			Weeks et al. 1979
	INTERMEDIATE EXPOSURE						
	Death						
7	Gn pig (Hartley)	6 wk 5d/wk 6hr/d				260 M (4/10 guinea pigs died)	Weeks et al. 1979
8	Dog (Beagle)	6 wk 5d/wk 6hr/d				260 M (1/4 dogs died)	Weeks et al. 1979

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

Key [a] to figure	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
Systemic							
9	Rat (Sprague-Dawley)	6 wk 5d/wk 6hr/d	Resp	48	260 (reduced resistance to endemic mycoplasia infection; mucopurulent exudate in the nasal cavities; lymphoid hyperplasia in the trachea and pneumonitis)		Weeks et al. 1979
			Cardio	260			
			Gastro	260			
			Musc/skel	260			
			Hepatic	260			
			Renal	260			
			Endocr	260			
			Derm	260			
			Ocular	48	260 (irritation)		
			Bd Wt	48	260 M (reduced body weight, quantitative data not provided)		
10	Rat (Sprague-Dawley)	6 wk 5d/wk 6hr/d	Resp	260 M			Weeks et al. 1979
			Hepatic	260 M			
			Renal	260 M			
			Bd Wt	48 M	260 M (mean body weights decreased 11% in older animals)		

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

Key [a] to figure	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)		LOAEL (effect) Less serious (ppm)		LOAEL (effect) Serious (ppm)	Reference
11	Gn pig (Hartley)	6 wk 5d/wk 6hr/d	Resp	260	M				Weeks et al. 1979
			Cardio	260	M				
			Gastro	260	M				
			Musc/skel	260	M				
			Hepatic	260	M				
			Renal	260	M				
			Derm	260	M				
			Ocular	260	M				
			Bd Wt	48	M	260	M	(reduced body weight gain, quantitative data not provided)	
12	Dog (Beagle)	6 wk 5d/wk 6hr/d	Resp	260	M				Weeks et al. 1979
			Cardio	260	M				
			Hemato	260	M				
			Musc/skel	260	M				
			Hepatic	260	M				
			Renal	260	M				
			Endocr	260	M				
			Derm	260	M				
			Ocular	48	M	260	M	(irritation)	
			Bd Wt	260	M				
Neurological									
13	Rat (Sprague-Dawley)	6 wk 5d/wk 6hr/d		260	M				Weeks et al. 1979

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

Key[a] to figure	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
14	Rat (Sprague-Dawley)	6 wk 5d/wk 6hr/d		48 c		260 (tremors)	Weeks et al. 1979
15	Dog (Beagle)	6 wk 5d/wk 6hr/d		48 M		260 M (tremors; ataxia; fasciculations; severe head bobbing)	Weeks et al. 1979

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

[b]Used to derive an acute-duration inhalation minimal risk level (MRL) of 6 ppm. The NOAEL was converted to a Human Equivalent Concentration (HEC) of 181 ppm by multiplying by (0.22 m^3/day/0.204 kg), the reference value for Sprague-Dawley rats (EPA 1988a), and dividing by (20 m^3/day/70kg), the reference value for humans (EPA 1988a). The HEC was divided by an uncertainty factor of 30 (3 to extrapolate from animals to humans, and 10 for human variability).

[c]Used to derive an intermediate-duration inhalation MRL of 6 ppm. The NOAEL was converted to a Human Equivalent Concentration (HEC) of 174 ppm by multiplying by (0.245 m^3/day/0.236 kg), the reference values for Sprague-Dawley rats (EPA 1988a), and divided by (20 m^3/day/70kg), the reference values for humans (EPA 1988a). The HEC was divided by an uncertainty factor of 30 (3 to extrapolate from animals to humans, and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Derm = dermal; Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestation day(s); Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

Figure 2-1. Levels of Significant Exposure to Hexachlorethane - Inhalation

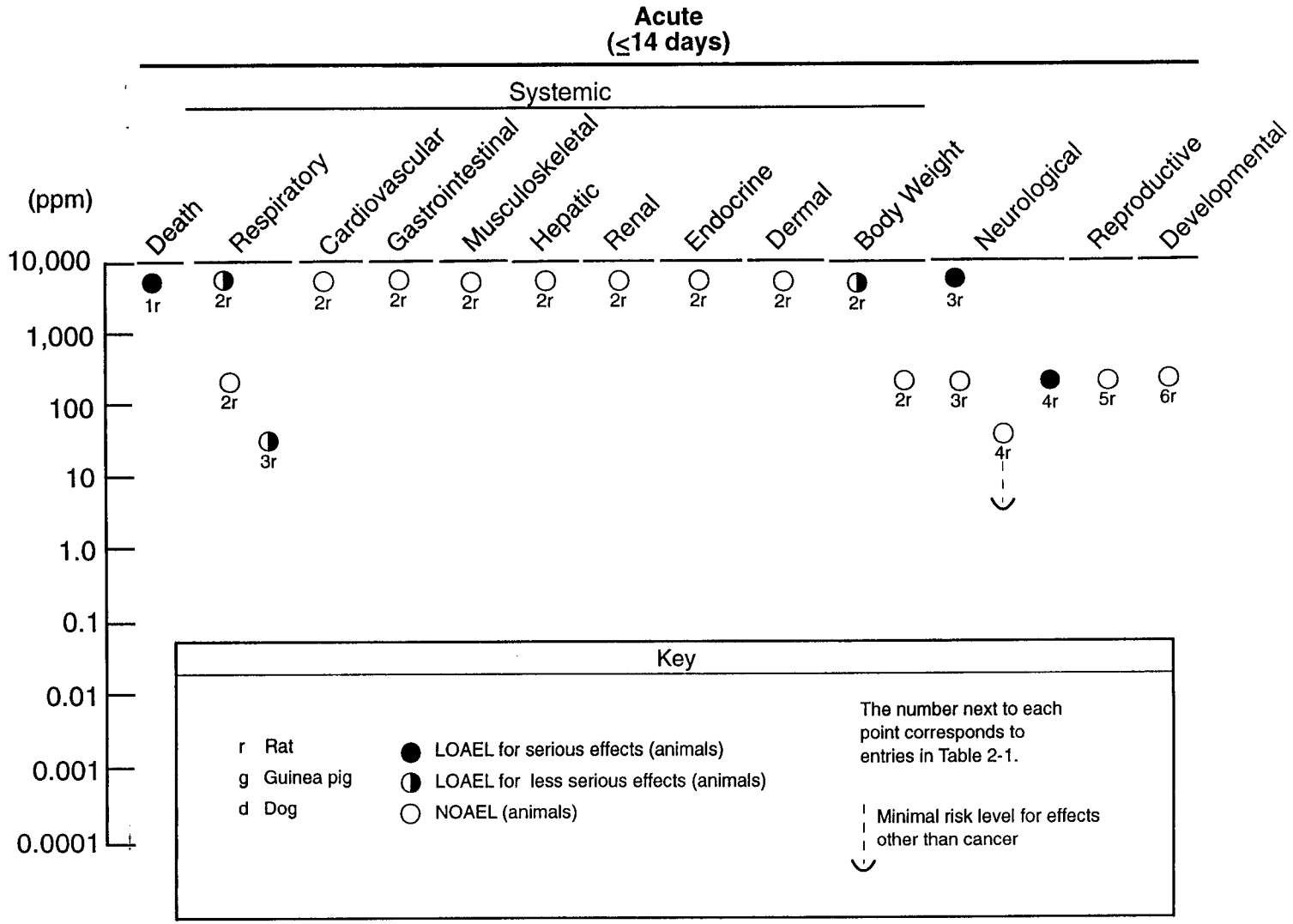
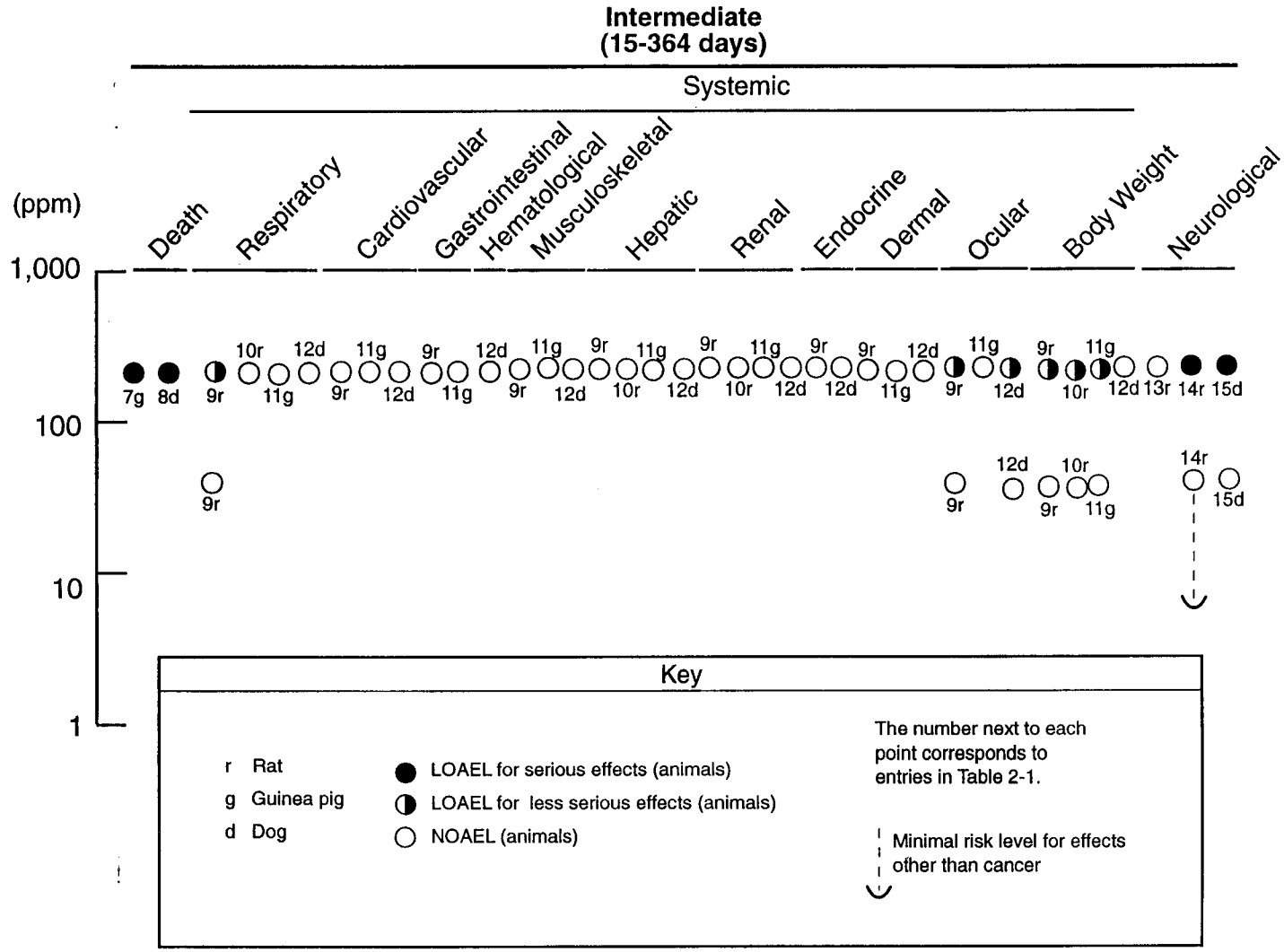


Figure 2-1. Levels of Significant Exposure to Hexachloroethane - Inhalation (continued)



2. HEALTH EFFECTS

2.2.1.2 Systemic Effects

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

Respiratory Effects. Pulmonary function tests (vital capacity, forced expiratory volume at 1 second) were in the normal range in 11 workers occupationally exposed to hexachloroethane at 0.5-2.1 ppm while wearing protective equipment including compressed-air-fed visors or full-facepiece masks with combination filters (Selden et al. 1994). The testing was completed 5 weeks after production at a smoke munitions plant resumed following a 5-week break. Plasma hexachloroethane levels were 0.08 ± 0.14 μg/L before production resumed and 7.3 ±6.04 μg/L 5 weeks later indicating that despite protective equipment, low-level exposure occurred (Selden et al 1993). Mild skin and mucous membrane irritation were reported in the exposed group, suggesting that exposure may have been through either the inhalation or dermal routes of exposure.

Acute exposure of rats to 5,900 ppm hexachloroethane for 8 hours caused interstitial pulmonary pneumonitis (Weeks et al. 1979). At this exposure concentration there were hexachloroethane particles present in the exposure chamber that were inhaled and probably contributed to the lung irritation. Changes in lung histopathology were noted when the animals were sacrificed after a 14-day recovery period. There were no changes in relative lung weights or tissue histopathology in animals that were exposed to 260 ppm for the same time period. When pregnant female rats were exposed to 0, 15,48, or 260 ppm hexachloroethane on gestation days 6-16, 85% of the animals in the 48-ppm dose group displayed nasal exudate, and all animals in the 260-ppm dose group were affected. There was an endemic mycoplasma infection in the colony of rats used in the Weeks et al. (1979) study. Therefore, it is not clear if the increase in nasal exudate observed at 48 ppm in the teratology study, but not at 48 ppm in the 6-week study (discussed below), was truly related to exposure.

In rats exposed to 260 ppm hexachloroethane for 6 weeks, there was a significant decrease in oxygen consumption as compared to the controls (Weeks et al. 1979). Oxygen consumption was determined by measuring carbon dioxide exhaled by rats placed in a water-sealed chamber for 15 minutes. The authors hypothesized that the decrease in oxygen consumption could have been a normal response to inhalation of a respiratory tract irritant. There were no significant changes in lung weights, but there was an increase in

mycoplasma lesions of the nasal turbinates, trachea, and lungs; lymphoid hyperplasia of the trachea; and pneumonitis of the bronchi when the animals were sacrificed after the 6-week exposure period. These changes were not seen in the animals exposed to 15 or 48 ppm or in rats exposed to 260 ppm and sacrificed after a 12-week recovery period. The authors hypothesized that the respiratory tract lesions were the result of hexachloroethane potentiation of an endemic mycoplasma infection rather than systemic effects from inhalation exposure to hexachloroethane. The infection could be the result of lowered host resistance due to either compromised immune defenses or a weakened mucosal barrier along the respiratory epithelium.

In older rats (12-14 weeks), there was a significant increase in relative lung weights as compared to controls following 6 weeks of exposure to 260 ppm hexachloroethane. Oxygen consumption was not measured in these animals, and it is not clear if the tissues were examined histologically (Weeks et al. 1979).

In dogs, there were no significant changes in pulmonary function with exposure to 15-260 ppm hexachloroethane for 6 weeks (Weeks et al. 1979). Intrapleural pressure, transpulmonary pressure, air flow, and tidal volume were measured to obtain scores for compliance and resistance. When the animals were sacrificed at either 6 weeks or after a 12-week recovery period, there were no histopathological changes observed in the lungs. There were also no apparent effects on the respiratory system in guinea pigs from exposure to 15-260 ppm hexachloroethane. Exposure of quail to 260 ppm was associated with increased mucus in the nasal turbinates in 2 of the 10 animals, but this increased mucus did not appear to be associated with a respiratory infection. These changes were considered to be the direct effect of hexachloroethane on the epithelium of the nasal cavity and are discussed in Section 2.2.3.2.

Exposure to hexachloroethane vapors can cause irritation to the respiratory system. Acute exposure to 260 ppm hexachloroethane had no apparent effect on the lungs and air passages in rats, but acute exposure to a concentration where particulate hexachloroethane was present in the atmosphere caused lung irritation (Weeks et al. 1979). .On the other hand, intermediate-duration exposure to 260 ppm hexachloroethane appeared to cause some irritation of the respiratory epithelium, which may have increased susceptibility to respiratory infection. When exposure ceased, the animals recovered, so there were no histopathological indications of tissue damage after a 12week recovery period. Lesions of the nasal passages, trachea, and bronchi; increased mycoplasma infections; mucus in the nasal cavities; and decreased oxygen

consumption were indicators of respiratory tract irritation from repeated episodes of hexachloroethane exposure.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after inhalation exposure to hexachloroethane.

There were no histopathological changes in the heart for rats, guinea pigs, dogs, or quail that were exposed to concentrations of 0, 260, or 5,900 ppm hexachloroethane for 8 hours or to 0, 1548, or 260 ppm hexachloroethane 6 hours/day, 5 days/week for 6 weeks (Weeks et al. 1979).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to hexachloroethane.

There were no histopathological changes in the stomach, small intestines, or large intestines for rats, guinea pigs, dogs, or quail that were exposed to concentrations of 0,260, or 5,900 ppm hexachloroethane for 8 hours or to 0, 15,48, or 260 ppm hexachloroethane 6 hours/day, 5 days/week for 6 weeks (Weeks et al. 1979).

Hematological Effects. Routine blood parameters (hemoglobin, erythrocyte, leukocyte and thrombocyte levels) measured in 11 hexachloroethane workers did not differ from those of the controls (Selden et al. 1994). Plasma hexachloroethane levels in these workers, who wore protective equipment, were 7.3 ± 6.04 μgL at the time of the hematological analysis and 0.08± 0.14 μg/L before production resumed (Selden et al. 1993). Mild skin and mucous membrane irritation were reported in the exposed group, suggesting that exposure may have been through either the inhalation or dermal routes of exposure.

There were no effects on the red blood cell counts of dogs exposed to 0, 15,48, or 260 ppm hexachloroethane for 6 weeks (Weeks et al. 1979). Although other hematological parameters were apparently determined, the red cell count was the only parameter that was specified. Accordingly, it is not possible to speculate whether inhalation exposure to hexachloroethane has any effect on other hematological parameters.

2. HEALTH EFFECTS

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

There were no treatment-related gross or histopathological lesions of the skeletal muscle or bone in rats, guinea pigs, dogs, or quail exposed to 0, 15,48, or 260 ppm hexachloroethane 6 hours/day, 5 days/week for 6 weeks (Weeks et al. 1979).

Hepatic Effects. Liver function tests (serum bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase) completed in 11 hexachloroethane workers were within the normal range (Selden et al. 1994). Plasma hexachloroethane levels in these workers, who wore protective equipment, were 7.3 ±6.04 μg/L at the time of the tests (Selden et al. 1993). Mild skin and mucous membrane irritation were reported in the exposed group, suggesting that exposure may have been through either the inhalation or dermal routes of exposure.

A single 8-hour exposure of rats to 260 ppm hexachloroethane had no effect on relative liver weight or tissue histopathology (Weeks et al. 1979). A single S-hour exposure to 5,900 ppm did not cause histopathological changes. Organ weights were not determined for the higher exposure concentration.

The relative liver weight was significantly increased (p value not given) in guinea pigs and rats, but not dogs or quail, that were exposed to 260 ppm 6 hours/day, 5 days/week for 6 weeks (Weeks et al. 1979). Since the increase in liver weight was not accompanied by any histological abnormalities, it is classified as a NOAEL rather than a LOAEL in Table 2-l and Figure 2-l. There were no changes in liver weights or histopathology in any species exposed to concentrations of 15 or 48 ppm for 6 weeks.

Renal Effects. Renal function tests (serum creatinine and urate, urinary hemoglobin, protein and glucose) completed in 11 hexachloroethane workers were within the normal range (Selden et al. 1994). Plasma hexachloroethane levels in these workers, who wore protective equipment, were 7.3 ± 6.04 μg/L at the time of the tests (Selden et al. 1993). Mild skin and mucous membrane irritation were reported in the exposed group, suggesting that exposure may have been through either the inhalation or dermal routes of exposure.

2. HEALTH EFFECTS

A single exposure of rats to 260 ppm hexachloroethane had no effect on relative kidney weight or tissue histopathology (Weeks et al. 1979). A single exposure to 5,900 ppm did not cause histopathological changes. Organ weights were not determined for the higher exposure concentration.

The relative kidney weight was significantly increased (p value not stated) in male rats, but not female rats, guinea pigs, dogs, or quail, that were exposed to 260 ppm 6 hours/day, 5 days/week for 6 weeks (Weeks et al. 1979). Since the increase in kidney weight was not accompanied by any histological abnormalities, it is classified as a NOAEL rather than a LOAEL in Table 2-1 and Figure 2-l. There were no changes in kidney weights or histopathology in any species exposed to 15 or 48 ppm hexachloroethane for 6 weeks.

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

There were no histopathological changes in the pancreas or adrenal glands of rats exposed to concentrations of 0,260, or 5,900 ppm hexachloroethane for 8 hours, or in the pancreas or adrenal glands of rats, guinea pigs, dogs, or quail exposed to 0, 15,48, or 260 ppm hexachloroethane 6 hours/day, 5 days/week for 6 weeks (Weeks et al. 1979).

Dermal Effects. Hexachloroethane exposed workers reported a slightly higher prevalence of dry skin and dry mucous membranes as well as itching and other skin problems than the unexposed controls (Selden et al. 1994). Clinical examinations of the 11 exposed workers did not reveal signs of abnormal dermatological or mucous membrane status. Plasma hexachloroethane levels in these workers, who wore protective equipment, were 7.3 ± 6.04 μg/L at the time of the examinations (Selden et al. 1993). The investigators indicate that the dermal effects may also have been a result of a local trauma effect of the protective equipment.

Ocular Effects; No studies were located regarding ocular effects in humans after inhalatioin exposure to hexachloroethane.

Dogs that were exposed to 260 ppm hexachloroethane for 6 hours per day, 5 days per week, kept their eyes closed during each exposure (Weeks et al. 1979). Since this effect occurred throughout the 6-week study, it can be regarded as an acute effect that was most likely the result of vapor contact with the eye. In

rats, a red exudate appeared about the eyes starting at week 4. This may have been a systemic effect. There were no reported effects on the eyes of guinea pigs or quail during 6 weeks of exposure to hexachloroethane.

Body Weight Effects. Rats exposed to a concentration of 5,900 ppm hexachloroethane for 8 hours had a decreased weight gain over the 14-day, postexposure observation period when compared to controls (Weeks et al. 1979). There were no differences in the weight gain for animals exposed to 260 ppm under the same conditions.

Guinea pigs and male rats had decreased weight gains starting at week 2 or 3 of an intermittent 6-week exposure to 260 ppm hexachloroethane, but there were no effects on dogs or quail (Weeks et al. 1979). Intermittent exposure to 15 or 48 ppm hexachloroethane for 6 weeks had no effect on weight gain in rats, dogs, guinea pigs, or quail.

2.2.1.3 Immunological and Lymphoreticular Effects

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

There were no treatment-related gross or histopathological lesions of the thymus and spleen and no changes in spleen weight in rats that were exposed to 260 or 5,900 ppm hexachloroethane for 8 hours, nor were there any effects on thymus and spleen histopathology in rats, guinea pigs, dogs, and quail that were exposed to 260 ppm 6 hours/day, 5 days/week for 6 weeks (Weeks et al. 1979). The relative spleen weight was significantly higher (p value not stated) than that for the controls in young male rats but was not affected in older male rats or any of the other species evaluated. No effects were seen in the 15 and 48 ppm dose groups.

There was an increased incidence of a mycoplasma respiratory tract infection in rats exposed to 260 ppm hexachloroethane for 6 weeks but not in rats exposed to lower doses or in other species. This could indicate compromised immune function or a weakened mucosal barrier along the respiratory epitbelium. There were no studies identified that evaluated a wide range of immunological parameters. Therefore, there are no reliable LOAELs or NOAELs for this end point. Increases in spleen weights are not classified as LOAELs since they were not accompanied by histopathological changes.

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans after inhalation exposure to hexachloroethane.

Acute 8-hour exposures to 5,900 ppm, but not 260 ppm, resulted in a staggering gait in one of six rats (Weeks et al. 1979). Tremors were also noted in pregnant rats exposed 6 hours per day to 260 ppm starting on the 6th day of an 1 l-day exposure period but not in animals exposed to 15 or 48 ppm (Weeks et al. 1979). Based on the NOAEL for neurological effects, an acute inhalation MRL of 6 ppm was calculated, as described in the footnote in Table 2-l.

When male rats were exposed to concentrations of 0, 15,48, or 260 ppm hexachloroethane 6 hours/day, 5 days/week for 6 weeks, foot shock avoidance behavior and spontaneous motor activity were not different from controls when measured at 1 day, 3 weeks, or 6 weeks (Weeks et al. 1979). However, a group of male and female rats exposed to 260 ppm experienced tremors beginning at 4 weeks and persisting for the remainder of the 6-week exposure period. Recovery was evident during the 12 week post-exposure period (Weeks et al. 1978). Tremors were not observed in rats exposed at 48 ppm. Based on the intermediate-duration NOAEL of 48 ppm for neurological effects, an intermediate inhalation MRL of 6 ppm was calculated, as described in the footnote in Table 2-l.

Dogs were apparently quite sensitive to neurological effects during hexachloroethane exposure (Weeks et al. 1979). The animals displayed tremors, ataxia, head bobbing, and fasciculation of the facial muscles with a 260 ppm exposure. Symptoms disappeared in the interval between exposures but returned intermittently over the 6-week exposure period. There were no differences in serum cholinesterase activity between control and exposed animals. Apparently, the levels of the neurotransmitter acetylcholine were not affected by hexachloroethane. There were no neurological responses in guinea pigs or quail with a 260-ppm exposure; and none of the species evaluated showed any overt neurological responses with an intermittent 6-week exposure at 15 or 48 ppm.

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2-l. Acute exposures

to hexachloroethane appear to cause neurological impairment during exposure of rats and dogs, but symptoms do not persist during the intervals between exposures or after exposure ceases.

2.2.1.5 Reproductive Effects

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

Hexachloroethane was maternally toxic at concentrations of 48 and 260 ppm in rats exposed 6 hours/day on gestation days 6-16, based on significantly decreased (p value not stated) maternal body weight gain, but it was not embryotoxic or fetotoxic (Weeks et al. 1979). There were no treatment-related gross or histopathological lesions of the testes in rats, dogs, guinea pigs, and quail that were exposed to concentrations of hexachloroethane up to 260 ppm 6 hours/day, 5 days/week for 6 weeks. However, relative testes weights were increased in rats when compared to the controls. No other reproductive organs were evaluated (Weeks et al. 1979). The highest NOAEL from each reliable study for reproductive effects in each species and duration category is recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.6 Developmental Effects

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

In animals, hexachloroethane did not cause skeletal or soft tissue abnormalities in offspring of rats that were exposed to vapors of hexachloroethane (1.5-260 ppm) 6 hours/day during gestation days 6-16 (Weeks et al. 1979). The highest NOAEL value from this study for developmental effects in rats is recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to hexachloroethane.

Genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

One case study was identified where a man who had been occupationally exposed to hexachloroethane was treated for a liver tumor (Selden et al. 1989). Exposure had occurred over a period of 6 years as a result of the presence of hexachloroethane in a degassing agent used during aluminum smelting. However, the hexachloroethane reacted at the 700°C use-temperature, releasing a gas that was 96% hexachlorobenzene with small amounts of other chlorinated compounds. Because there was occupational exposure to a mixture of chlorinated compounds rather than just hexachloroethane, it is highly unlikely that the tumor was the result of hexachloroethane exposure alone. Occupational exposure to mineral oil mists for 20 years was also part of the subject's employment history.

No studies were located regarding cancer incidence in animals after inhalation exposure to hexachloroethane. EPA has derived an inhalation unit risk (cancer slope factor) of 1.4x10-' $(mg/kg/day)^{-1}$ for hexachloroethane (IRIS 1995). This inhalation unit risk was calculated using data from oral studies (see Section 2.2.2.8) and Figure 2-2.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to hexachloroethane.

When hexachloroethane was administered to rats by gavage with corn oil as the solvent, the LD_{50} value was 5,160 mg/kg for males and 4,460 mg/kg for females (Weeks et al. 1979). Kinkead and Wolfe (1992) reported an LD_{50} value of 4,489 mg/kg for both male and female rats treated with hexachloroethane in corn oil. When hexachloroethane was dissolved in aqueous methyl cellulose solution, the LD_{50} was 7,690 mg/kg for male and 7,080 mg/kg for female rats (Weeks et al. 1979). The lower LD_{50} for the corn oil solvent indicates that the absorption from this hydrophobic medium is greater than that from a hydrophilic medium such as methyl cellulose solution. The LD_{50} of 4,970 mg/kg for male guinea pigs given hexachloroethane in corn oil is similar to that for rats (Weeks et al. 1979). According to the classification system of Hodge and Sterner (1949), these LD_{50} values indicate that hexachloroethane is slightly toxic by acute oral exposure.

2. HEALTH EFFECTS

With repeated administration of hexachloroethane, a dose of 750 mg/kg/day in corn oil was lethal to 1 of 5 male rats and 2 of 5 females within 15 days (NTP 1989). The earliest death occurred in a male rat on day 5. All animals died between day 2 and day 8 with doses of 1,500 and 3,000 mg/kg/day.

With 6-week hexachloroethane exposures, there were some deaths among rats given a dose of 1,000 mg/kg/day in corn oil, and all animals died with a dose of 1,780 mg/kg/day (NTP 1977). The number of animals that died at the 1,000 mg/kg/day dose level was not specified and the time of death was not given for any of the doses. There were no deaths in animals given doses of 562 mg/kg/day or lower. Mice were more resistant to hexachloroethane exposure than rats because all of the mice survived doses of 1,000 mg/kg/day in corn oil for 6 weeks (NTP 1977). Some male mice died with a 1,780 mg/kg/day dose, but the exact number was not specified.

With a 13-week exposure duration, doses of 750 mg/kg/day in corn oil were lethal to some male and female rats (NTP 1989). The earliest death occurred among the males at 7 weeks. Between 7 weeks and 13 weeks (the end of the exposure period), 5 of 10 males died; during week 13, 2 of 10 females died.

Chronic (2-year) exposure of male rats to 20 mg/kg/day hexachloroethane and female rats to 160 mg/kg/day had no effect on survival (NTP 1989), but the longevity of rats exposed to doses of 212 and 423 mg/kg/day for 66 weeks was decreased as compared to controls (NTP 1977; Weisburger 1977). The hexachloroethane was given by gavage in corn oil for both studies.

Doses of 750 mg/kg/day and greater can be lethal with both acute- and intermediate-duration exposures, and a chronic intake of 212 mg/kg/day or greater can shorten the lifespan of rats. There were no apparent effects on lifespan with chronic administration of a 160 mg/kg/day dose in female rats or a dose of 20 mg/kg/day in male rats.

All identified LOAEL values for lethality in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

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

TABLE 2-2. Levels of Significant Exposure to Hexachloroethane - Oral

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less Serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Death						
1	Rat (Sprague-Dawley)	Once (GO)				4489 (LD50)	Kinkead and Wolfe 1992
2	Rat (Sprague-Dawley)	Once[b] (G)				7080 F (LD50)	Weeks et al. 1979
3	Rat (Sprague-Dawley)	Once[b] (G)				7690 M (LD50)	Weeks et al. 1979
4	Rat (Sprague-Dawley)	Once (GO)				5160 M (LD50)	Weeks et al. 1979
5	Rat (Sprague-Dawley)	Once (GO)				4460 F (LD50)	Weeks et al. 1979
6	Gn pig (Hartley)	Once (GO)				4970 M (LD50)	Weeks et al. 1979

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

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)		LOAEL (effect) Less Serious (mg/kg/day)		LOAEL (effect) Serious (mg/kg/day)		Reference
	Systemic									
7	Rat (Sprague-Dawley)	11d Gd 6-16 (GO)	Resp	100	F	500 F	(increased mucus in nasal turbinates; subclinical pneumonitis)			Weeks et al. 1979
			Cardio	500	F					
			Gastro	500	F					
			Musc/skel	500	F					
			Hepatic	500	F					
			Derm	500	F					
			Ocular	500	F					
			Bd Wt	100	F	500 F	(reduced body weight gain, quantitative data not provided)			
8	Rabbit (New Zealand)	12 d (GW)	Resp	1000	M					Weeks et al. 1979
			Cardio	1000	M					
			Gastro	1000	M					
			Musc/skel	1000	M					
			Hepatic	100 [c]	M	320M	(hepatocellular degeneration)	1000 M	(coagulation; necrosis; hemorrhage)	
			Renal	100	M	320M	(tubular nephrosis; tubular nephrocalcinosis)			
			Endocr	1000	M					
			Ocular	1000	M					
			Bd Wt	100	M	320M	(reduced body weight, quantitative data not provided)			

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

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less Serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
9	Sheep	Once (GO)	Hepatic		500M (elevated sorbital and glutamate dehydrogenases; ornithine carbamoyl transferase; decreased bromosulphthalein excretion)		Fowler 1969b
	Neurological						
10	Rat (Wistar)	Gd 7-17 (GO)		56 F		167 F (decreased motor activity)	Shimizu et al. 1992
11	Rat (Sprague-Dawley)	11d Gd 6-16 (GO)		100 F		500 F (tremors)	Weeks et al. 1979
	Reproductive						
12	Rat (Wistar)	Gd 7-17 (GO)		167		500 (increased late-stage fetal resorptions)	Shimizu et al. 1992
13	Rat (Sprague-Dawley)	11d Gd 6-16 (GO)		100 F		500 F (increased fetal resorptions; reduced gestation indices, quantitative data not provided)	Weeks et al. 1979
	Developmental						
14	Rat (Wistar)	Gd 7-17 (GO)		167		500 (20-25% decrease in fetal body weights; increase in skeletal anomalies)	Shimizu et al. 1992
15	Rat (Sprague-Dawley)	11d Gd 6-16 (GO)		100	500 (delayed development, details not provided)		Weeks et al. 1979

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

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)		LOAEL (effect) Less Serious (mg/kg/day)		LOAEL (effect) Serious (mg/kg/day)		Reference
	INTERMEDIATE EXPOSURE									
	Death									
16	Rat (Fischer-344)	13 wk 5d/wk (GO)						750	B (death of 5/10 males and 2/10 females)	NTP 1989
17	Rat (Fischer-344)	2-16 d 5d/wk (GO)						750	B (death of 1/5 males and 2/5 females)	NTP 1989
								1500	B (100% mortality)	
	Systemic									
18	Rat (Fischer 344)	16 wk (F)	Resp	62	B					Gorzinski et al. 1985
			Cardio	62	B					
			Gastro	62	B					
			Hemato	62	B					
			Musc/skel	62	B					
			Hepatic	1 [d]	B	15M	(swelling of hepatocytes in 6/10 males)			
			Renal	1	B			15 M	(increased kidney weight 10%; increased relative kidney weight 5.5%; tubular atrophy and hypertrophy)	
			Endocr	62	B					
			Derm	62	B					
			Ocular	62	B					
			Bd Wt	62	B					
19	Rat (Osborne-Mendel)	7 wk 5d/wk (GO)	Hepatic			497M	(significantly increased mean liver weight)			Milman et al. 1988; Story et al. 1986

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

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less Serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
20	Rat (Osborne-Mendel)	6 wk 5d/wk (GO)	Bd Wt	316	562 M (decreased body weight gain, amount not specified)	1000 M (38% decreased body weight gain)	NTP 1977
21	Rat (Fischer-344)	2-16 d 5d/wk (GO)	Resp	375 B		750 B (shortness of breath)	NTP 1989
			Renal		187 M (hyaline droplet formation; granular cast)		
			Ocular	375 B	750 B (lacrimation)		
			Bd Wt	375 B		750 B (mean body weight decreased 24% in females; males gained 24% of the amount gained by controls)	
22	Rat (Fischer-344)	13 wk 5d/wk (GO)	Resp	750 B			NTP 1989
			Cardio	750 B			
			Gastro	750 B			
			Hepatic	94 B		188 F (centrilobular necrosis and increased liver weight)	
			Renal		47 M (hyaline droplets; tubular degeneration)		
			Derm	750 B			
			Ocular	750 B			
			Bd Wt	375 B	750 M (19% reduction in mean body weight)		
23	Mouse (B6C3F1)	6 wk 5d/wk (GO)	Bd Wt	1000 B	1780 B (reduced body weight gain, quantitative data not provided)		NTP 1977

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

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)		LOAEL (effect) Less Serious (mg/kg/day)		LOAEL (effect) Serious (mg/kg/day)		Reference
	Neurological									
24	Rat (Fischer-344)	13 wk 5d/wk (GO)		47	B	94 B	(post-gavage hyperactivity)	375 B	(convulsions)	NTP 1989
	CHRONIC EXPOSURE									
	Death									
25	Rat (Osborne-Mendel)	66 wk 5d/wk (GO)						212 B	(26/50 males and 23/50 females died before the end of the study)	NTP 1977; Weisburger 1977
	Systemic									
26	Rat (Osborne-Mendel)	66 wk 5d/wk (GO)	Renal					212 B	(tubular necrosis; interstitial nephritis; regenerative epithelium; fibrosis and casts)	NTP 1977; Weisburger 1977
			Bd Wt					212 M	(30% reduction of weight gain)	
27	Rat (Fischer-344)	2 yr 5d/wk (GO)	Resp	160	F					NTP 1989
			Cardio	160	F					
			Gastro	160	F					
			Hepatic	160	F					
			Renal			10M	(mineralization of renal papillae; renal tubule hyperplasia)	20 M	(necrosis; regenerative epithelium; interstitial fibrosis)	
			Derm	160	F					

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

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less Serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
28	Mouse (B6C3F1)	78 wk 5d/wk (GO)	Renal			590 B (tubular nephropathy; degeneration of the tubular epithelium; inflammation, fibrosis; calcium deposits)	NTP 1977; Weisburger 1977
			Bd Wt	590 B			
	Cancer						
29	Rat (Fischer-344)	2 yr 5d/wk (GO)				20 M (CEL: renal tubular adenoma or adenocarcinoma in 7/50) 10 M (CEL: pheochromocytomas in adrenal gland 28/45)	NTP 1989
30	Mouse (B6C3F1)	78 wk 5d/wk (GO)				590 B (CEL: hepatocellular carcinomas 35/50)	NTP 1977; Weisburger 1977

[a]The numbers correspond to entries in Figure 2-2.

[b]Administered in methylcellulose solution.

[c]Used to derive an acute-duration oral minimal risk level (MRL) of 1 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[d]Used to derive an intermediate-duration oral MRL of 0.01 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

B = both; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Derm = dermal; Endocr = endocrine; F = female; (F) = food; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day(s); Gn pig = guinea pig; (GO) = gavage oil; (GW) = gavage water; Hemato = hematological; LD50 = lethal dose (50% kill); LOAEL = lowest-observed-adverse-effect level; M = male;; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); yr = year(s)

Figure 2-2. Levels of Significant Exposure to Hexachlorethane - Oral

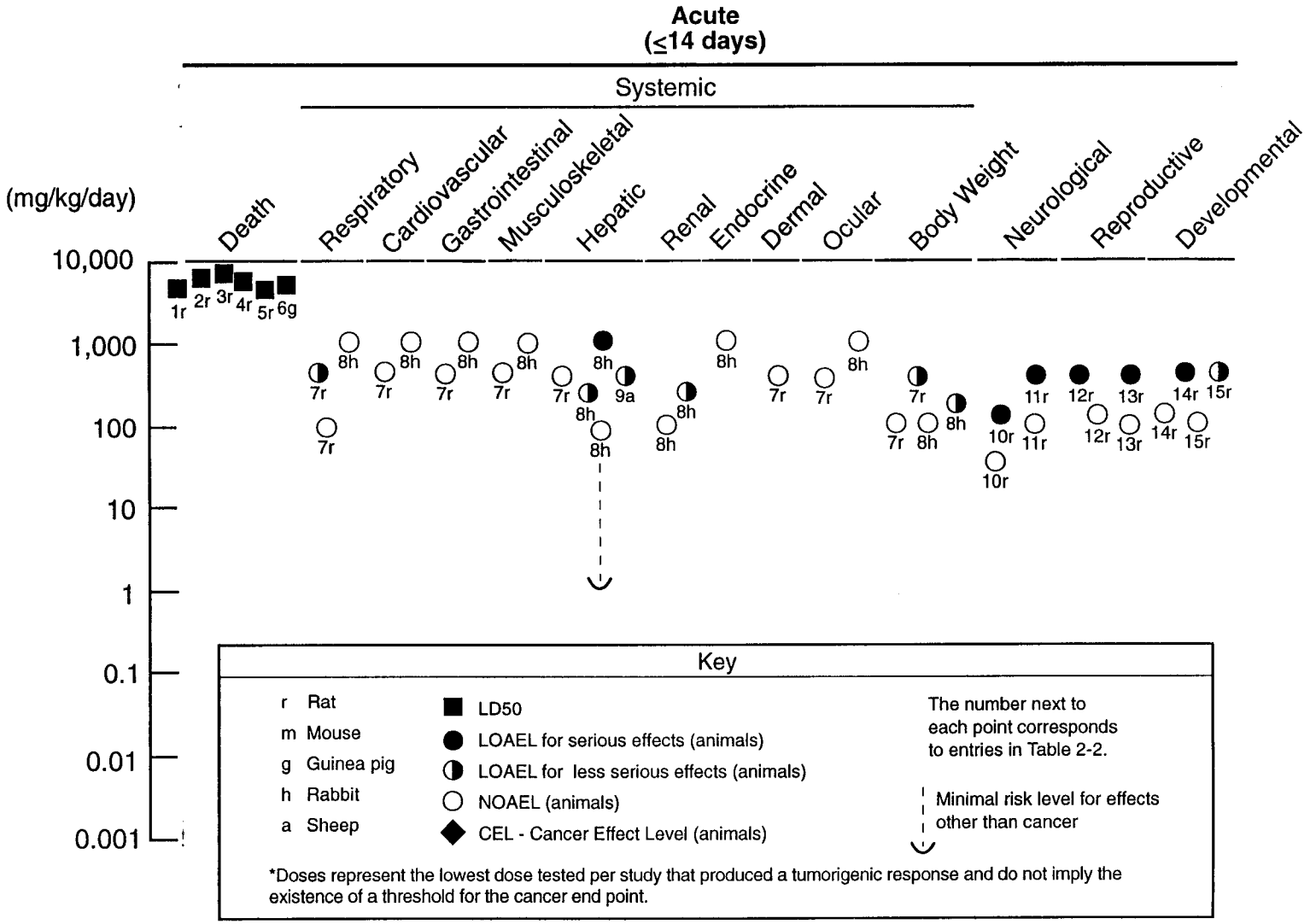


Figure 2-2. Levels of Significant Exposure to Hexaxhlorethane - Oral (continued)

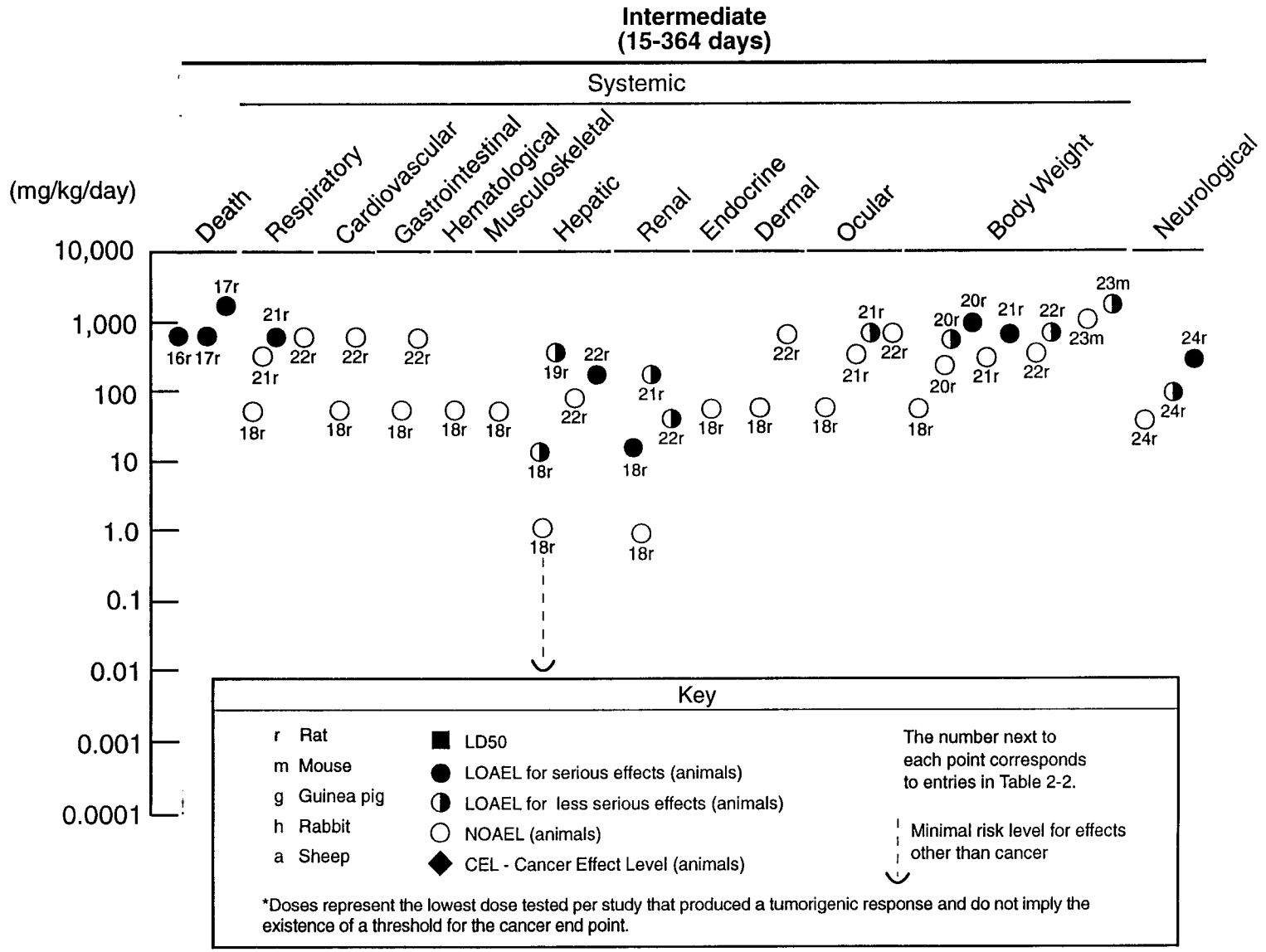
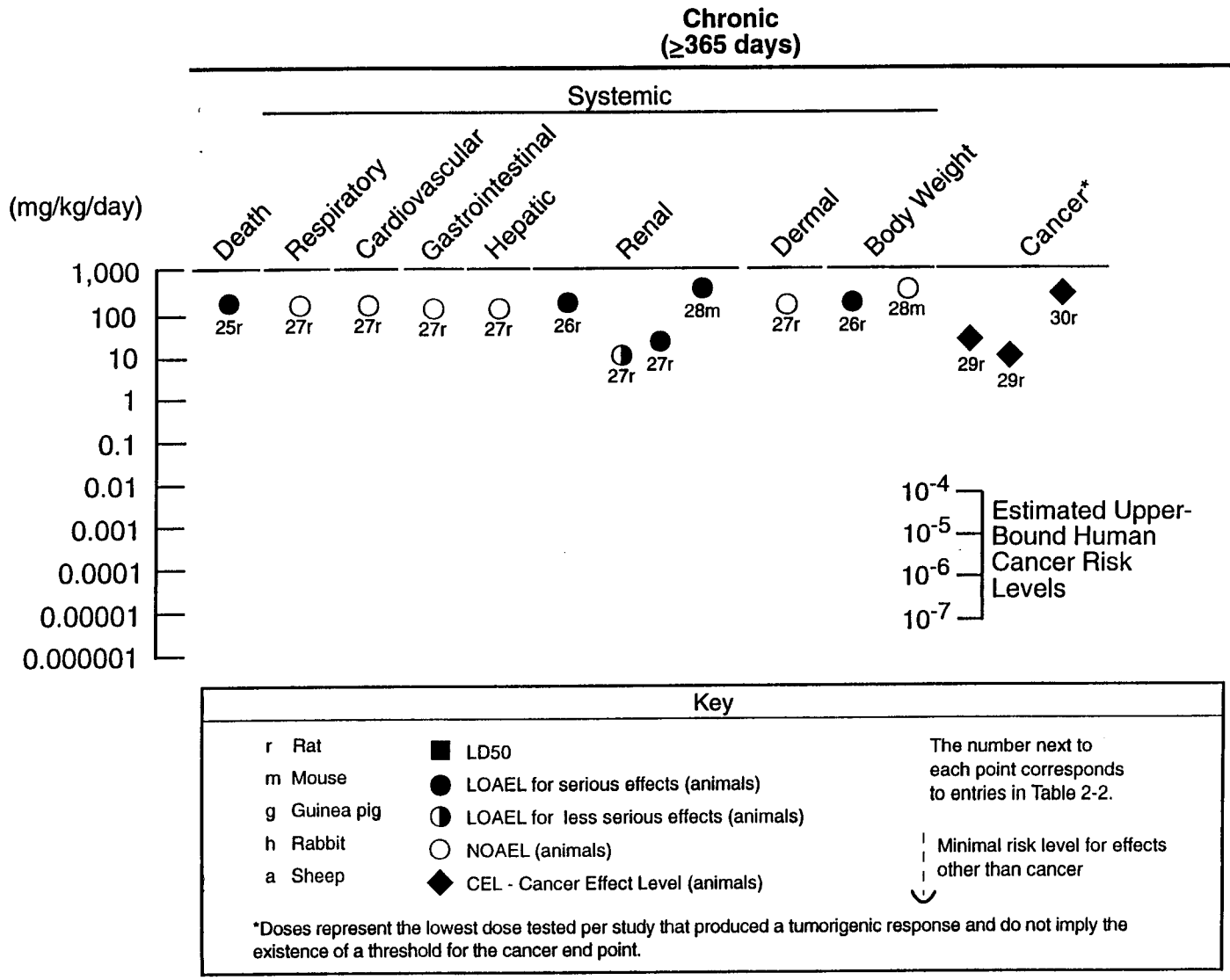


Figure 2-2. Levels of Significant Exposure to Hexachlorethane - Oral (continued)



2. HEALTH EFFECTS

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to hexachloroethane.

Pregnant female rats were given 100 or 500 mg/kg/day hexachloroethane in corn oil by gavage for 11 days (gestation days 6-16) (Weeks et al. 1979). In the high dose group, 75% of the animals showed an increased incidence of upper respiratory tract irritation compared to only 10% of the controls. Subclinical pneumonitis was evident in 20% of the animals in the high dose group as was increased mucous in the nasal turbinates. There were no effects on the respiratory tract for the animals exposed to 100 mg/kg/day when compared to the controls.

No changes in lung histopathology or in lung weights were observed in rabbits exposed by gavage to 0, 100,320, or 1,000 mg/kg/day hexachloroethane in methyl cellulose solution for 12 days (Weeks et al. 1979).

When rats were exposed to 750 mg/kg/day or less hexachloroethane in corn oil by gavage for 13 weeks, there were no effects on the histopathology of the nasal cavity, nasal turbinates, larynx, trachea, bronchi, or lungs (NTP 1989). There were also no changes in the trachea or lungs of rats when hexachloroethane was fed in the diet at a dose of 62 mg/kg/day for 16 weeks (Gorzinski et al. 1985). Doses of 20 mg/kg/day for males and 160 mg/kg/day for females had no effects on the nasal cavity, nasal turbinates, larynx, trachea, bronchi, or lungs when given to rats by gavage in corn oil over their lifetimes (NTP 1989). It appears that hexachloroethane can cause irritation of the respiratory passages in rats even when given orally. The presence of mycoplasma in the animal colony may have contributed to the appearance of lesions and, thus, the lesions may be the result of a synergistic interaction between the microorganism and the hexachloroethane. Based on the data from inhalation exposures as well as the findings of upper respiratory tract infections in pregnant rats that were orally exposed to hexachloroethane (Weeks et al. 1979), it appears that hexachloroethane may weaken resistance to bacterial infections.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to hexachloroethane.

There were no histopathological changes in the hearts of rabbits that were exposed by gavage to doses of 0, 100,320, or 1,000 mg/kg/day hexachloroethane in methyl cellulose solution for 12 days (Weeks et al.

1979). This was also true for rats that were exposed to doses of up to 62 mg/kg/day in the diet for 16 weeks (Gorzinski et al. 198.5) or rats exposed to doses of up to 750 mg/kg/day by gavage in corn oil for 13 weeks (NTP 1989). There were significant increases in heart weight for male rats receiving doses of 188-750 mg/kg/day and female rats receiving 750 mg/kg/day for 13 weeks (NTP 1989). Since these changes were not accompanied by any histopathological lesions, they are regarded in Table 2-2 and Figure 2-2 as NOAEL values rather than LOAELs. The heart does not appear to be a target organ when hexachloroethane is administered orally.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to hexachloroethane.

There were no histopathological changes in the stomach, small intestines, or large intestines of rabbits exposed by gavage to 1,000 mg/kg/day hexachloroethane in methyl cellulose solution for 12 days (Weeks et al. 1979). No effects were noted in rats that were exposed by gavage to concentrations of up to 750 mg/kg/day hexachloroethane in corn oil or 62 mg/kg/day in feed for 13 or 16 weeks (Gorzinski et al. 1985; NTP 1989). Lifetime doses of up to 20 mg/kg/day for male and 160 mg/kg/day for female rats were without effect on the histopathology of the stomach or intestines (NTP 1989). Hexachloroethane appears to have no effects on the gastrointestinal system when administered orally.

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to hexachloroethane.

There were no significant changes in red cell counts, hemoglobin concentration, or white cell counts in rats fed doses of 0, 1, 15, or 62 mg/kg/day in the diet for 16 weeks (Gorzinski et al. 1985).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to hexachloroethane.

There were no treatment-related gross or histopathological lesions of the skeletal muscle or bone in rabbits exposed by gavage to l00-1,000 mg/kg/day hexachloroethane in water for 12 days (Weeks et al. 1979). Histopathological changes were not observed in the skeletal muscle of rats exposed to hexachloroethane in drinking water at 62 mg/kg/day for 16 weeks (Gorzinski et al. 1985).

2. HEALTH EFFECTS

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

The liver appeared to be a target organ for hexachloroethane following oral administration. When one dose of 500 mg/kg was administered in an olive oil aqueous emulsion to male sheep, the levels of glutamate dehydrogenase, sorbitol dehydrogenase, ornithine carbamyl transferase, and aspartate aminotransferase in serum increased in the 2-day period after compound administration and then normalized (Fowler 1969b). Hexachloroethane had no effect on bromsulphthalein uptake from the blood by liver cells, but the transfer of this dye to bile was reduced in sheep exposed to doses of 500-l,000 mg/kg/day.

On the other hand, in rats, a single dose of 6,156 mg/kg hexachloroethane in mineral oil had no effects on a different set of biochemical indicators of liver function (microsomal protein, oxidative demethylase, NADP-NT reductase, glucose-6-phosphatase, or lipid conjugated diene concentration) when measured 2 hours after compound administration (Reynolds 1972). Each of these parameters is an indicator of microsomal function. The authors postulated that the observed lack of effects could have been the result of slow uptake of hexachloroethane by the liver in a 2-hour period. Gastrointestinal absorption of hexachloroethane in mineral oil is probably minimal because, unlike olive oil, mineral oil cannot be digested. Dissolved lipophilic materials could be excreted in the feces soon after administration because mineral oil can act as a laxative. Thus, the author's hypothesis that minimal hexachloroethane would reach the liver in 2 hours is reasonable.

In rabbits, relative liver weights were increased by a dose of 1,000 mg/kg/day hexachloroethane in methyl cellulose solution when given by gavage for 12 days (Weeks et al. 1979). Doses of 320 and 1,000 mg/kg/day were associated with hepatic necrosis, fatty degeneration, hemosiderin-laden macrophages, eosinophilic change, hemorrhage, and coagulation necrosis. The occurrence and severity of each effect at each dose was not presented in the published report of this study. There were also nonsignificant increases in the serum levels of alkaline phosphatase, aspartate aminotransferase, and bilirubin with the 1,000 mg/kg/day dose. No effects were seen with a dose of 100 mg/kg/day. As described in the footnote of Table 2-2, this NOAEL was used to calculate an MRL of 1 mg/kg/day for acute oral exposures.

Liver weights were increased with doses of 15-497 mg/kg/day in rats and exposure durations of 7-16 weeks (Gorzinski et al. 1985; Milman et al. 1988; NTP 1989; Story et al. 1986). The lowest LOAEL

was 15 mg/kg/day from a 16-week study where the hexachloroethane was fed in the diet (Gorzinski et al. 1985). At this LOAEL, hepatocytes were visibly enlarged in 6 of 10 males. At a 62 mg/kg/day dose, 8 males had enlarged hepatocytes and liver weights were increased 10%. No hepatic effects were noted in rats fed 1 mg/kg/day in this study. Based on this value, an intermediate oral MRL of 0.01 mg/kg/day was calculated as described in the footnote in Table 2-2. In a different study, hepatic necrosis in the centrilobular area was seen in 40% of the female rats with a dose of 188 mg/kg/day and in both sexes at doses of 375 mg/kg/day and greater when hexachloroethane was given by gavage in corn oil for 13 weeks (NTP 1989). With the 750 mg/kg/day dose, 40% of the males and 80% of the females were affected.

No effects were seen on liver histopathology in male rats given up to 20 mg/kg/day hexachloroethane for their 2-year lifetime or females given up to 160 mg/kg/day (NTP 1989).

The liver is sensitive to hexachloroethane following both acute and longer term exposure scenarios. Evidence of effects on the liver include increased weight and centrilobular necrosis in rats and rabbits and increased serum levels of liver enzymes in sheep. There can also be fatty degeneration of the tissues and hemorrhage when damage is severe.

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to hexachloroethane.

Male New Zealand rabbits displayed nephrosis of the convoluted tubules and nephrocalcinosis when given doses of 320 and 1,000 mg/kg/day hexachloroethane in methyl cellulose solution for 12 days (Weeks et al. 1979). Kidney weights were increased significantly for the 1,000 mg/kg/day dose. There were no observed effects on the kidney with a dose of 100 mg/kg/day.

In male rats, hyaline droplets could be seen in tubular epithelial cells after 12 gavage doses of 187-750 mg/kg/day in corn oil over a 16-day period (NTP 1989). No adverse histopathologic effects were seen in the kidneys of females. Hyaline droplet formation, tubular regeneration, and tubular casts were present with doses of 47-750 mg/kg/day when the hexachloroethane was administered in corn oil by gavage for 13 weeks (NTP 1989). Renal tubular necrosis and papillary necrosis were present in five males that died during weeks 7-12 when given 750 mg/kg/day hexachloroethane. The kidneys of the five survivors were not examined. Kidney weights were increased significantly in males at doses of

94 mg/kg/day or greater and in females at 375 and 750 mg/kg/day. Hemorrhagic necrosis of the urinary bladder was present in the males from the highest dose group.

When hexachloroethane was given in the diet for 16 weeks, male rats showed a dose-related increase in tubular hypertrophy, dilation, atrophy, peritubular fibrosis, and tubular degeneration (Gorzinski et al. 1985). These signs of nephropathy were present in all of the males at the 62 mg/kg/day dose and 70% of the males at the 15 mg/kg/day dose. Kidney weights were significantly increased for the 62 mg/kg/day dose group. Renal effects were also present in female rats, but they were less severe than the effects seen in males and occurred at higher doses. A dose of 62 mg/kg/day in the diet for 16 weeks was associated with atrophy and degeneration of the tubules in 60% of the females (Gorzinski et al. 1985).

Chronic exposure of both rats and mice resulted in tubular nephropathy in both males and females. In rats, lesions were present in 45-66% of the males when they were sacrificed at 110 weeks after receiving 212 and 423 mg/kg/day hexachloroethane for 66 weeks of a 78-week exposure period (NTP 1977; Weisburger 1977). The renal lesions were characterized by hyperchromic regenerative epithelium, necrosis, interstitial nephritis, fibrosis, focal pyelonephritis, tubular ectasis, and hyaline casts. Lesions were also present in females but had a lower incidence (18% and 59%) for the two dose groups. Two-year exposures of male rats to much lower doses (10 and 20 mg/kg/day) resulted in similar effects on the kidneys (NTP 1989). Minimal to mild nephropathy was present in females for doses of 80 and 160 mg/kg/day. Over 90% of the male and female mice exposed to 590 and 1,179 mg/kg/day hexachloroethane for 78 weeks displayed tubular nephropathy when sacrificed at 90 weeks (NTP 1977; Weisburger 1977). Regenerative tubular epithelium was visible and degeneration of the tubular epithelium occurred at the junction of the cortex and the medulla. Hyaline casts were present in the tubules, and fibrosis, calcium deposition, and inflammatory cells were noted in the kidney tissues.

Male rats are sensitive to renal tubular nephropathy after exposure to hexachloroethane. The lesions observed are characteristic of hyaline droplet nephropathy. They are most likely the result of hexachloroethane or one of its metabolites binding to the excretory protein $\alpha 2\mu$-globulin, altering its kidney transport, and leading to the formation of hyaline droplets. This protein is synthesized by male rats and accounts for 26% of their urinary protein excretion (Olson et al. 1990). It is not excreted in female rats except in minimal quantities. Since some effects are also seen in kidneys of female rats and in male and female mice that do not synthesize $\alpha 2\mu$-globulin hexachloroethane must also have milder adverse effects on the kidney through a different mechanism.

2. HEALTH EFFECTS

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to hexachloroethane.

Histopathological changes were not observed in the pancreas or adrenal glands of pregnant rats treated by gavage with hexachloroethane in corn oil for 11 days at doses up to 500 mg/kg/day, or in the pancreas of male rabbits treated for 12 days at doses up to 1,000 mg/kg/day (Weeks et al. 1979). Following 16 weeks of dietary treatment, hexachloroethane did not result in histopathologic changes in the pancreas, adrenal glands, thyroid, or parathyroid glands of rats treated at doses up to 62 mg/kg/day (Gorzinski et al. 1985).

An increased incidence of pheochromocytomas in the adrenal gland was observed in male rats treated by gavage with hexachloroethane in corn oil at 10 and 20 mg/kg/day 5 days/week for 2 years (NTP 1989). This effect is discussed further in Section 2.2.2.8, Cancer.

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to hexachloroethane.

Histopathological changes in the skin were not observed in pregnant rats given hexachloroethane in corn oil by gavage for 11 days at doses up to 500 mg/kg/day (Weeks et al. 1979). Treatment of rats with doses of hexachloroethane in the diet for 13 weeks at 62 mg/kg/day (Gorzinski et al. 1985), by gavage for 13 weeks at 750 mg/kg/day, and by gavage for 2 years at 20 mg/kg/day for males and 160 mg/kg/day for females (NTP 1989) did not result in histopathologic changes in the skin.

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to hexachloroethane.

An oral dose of 750 mg/kg/day of hexachloroethane for 12 of 16 days resulted in lacrimation in rats during exposure,-but this effect was not mentioned for this dose in the discussion of the results following 13-weeks of treatment (NTP 1989). There were no histopathological effects of hexachloroethane on the eyes of rats at doses up to 750 mg/kg/day for 13 weeks or for lifetime administration of doses of 10 or 20 mg/kg/day to male rats and 80 or 160 mg/kg/day to females rats (NTP 1989).

2. HEALTH EFFECTS

Body Weight Effects. Rabbit weight gain was reduced by doses of 320 and 1,000 mg/kg/day hexachloroethane in methyl cellulose solution given by gavage for 12 days (Weeks et al. 1979). Body weight gain was also reduced in rats exposed by gavage to 750 mg/kg/day hexachloroethane in corn oil for 12 of 16 days, but not in males receiving doses of 375 mg/kg/day and lower (NTP 1989). Females in the 375 mg/kg/day dose groups gained only 67 ± 7% of the weight gained by the controls, and the females in the 750 mg/kg/day dose group lost 25± 2% of their initial body weight.

With exposures of 6 to 16 weeks, doses of 562 mg/kg/day and greater were associated with decreased weight gain in rats (NTP 1977, 1989). No effects on weight were seen with doses of 375 mg/kg/day and lower (Gorzinski et al. 1985; NTP 1977, 1989). Mice were more resistant to effects on weight gain with a NOAEL of 1,000 mg/kg/day and an LOAEL of 1,760 mg/kg/day for a 6-week exposure (NTP 1977).

With chronic exposures, the doses that had no effect on weight gain in rats were 160 mg/kg/day or lower (NTP 1989). A dose of 212 mg/kg/day was associated with a 30% reduction of weight gain in males (NTP 1977). Chronic exposure of mice to doses as high as 1,179 mgfkg/day had no apparent effect on weight gain (NTP 1977).

2.2.2.3 Immunological and Lymphoreticular Effects

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

There were no treatment-related gross or histopathological lesions of the thymus, spleen, or lymph nodes in animals that were exposed to hexachloroethane over any duration (Gorzinski et al. 1985; NTP 1977, 1989; Weeks et al. 1979). For acute exposures, doses of 1,000 mg/kg/day or less were given to rabbits for 12 days (Weeks et al. 1979). In the intermediate-duration exposure category, doses of 750 mg/kg/day or less were tested in rats (Gorzinski et al. 1985; NTP 1989) while for chronic exposures, doses of 20 mg/kg/day or-less were given to male rats and 160 mg/kg/day or less were given to female rats (NTP 1989). No studies were identified that evaluated a wide range of immunological parameters; therefore, there is no reliable LOAEL or NOAEL for this end point.

2. HEALTH EFFECTS

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to hexachloroethane.

Acute exposure of sheep to 500 mg/kg hexachloroethane resulted in tremors of the facial muscles immediately after the exposure (Fowler 1969b). In sheep that were suffering from liver fluke infections, the neurotoxicity of hexachloroethane was even more pronounced. A dose of 170 mg/kg given for treatment of the fluke infection rendered 2 of 15 sheep immobile and unable to stand on the day after treatment, and a dose of 338 mg/kg affected 6 of 15 animals. Tremors of the facial muscles, neck, and forelimbs were apparent. The animals that were able to stand had a staggering gait, and when they fell, they were unable to return to their feet (Southcott 1951). Treatment with calcium borogluconate relieved most of the neuromuscular symptoms although the twitches of the facial muscles persisted.

Tremors were also noted in pregnant rats exposed to 500 mg/kg/day for 11 days during gestation (Weeks et al. 1979). Decreased motor activity was observed in pregnant rats treated with oral doses of 167 mg/kg/day hexachloroethane on gestation days 7-17 (Shimizu et al. 1992). No effects were observed at 56 mg/kg/day. Male and nonpregnant female rats exposed to 750 mg/kg/day for 12 of 16 days suffered from ataxia and prostration (NTP 1989). When exposures were carried out for 13 weeks, a dose of 94 mg/kg/day was associated with postgavage hyperactivity and doses of 375 and 750 mg/kg/day were associated with convulsions (NTP 1989). There were no effects noted on brain histopathology for doses of 750 mg/kg/day or less in rats given hexachloroethane by gavage in corn oil for 13 weeks, but brain weights were increased significantly in both sexes at this dose (NTP 1989).

Chronic exposure of male rats to doses of 20 mg/kg/day or less and of female rats to doses of 160 mg/kg/day or less had no effect on the histopathology of the brain or spinal cord (NTP 1989). Hyperactivity was reported in females, but it was not clear if one or both dose groups were affected.

There has been no comprehensive evaluation of neurological function in animals after oral exposure to hexachloroethane. The data are limited primarily to clinical signs immediately after exposure and to histopathological evaluations of the brain tissues, which showed no effects. The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 2-2 and Figure 2-2.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to hexachloroethane.

In rats, fertility was adversely affected in dams that were administered 500 mg/kg/day (highest dose tested) as evidenced by a reduction in gestation indices and the number of live fetuses per dam. Similar effects were not seen in concurrent vehicle controls. Also, fetal resorption rates were higher at this dose than in the control group (Weeks et al. 1979). Maternal body weight gain was also suppressed. It should be noted that quantitative data were not provided for evaluation. No effects on the number of corpora lutea, the number of implants, or the number of live fetuses were observed in rats treated with hexachloroethane by gavage at 500 mg/kg/day on gestation days 7-17 (Shimizu et al. 1992). The number of late gestation resorptions was increased at 500 but not 167 mg/kg/day. The 500-mg/kg/day dose also resulted in maternal body weight gains that were about 35% less than those of the controls. The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to hexachloroethane.

A slowing of fetal development was observed in offspring of rats that were exposed to a dose of 500 mg/kg/day hexachloroethane during gestation days 6-16; however, no effects were seen at doses of 100 mg/kg/day or less (Weeks et al. 1979). Hexachloroethane was not teratogenic under the conditions of this study. It should be noted that the authors did not provide quantitative data for evaluation. These results have been confirmed in a study by Shimizu et al. (1992) in which decreased fetal body weights and delayed ossification were observed in the offspring of rats treated with hexachloroethane at 500 mg/kg/day on gestation days 7-17. This dose also resulted in maternal body weight gains that were ab-dut 35% less than those of the controls. An increase in fetal anomalies was not observed, with no significant fetal effects at 167 mg/kg/day. The highest NOAEL values and all LOAEL values from each reliable study in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to hexachloroethane.

Genotoxicity studies are discussed in Section 2.5

2.2.2.8 Cancer

No studies were located regarding cancer in humans after oral exposure to hexachloroethane.

There have been three bioassays of hexachloroethane; two were conducted using rats as the test species and one used mice. In the first rat bioassay, there were no statistically significant increases in tumors that could be attributed to compound administration (NTP 1977; Weisburger 1977). Time weighted average doses of 212 or 423 mg/kg/day were given in corn oil by gavage 5 days per week for 66 of 78 weeks. The animals were not exposed to hexachloroethane for 32 weeks before they were sacrificed at 110 weeks.

The total number of tumors for the exposed animals was 22/49 for the males in the low-dose group and 12/50 for the high-dose group, compared to a value of 13120 for the controls (Weisburger 1977). In the females, the number of tumors for the controls was 22/20; for the low-dose group, 50/50; and for the highdose group, 27/49. When evaluated by tumor type there were no statistically significant patterns apparent.Tumors seen in control and treated animals were thyroid adenomas and carcinomas; pituitary adenomas; adrenal tumors; mammary fibromas, fibroadenomas, and carcinomas; and kidney tumors.

A significant and dose-related increase in adenomas and adenocarcinomas of the kidney was observed in male rats given doses of 0, 10, or 20 mg/kg/day for 2 years (NTP 1989). The combined incidence of adenomas and adenocarcinomas was l/50 for the vehicle controls, 2/50 for the low-dose group, and 7/50 for the high-dose group. These tumors are considered to be unique to male rats and are not-indicative of tumorigenic potential in other species because they were associated with hyaline droplet nephropathy. There was no increase in renal adenomas and carcinomas for the female rats, even though they were given doses of 80 and 160 mg/kg/day. In this study, there was also an increased incidence of pheochromatomas in the adrenal glands of male rats when compared to the controls. In the vehicle controls, tumor incidence

was 30% (15/50), in the low-dose group it was 62% (28/45), and in the high-dose group it was 43% (21/49).

In mice, there was an increase in hepatocellular carcinomas when the animals were sacrificed at 90 weeks after being exposed to doses of 590 and 1,179 mg/kg/day for 78 weeks (NTP 1977; Weisburger 1977). The total number of tumors for the exposed animals was 4/20 for the male controls, 17150 for the males in the low-dose group, and 37/49 for the males in the high-dose group. In females, the number of tumors was 9/20 for the controls, 40/50 for the low-dose group, and 30/49 for the high-dose group. When evaluated by tumor type, there was a dose-related trend of 3/20, 15/50, and 29/49 for liver hepatocellular carcinomas in males but not in females, where the corresponding values were 2/20,20/50, and 15/49. Other tumors seen in control and experimental animals included lung adenomas and carcinomas and histolytic lymphomas.

An investigation of the incidence of gamma glutamyl transpeptidase (GGT+) lesions in the liver indicates that hexachloroethane is a promoter of carcinogenicity rather than an initiator. These lesions are markers for preneoplastic cellular changes. When male rats were given a single dose of 497 mg/kg hexachloroethane followed by treatment with a known promotor (phenobarbital) for 7 weeks, there was no increase in number of liver GGT+ foci (Milman et al. 1988). However, when a single dose of a known initiator (dimethylnitrosamine) was followed by 7 weeks of dosing with 497 mg/kg/day hexachloroethane, the number of GGT+ foci was four times the number seen with a single dose of dimethylnitrosamine in the absence of hexachloroethane treatment.

All CELs from each reliable study are included in Table 2-2 and plotted in Figure 2-2. EPA has derived an oral slope factor of 1.4×10^{-2} $(mg/kg/day)^{-1}$ for hexachloroethane based on hepatocellular carcinomas in male mice (IRIS 1995). Doses that correspond to excess cancer risks of 10^{-4} to 10^{-7} are shown in Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

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

2. HEALTH EFFECTS

In rabbits, a dermal LD_{50} of greater than 32,000 mg/kg for a 24-hour exposure to a water paste of hexachloroethane was reported. Ataxia, tremors, and convulsions were noted in those animals that died from exposure (Weeks et al. 1979). The LD_{50} value is reported in Table 2-3.

2.2.3.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, or musculoskeletal effects after dermal exposure to hexachloroethane. The highest NOAEL values and all reliable LOAEL values in each species and duration category are recorded in Table 2-3.

Respiratory Effects. Pulmonary function tests (vital capacity, forced expiratory volume at 1 second) were in the normal range in 11 workers occupationally exposed to hexachloroethane at 0.5-2.1 ppm for 5 weeks while wearing protective equipment including respiratory protection (Selden et al. 1994). Plasma hexachloroethane levels were 7.3 ± 6.04 yg/L at the time of testing indicating that despite protective equipment, low-level exposure occurred (Selden et al. 1993). Mild skin and mucous membrane irritation were reported in the exposed group, suggesting that exposure may have been through either the inhalation or dermal routes of exposure.

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

Hematological Effects. Routine blood parameters (hemoglobin, erythrocyte, leukocyte and thrombocyte levels) measured in 11 hexachloroethane workers that wore protective clothing did not differ from those of the controls (Selden et al. 1994). Mild skin and mucous membrane irritation were reported in the exposed group, suggesting that exposure may have been through either the inhalation or dermal routes of exposure.

No studies were located regarding hematological effects in animals after dermal exposure to. hexachloroethane.

TABLE 2-3. Levels of Significant Exposure to Hexachloroethane - Dermal

Species/ (strain)	Exposure duration/ frequency (Specific route)	System	NOAEL	LOAEL (effect) Less Serious	LOAEL (effect) Serious	Reference
ACUTE EXPOSURE						
Death						
Rabbit (New Zealand)	24 hr				>32 g/kg M (LD50)	Weeks et al. 1979
Systemic						
Rabbit (New Zealand)	24 hr	Derm	132 mg/kg M			Weeks et al. 1979
Rabbit (New Zealand)	Once	Ocular		100 mg M (corneal opacity; iritis)		Weeks et al. 1979
INTERMEDIATE EXPOSURE						
Immunological/Lymphoreticular						
Gn pig (Hartley)	3 wk		1000 ppm M	(no skin sensitization)		Weeks et al. 1979

Derm = dermal; Gn pig = guinea pig;; hr = hour(s); LD50 = lethal dose (50% kill); LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; wk = week(s)

2. HEALTH EFFECTS

Hepatic Effects. Liver function tests (serum bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase) completed in 11 hexachloroethane workers who wore protective clothing were within the normal range (Selden et al. 1994). Mild skin and mucous membrane irritation were reported in the exposed group, suggesting that exposure may have been through either the inhalation or dermal routes of exposure.
No studies were located regarding hepatic effects in animals after dermal exposure to hexachloroethane.

Renal Effects. Renal function tests (serum creatinine and urate, urinary hemoglobin, protein and glucose) completed in 11 hexachloroethane workers who wore protective clothing were within the normal range (Selden et al. 1994). Mild skin and mucous membrane irritation were reported in the exposed group, suggesting that exposure may have been through either the inhalation or dermal routes of exposure.
No studies were located regarding renal effects in animals after dermal exposure to hexachloroethane.

Dermal Effects. Hexachloroethane-exposed workers reported a slightly higher prevalence of dry skin and dry mucous membranes as well as itching and other skin problems than the unexposed controls (Selden et al. 1994). Clinical examinations of the 11 exposed workers did not reveal signs of abnormal dermatological status. Plasma hexachloroethane levels in these workers, who wore protective equipment, were 7.3 ± 6.04 μg/L at the time of the examinations (Selden et al. 1993). The investigators indicate that the dermal effects may also have been a result of a local trauma effect of the protective equipment.

Hexachloroethane had no effects on intact or abraded skin of rabbits when 500 mg was applied to shaved skin as the pure solid (Weeks et al. 1979). There was only a slight redness at the application site when it was applied as a water paste. All redness disappeared after 72 hours. The NOAEL for dermal effects in rabbits (132 mg/kg) is reported in Table 2-3.

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

2. HEALTH EFFECTS

Contact with crystalline hexachloroethane (100 mg caused swelling, iritis, cornea1 opacity, and discharge when placed in rabbit eyes overnight. All signs of ocular irritation were reversed 72 hours later (Weeks et al. 1979). This LOAEL for ocular effects in rabbits is reported in Table 2-3.

Contact with hexachloroethane vapors at a concentration of 260 ppm was apparently irritating to the eyes of dogs because the animals kept their eyes closed during all exposure periods (Weeks et al. 1979). In rats, a red exudate was observed about the eyes after 4 weeks of exposure to hexachloroethane vapors, and in rabbits, after a single dermal exposure to a water paste of hexachloroethane (Weeks et al. 1979). The red exudate did not appear until after 4 weeks of exposure to hexachloroethane vapor and, thus, may be a systemic effect rather than the effect of direct contact of the eye with hexachloroethane.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans following dermal exposure to hexachloroethane.

Hexachloroethane did not act as a sensitizer in guinea pigs when a challenge dose was given 2 weeks after the end of a 3-week sensitization period (Weeks et al. 1979). Accordingly, it did not stimulate antibody formation during sensitization. The NOAEL for dermal sensitization is reported in Table 2-3.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans following dermal exposure to hexachloroethane.

Rats that died after dermal exposure to unspecified doses of hexachloroethane during an LD_{50} test protocol displayed ataxia, tremors, and convulsions before death (Weeks et al. 1979).

2. HEALTH EFFECTS

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

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to hexachloroethane.

2 . 3 TOXICOKINETICS

Hexachloroethane has been found in the plasma of workers wearing protective clothing and respiratory protection suggesting that hexachloroethane can be absorbed following inhalation and/or dermal exposure. Based on the minimal effects seen on target tissues (liver and kidney) in animal studies, absorption from the lungs seems to be limited. Dermal absorption was also estimated to be low based on calculated dermal penetration rates.

Data on absorption across the gastrointestinal tract indicate that hexachloroethane is absorbed, but the percentage of a dose that is absorbed varies. Absorption estimates based on excretory products in rabbits suggest that a moderate portion of a 500 mg/kg dose (perhaps 40-50%) is absorbed. Data on excretory products from rats and mice indicate that a much larger portion (62-88%) of this same dose is absorbed.

Hexachloroethane distributes preferentially to the adipose tissue. Relatively high concentrations are also found in male rat kidneys. Moderate concentrations of hexachloroethane are found in the liver, female kidney, and blood and small amounts in muscle, lungs, and brain. If the hexachloroethane is generated endogenously from carbon tetrachloride, the concentration in the rat liver exceeds that in the kidneys.

2. HEALTH EFFECTS

Hexachloroethane is metabolized by the mixed function oxidase system by way of a two-step reduction reaction involving cytochrome P-450 and either reduced nicotinamide adenine dinucleotide phosphate (NADPH) or cytochrome b, as an electron donor. The first step of the reduction reaction results in the formation of the pentachloroethyl free radical. In the second step, tetrachloroethene is formed as the primary metabolite. Two chloride ions are released. Pentachloroethane is a minor metabolic product that is generated from the pentachloroethyl free radical.

The primary metabolites of hexachloroethane are eventually oxidized to form trichloroethanol and trichloroacetic acid. These ultimate metabolites are excreted along with unchanged hexachloroethane, tetrachloroethene, and pentachloroethane. A small amount of the absorbed hexachloroethane is oxidized completely to carbon dioxide. Hexachloroethane and its metabolites are removed from the body in exhaled air, urine, and bile. In rats and mice, 60-70% of the radiolabeled hexachloroethane was in exhaled air and was present as volatiles other than carbon dioxide.

2.3.1 Absorption

2.3.1.I Inhalation Exposure

No information was located regarding absorption in either humans or animals after inhalation exposure to hexachloroethane.

The minor effects of hexachloroethane on organs other than the lungs in animal studies indicates that absorption does occur, but is probably minimal. Given the lipophilic nature of hexachloroethane, absorption across the lung epithelium is possible.

2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans following oral exposure to hexachloroethane. When sheep were administered a dose of 500 mg/kg hexachloroethane dissolved in olive oil and emulsified in water, absorption was slow based on the appearance of hexachloroethane in the venous blood (Fowler 1969b). The maximum concentration in blood was observed 24 hours after compound administration in one sheep.

2. HEALTH EFFECTS

Based on the amount of label found in rabbit urine and exhaled air, 19-29% of a 500 mg/kg dose was absorbed (Jondorf et al. 1957). Since some hexachloroethane would be excreted in bile and found in fecal matter, the actual amount absorbed was larger than 30%, perhaps 40-50%.

Data from studies in rats and mice using ^{14}C-radiolabeled hexachloroethane suggest that much higher proportions of a 500 mg/kg/day dose of hexachloroethane were absorbed (Mitoma et al. 1985). Rats exhaled 65% of the radiolabel in expired air and 6% in the excreta. This indicates that more than 65-70% of the hexachloroethane was absorbed. Comparable data from mice given 999 mg/kg/day indicate that more than 72-88% of the dose was absorbed. The radiolabel in expired air was 72% of the dose in mice and there was 16% of the label in the excreta (Mitoma et al. 1985).

Hexachloroethane is apparently absorbed to a greater extent when administered in corn oil than when administered in an aqueous medium, based on the fact that the LD_{50} values for hexachloroethane dissolved in methyl cellulose solution are higher than those for a corn oil solvent in both male and female rats (Weeks et al. 1979). The ratio of LD_{50} values suggests that about one-third less material is absorbed from an aqueous medium.

2.3.1.3 Dermal Exposure

Despite wearing protective equipment that included disposable overalls and compressed-air-fed visors or full-facepiece masks with filters for dusts and vapors, hexachloroethane was detected in the plasma of exposed workers (Selden et al. 1993). After 5 weeks of exposure, plasma levels of hexachloroethane in 12 workers were 7.3 k 6 μg/L. Mild dermal irritation was also noted. If the skin irritation was a response to hexachloroethane rather than trauma from the protective clothing, the irritation suggests that the principal exposure route may have been dermal. Absorption of a saturated hexachloroethane solution across human skin was estimated to be 0.0230 mg/cm^2/hour based on the physical properties of hexachloroethane (Fiserova-Bergerova et al. 1990).

No information was located regarding absorption of hexachloroethane in animals after dermal exposure.

2. HEALTH EFFECTS

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No information was located regarding distribution in humans or animals following inhalation exposure to hexachloroethane.

2.3.2.2 Oral Exposure

No information was located regarding distribution in humans following oral exposure to hexachloroethane.

After oral exposure of rats to hexachloroethane for 8-16 weeks, the largest concentration of hexachloroethane was found in the adipose tissues (Gorzinski et al. 1985; Nolan and Karbowski 1978). The kidneys of male rats, but not females, also contained high concentrations of hexachloroethane. When rats were given doses of 3,30, or 100 mg/kg/day for 110-l11 days, the concentration in the male kidney was four times larger than that in the female kidney at the lowest dose and 48 times larger at the highest dose (Nolan and Karbowski 1978). These proportions are very much like the relationship found with doses of 1, 15, or 62 mg/kg/day given to rats where the male kidney contained four times as much label as the female kidney at the low dose and 45 times as much as the female kidney at the high dose (Gorzinski et al. 1985).

Hexachloroethane is also found in the liver and blood after oral exposure to hexachloroethane, although the levels found in these tissues are much lower than those found in adipose tissue and male rat kidney (Gorzinski et al. 1985; Nolan and Karbowski 1978). With a dose of 1 mg/kg/day, adipose tissue samples from male rats contained 3.15 μg/g; the kidneys contained 1.36 μg/g; the liver, 0.29 μg/g; and the blood, 0.08 ug/g after 16 weeks of exposure (Gorzinski et al. 1985). In the female rat, the adipose tissue contained 2.59 μg/g; the kidneys, 0.39 μg/g; the liver, 0.26 μg/g; and the blood, 0.07 μg/g. As the doses were increased, the concentrations in the tissues also increased.

There is a relatively rapid turnover of hexachloroethane in the tissues. In studies where doses of 62 or 100 mg/kg/day hexachloroethane were fed in the diet for about 8 weeks, the level in the tissue decayed

with a half-life of 2.3-2.7 days following first order kinetics (Gorzinski et al. 1985; Nolan and Karbowski 1978).

In sheep fed hexachloroethane in olive oil emulsified in water, the hexachloroethane was found primarily in the liver, kidneys, and adipose tissue 8 hours after exposure; much smaller amounts were found in brain and muscle 8 hours after exposure. The maximum concentration of hexachloroethane in blood occurred 24 hours after dosing (Fowler 1969b).

2.3.2.3 Dermal Exposure

No information was located regarding distribution in humans or animals after dermal exposure to hexachloroethane.

2.3.2.4 Other Routes of Exposure

The tissue distribution of intraperitoneal ^{14}C hexachloroethane in male rats differed from that in male mice based on the concentrations that were bound to DNA, RNA, and protein (Lattanzi et al. 1988). In both species the highest concentrations of label were found in the kidney, followed by the liver, lungs, and stomach in descending order. The amount of bound label in the mice, however, was about twice that in the rat for both kidney and liver. The higher concentration of label in mouse liver may help to explain why hepatocellular cancer has been seen in mice but not in rats.

Hexachloroethane can be generated endogenously from exposure to carbon tetrachloride. Hexachloroethane is formed in the liver through the union of two trichloromethyl free radicals. The tissue distribution of endogenously generated hexachloroethane differed from that of exogenous hexachloroethane. After oral administration of 1 mL/kg carbon tetrachloride to rabbits, adipose tissue contained the highest concentration of hexachloroethane (4.1 ±1.2, 16.5 ±1.6, and 6.8± 2.4 ng/g) at 6,24, and 48 hours (Fowler 1969a). This was similar to the distribution found after oral and intraperitoneal exposure to hexachloroethane (Gorzinski et al. 1985; Lattanzi et al. 1988; Nolan and Karbowski 1978). However, the amount in the liver was about twice that in the kidney at both 6 and 24 hours. At 6 hours, the liver contained 1.6 ±0.5 ng/g and the kidney 0.7 ±0.2 ng/g, while at 24 hours the liver contained 4.2 ± 1.8 ng/g and the kidney contained 2.2± 1.1 ng/g (Fowler 1969a). Only small amounts were found in the muscle.

2. HEALTH EFFECTS

2.3.3 Metabolism

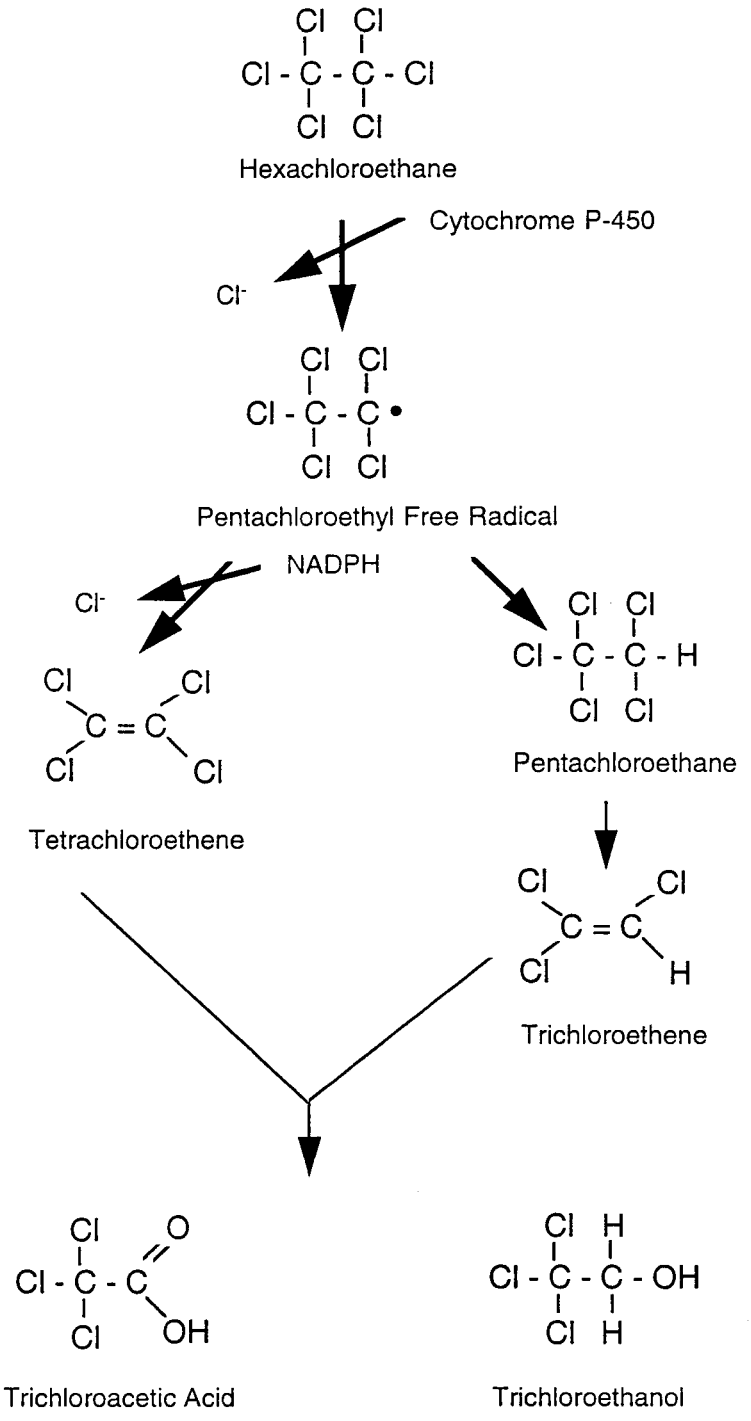
Most of the information on the metabolism of hexachloroethane has been collected by *in vitro* techniques using rat liver slices or rat liver microsomes. Figure 2-3 summarizes the results of these studies. The identification of tetrachloroethene and pentachloroethane as the initial metabolites of hexachloroethane metabolism *in vitro* agrees with *in vivo* data from sheep that were orally exposed to doses of 500-l ,000 mg/kg hexachloroethane (Fowler 1969b).

The initial steps of hexachloroethane metabolism take place in liver microsomes under anaerobic conditions (Nastainczyk et al. 1982a, 1982b; Salmon et al. 1981, 1985; Town and Leibman 1984). Cytosolic enzymes are minimally involved with hexachloroethane metabolism (Town and Leibman 1984). Hexachloroethane is dechlorinated in a two-step reduction reaction. In the first step, cytochrome P-450 contributes one electron to hexachloroethane, leading to the loss of a chloride ion and the formation of a pentachloroethyl free radical. In the second step, a second electron is contributed by either NADPH or cytochrome b_5 and a second chloride is lost, producing tetrachloroethene (Nastainczyk et al. 1982a). A smaller amount of the pentachloroethyl free radical becomes pentachloroethane by abstraction of a hydrogen atom from a hydrogen donor.

In studies using liver microsomes, approximately 99.5% of the hexachloroethane was converted to tetrachloroethene at physiological pHs (Nastainczyk et al. 1982b). When the reaction occurred at higher pHs (8.4-8.8), the ratio of pentachloroethane to tetrachloroethene was increased. The specific cytochrome P-450 involved in this series of reactions was stimulated by phenobarbital and not by 3-methylchloanthrene (Nastainczyk et al. 1982a; Salmon et al. 1985; Thompson et al. 1984; Town and Leibman 1984).

Both tetrachloroethene and pentachloroethane undergo subsequent hepatic metabolism. Pentachloroethane is reductively dechlorinated by microsomes to yield trichloroethene. (Reductive dechlorination was favored when there were three chlorines on one carbon and at least one chlorine on the vicinal carbon [Thompson et al. 1984], a characteristic shared by hexachloroethane and pentachloroethane). Trichloroethene and tetrachloroethene were then oxidized by hepatic enzymes to form trichloroethanol and trichloroacetic acid as terminal reaction products. Apparently additional dechlorination reactions can occur since labeled dichloroethanol, dichloroacetic acid, monochloroacetic acid, and oxalic acid have been

FIGURE 2-3. Metabolism of Hexachloroethane



found in the urine of animals given an oral dose of labeled hexachloroethane (Jondorf et al. 1957; Mitoma et al. 1985). Some hexachloroethane (about 2%) was completely dechlorinated and metabolized to carbon dioxide in rats and mice (Mitoma et al. 1985).

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No data were located regarding excretion in humans or animals after inhalation exposure to hexachloroethane.

2.3.4.2 Oral Exposure

Orally ingested hexachloroethane is exhaled and excreted in urine and fecal matter. The portion of the hexachloroethane found in fecal matter is the result of excretion in bile. The results of studies that measured the amount of residual hexachloroethane in excreta can be misleading, since much of the absorbed hexachloroethane is metabolized to other compounds. Measurement of ^{14}C label after exposure to labeled compound presents a more complete picture of ultimate hexachloroethane fate and excretion than measurement of hexachloroethane.

In rats and mice, 65-70% of an oral dose of radiolabeled hexachloroethane (500 mg/kg/day for rats and 999 mg/kg/day for mice) was present in exhaled air (Mitoma et al. 1985). Only about 2% of this amount was exhaled as carbon dioxide. The remainder was present as other volatile compounds. In rabbits, a much smaller portion of the label was found in exhaled air (14-24%) after oral administration of 500 mg/kg hexachloroethane. The amount of labeled carbon dioxide was not determined (Jondorf et al. 1957).

Relatively little hexachloroethane, pentachloroethane, and tetrachloroethene was found in the urine of sheep after oral administration of 500 mg/kg hexachloroethane (Fowler 1969b), and relatively little label (5%) was found in the urine of rabbits given 500 mg/kg (Jondorf et al. 1957). The major urinary metabolites were trichloroethanol and trichloroacetic acid in rats, rabbits, and mice (Jondorf et al. 1957; Mitoma et al. 1985). In rabbits, smaller amounts of dichloroethanol, dichloroacetic acid, monochloroacetic acid, and oxalic acid were also present (Jondorf et al. 1957).

In sheep, 80% of the hexachloroethane, tetrachloroethene, and pentachloroethane fecal excretions were excreted within 24 hours (Fowler 1969b). Some of this was unabsorbed hexachloroethane and the remainder was material that had been absorbed and was excreted with the bile. Hexachloroethane was present in bile within 15 minutes of dosing and the concentration in bile was 8-10 times greater than that in blood at that time. Traces of hexachloroethane, tetrachloroethene, and pentachloroethane were present in the 48-72 hour fecal collections.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion by humans or animals after dermal exposure to hexachloroethane.

2.4 Mechanisms of Action

The kidney and liver are the primary target organs for hexachloroethane based on the results of toxicity testing and supported by toxicokinetic information from tissue distribution and binding studies (Lattanzi et al. 1988). Male rats were more susceptible to kidney damage than female rats (NTP 1989), and the kidneys of male rats contained 4-45% more hexachloroethane radiolabel than the kidneys of female rats (Gorzinski et al. 1985). However, there were some effects on kidneys of both sexes.

The mechanism of toxicity leading to tubular nephropathy and renal tumorigenesis in male rats is related to the synthesis and excretion of the protein α2μ-globulin. This protein is synthesized in the liver and secreted into the blood. It is filtered through the glomeruli of the kidneys and partially reabsorbed through the proximal tubules where it is partially hydrolyzed (Swenberg 1993). The remainder is excreted, comprising 26% of the urinary protein (NTP 1989; Olson et al. 1990). Other species of laboratory animals, female rats, and humans produce minimal amounts of an α2μ-globulin-type protein. In the presence of hexachloroethane and other nonpolar hydrocarbons or their metabolites, α2μ-globulin accumulates in hyaline droplets in the tubular epithelium. The accumulation of hyaline droplets damages the epithelial cells, leading to exfoliation and the appearance of hyaline casts in the urine. Regenerative repair of the epithelium leads to hyperplasia and increases the risk for tumors when mutated cells divide before DNA repair can occur.

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Although binding of hexachloroethane to α2μ-globulin can explain kidney damage in male rats, it does not explain the less severe kidney changes in female rats (NTP 1989). Thus, other mechanisms must be involved in the nephrotoxicity of hexachloroethane. When DNA, RNA, and protein were isolated from kidney cells of male rats, it was found that hexachloroethane was bound more strongly to RNA and protein than to DNA (Lattanzi et al. 1988). The highest concentrations were found bound to RNA. Epigenetic interference with protein synthesis and cell function could lead to the kidney nephropathy seen in female rats and contribute to the damage in male rats. However, no studies were identified that would support this hypothetical mechanism.

Liver necrosis is another concern following hexachloroethane exposure. Hexachloroethane is metabolized in the centrilobular area of the liver by way of the microsomal mixed function oxidase system. The relatively nonpolar pentachloroethyl free radical is an intermediate in this pathway. The reaction of the free radical with unsaturated lipids in the cellular or organelle membranes could contribute to hepatocyte damage and necrosis.

Conjugated dienes and malondialdehyde serve as a markers for free radical-induced lipid peroxidation. There was a uniform increase in malondialdehyde in eight assays of rat liver microsomes that were incubated with hexachloroethane (Town and Leibman 1984). Conjugated dienes were increased in some, but not all, of the samples. No changes were seen in the concentration of conjugated dienes in the hepatic endoplasmic reticulum of male rats, 2 hours after hexachloroethane exposure (Reynolds 1972). The authors hypothesized that the poor solubility of hexachloroethane in body fluid and the use of a mineral oil solvent limited the concentration of hexachloroethane in the liver at 2 hours and, thus, the lack of its effects on conjugated dienes could not be used to eliminate the possibility of free radical cellular damage at a later point in time. Although limited, the data provide some support for a free radical mechanism for the hepatic toxicity of hexachloroethane.

Clinical signs of neurotoxicity (tremors and ataxia) have been observed in sheep, dogs, and rats during or immediately after both oral and inhalation exposure. Sometimes tremors developed early irrthe treatment regime and other times the tremors became apparent only after repeated exposures. Fluke-infected sheep experienced tremors of the facial muscles, neck, and forelimbs and were unable to stand after treatment with hexachloroethane. They were successfully treated with calcium borogluconate. This suggests that the neurological action of hexachloroethane may be the result of interference with the availability of calcium within excitable cells.

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2.5 RELEVANCE TO PUBLIC HEALTH

Hexachloroethane is a solid crystalline material that has entered the environment as a result of its use in military pyrotechnics and as a component of smoke-producing devices used for screening or signaling purposes. It is an intermediate in the production of fluorocarbons, cleaning agents, and refrigerants and was once used in veterinary medicine to control liver flukes in sheep. It can be found at military disposal sites and at hazardous waste sites. In addition, hexachloroethane can be formed during incineration of chlorinated organic compounds and during chlorination of drinking water. Accordingly, there is some risk that humans can be exposed to this material.

Respiratory, hematological, liver, and renal effects were not observed in 11 hexachloroethane-exposed workers. The identification of hexachloroethane in the plasma of these workers confirmed exposure, although the workers were wearing protective equipment. Mild dermal irritation was noted that may have been from exposure or a result of a local trauma effect of the protective equipment.

Animal studies identify the kidney and liver as the primary target organs for hexachloroethane. Renal problems were most severe in male rats and were associated with α2μ-globulinlhyaline droplet nephropathy. Minimal to mild lesions were also seen in female rat kidneys and in male and female mice, indicating that some mechanism, in addition to hyaline droplet formation, is involved in renal toxicity. The liver responds to hexachloroethane exposure with increases in liver weight, increases in serum levels of liver enzymes, centrilobular necrosis, fatty degeneration, hemosiderin-laden macrophages, and hemorrhage. Effects on the liver and kidneys were mild with inhalation exposure and more pronounced with oral exposure. No data were available for effects on the liver and kidneys by the dermal exposure route.

Hexachloroethane vapors and ingested hexachloroethane act as irritants on the lining of the lung, nasal cavity, trachea, and other tissues of the respiratory tract. Pulmonary irritation was associate&with an increased incidence of mycoplasma infection in rats. Hexachloroethane exposure can also irritate the eyes. The irritation of the eye and respiratory tract are reversible once exposure has ceased.

Both oral and inhalation exposures to high concentrations of hexachloroethane were associated with hyperactivity, ataxia, convulsions, and/or prostration in rats, sheep, and dogs. The mechanism for these

neurological effects is not clear since there were no apparent histopathological lesions in the brains of the affected animals. Neurological effects were only noted with the high-dose exposures.

There has been no comprehensive evaluation of the reproductive and developmental effects of hexachloroethane. Limited data indicate that it is maternally toxic and retards fetal development. It does not appear to be a teratogen.

Minimal Risk Levels for Hexachloroethane

Inhalation MRLs

- An MRL of 6 ppm has been derived for acute inhalation exposure to hexachloroethane. This MRL is based on a study in pregnant female rats exposed to concentrations of 0, 15,48, or 260 ppm hexachloroethane for 6 hours/day on gestation days 6-16 (Weeks et al. 1979). Tremors were observed in the 260-ppm dose group during exposure starting on day 12 and persisting through day 16. Excess mucus was present in the nasal turbinates of all of the dams in the 260-ppm dose group and 85% of the dams in the 48-ppm dose group. This effect was not observed at 48 ppm in the 6-week study, and the endemic mycoplasma infection that was present in the colony of rats used in the Weeks et al. (1979) study may have contributed to this effect. Based on the NOAEL of 48 ppm for neurological effects observed in the teratology study by Weeks et al. (1979), an acute inhalation MRL was calculated by adjusting to a Human Equivalent Concentration (HEC) of 181 ppm using reference ventilation rates (rat, 0.22 m3/day; human, 20 m3/day) and body weights (rat, 0.204 kg; human, 70 kg) from EPA (1988a) and by dividing by an uncertainty factor of 30. A factor of 3 was used to extrapolate from animals to humans, and a factor of 10 was used to account for human variability.

- An MRL of 6 ppm has been derived for intermediate-duration inhalation exposure to hexachloroethane. This MRL is based on the 6-week study in rats by Weeks et aG(1979) in which tremors were observed at 260 ppm but not at 48 ppm. Based on the NOAEL of 48 ppm for neurological effects observed in the 6-week study (Weeks et al. 1979), an intermediate inhalation MRL was calculated by adjusting the NOAEL to an HEC of 174 ppm using reference ventilation rates (rat, 0.245 m^3/day; human, 20 m^3/day) and body weights (rat, 0.236 kg; human, 70 kg) from EPA (1988a) and by dividing by an uncertainty factor of 30. A factor of 3 was used

to extrapolate from animals to humans, and a factor of 10 was used to account for human variability.

A chronic MRL for inhalation exposure has not been derived because no data were located on the effects of long-term exposures in humans or animals.

Oral MRLs

- An MRL of 1 mg/kg/day has been derived for acute oral exposure to hexachloroethane. This MRL was derived from a NOAEL of 100 mg/kg/day in a study where groups of five male New Zealand rabbits were given doses of 0, 100,320, and 1,000 mg/kg/day hexachloroethane dissolved in methyl cellulose solution by gavage for 12 days (Weeks et al. 1979). Dose-dependant liver degeneration and necrosis were noted at dose levels of 320 and 1,000 mg/kg/day. Effects were characterized as fatty degeneration, coagulation necrosis, hemorrhage, ballooning degeneration, eosinophilic change, hemosiderin-laden macrophages and giant cells. Comparable effects were not seen in the l00-mg/kg/day dose group. Liver weights increased at the highest dose tested; however, quantitative data were not provided. The NOAEL of 100 mg/kg/day was divided by an uncertainty factor of 100, 10 each for interspecies and intraspecies variability.

- Toxic tubular nephrosis and minimal nephrocalcinosis of the convoluted tubules were seen at dose levels of 320 and 1,000 mg/kg/day, however comparable effects were not seen at the lowest dose tested. Kidney weights increased significantly ($p<0.05$) at the highest dose tested. For the most part, serum clinical parameters (blood urea nitrogen, protein bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and sodium) were not affected significantly. Levels of potassium and glucose were decreased significantly at dose levels of 320 mg/kg/day or greater. Body weights were reduced significantly ($p<0.05$) at exposure levels of 320 and 1,000 mg/kg/day. Quantitative data were not provided for any of the eTfects noted in this study, although the degree of significance and the dose-related nature of the effects were included in the discussion of the results.

- An MRL of 0.01 mg/kg/day has been derived for intermediate oral exposure to hexachloroethane. The MRL was derived from a NOAEL of 1 mg/kg/day in a study where

groups of 10 male and 10 female rats were given hexachloroethane at 1, 15, or 65 mgikg/day in the diet for 16 weeks (Gorzinski et al. 1985). All rats survived the 16-week exposure period and there were no clinical signs of compound toxicity. Organ weights were not significantly different than those of the controls except for absolute and relative liver weights and kidney weights of males treated at the highest dose. Swelling of the hepatocytes was present in males at the two highest doses. At the 15-mg/kg dose, swollen hepatocytes were noted in 6 of 10 males, and 8 of 10 males were affected at the 62-mg/kg/day dose. Swollen hepatocytes were seen in four control males and in three males from the lowest dose group. Hepatocyte size was not affected in females, but absolute and relative liver weights were increased in the highest dose group. The male rats exhibited renal tubular atrophy, hypertrophy, dilation, and degeneration for both the 15- and 62-mg/kg/day doses. Atrophy and tubular degeneration was also present in 6 of 10 females at the 62-mg/kg/day dose and 2 of 10 females at the 15 mg/kg/day dose. The 15 mg/kg/day dose was identified as the LOAEL in this study with the 1 -mg/kg/day dose as the NOAEL. This NOAEL was used with an uncertainty factor of 100 (10 each for interspecies and intraspecies variability) to derive the MRL.

Insufficient information was available to derive a chronic-duration oral exposure MRL for hexachloroethane.

Death. No studies were located regarding lethality in humans after exposure to hexachloroethane. LD_{50} values for animals range fi-om 4,460 to 5,160 mg/kg when hexachloroethane is administered by gavage in corn oil and from 7,080 to 7,690 mg/kg when administered in an aqueous methyl cellulose solution (Weeks et al. 1979). The higher LD_{50} value for the aqueous solution indicates that absorption from this medium is lower than from a digestible food oil. When exposures occurred by the inhalation route, 1 of 6 rats died during an 8-hour exposure to 5,900 ppm (Weeks et al. 1979). At this concentration, the inhalation chamber contained crystalline hexachloroethane as well as hexachloroethane vapors. The dermal LD_{50} was greater than 32,000 mg/kg when hexachloroethane was applied to shaved rabbit skin for 24 hours (Weeks et al. 1979). This suggests poor dermal absorption of hexachloroethane and agrees with a calculated low dermal absorption rate of 0.023 $mg/cm^2/hr$ based on physical properties (Fiserova-Bergerova et al. 1990).

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There were some deaths among dogs, rats, and guinea pigs with exposure to 260 ppm in air for 6 weeks (Weeks et al. 1979). Following oral exposure, death occurred in rats at doses of 750 mg/kg/day (NTP 1989) and in mice at doses of 1,780 mg/kg/day (NTP 1977). Lower doses were nonlethal.

Chronic oral exposure to 212 mg/kg/day shortened the life expectancy of male and female rats (NTP 1977), but doses of 20 mg/kg/day in males and 160 mg/kg/day in females did not (NTP 1989). Although mice were exposed to oral doses of 590 and 1,170 mg/kg/day hexachloroethane for 78 weeks, poor survival among male controls made it difficult to evaluate the effects of hexachloroethane. Survival for the high-dose females was slightly less than that for vehicle controls, but the differences were not significant (NTP 1977).

LD_{50} values and the lowest lethal doses for acute- and intermediate-duration exposures classify hexachloroethane as slightly toxic (Hodge and Sterner 1949). It is unlikely that exposures to hexachloroethane at levels found at hazardous waste sites would cause death in humans.

Systemic Effects

There are no data for cardiovascular, gastrointestinal, musculoskeletal, endocrine, or ocular effects in humans following exposure to hexachloroethane by any route. Data are available for inhalation and oral exposures in several animal species. The only available dermal exposure data apply to dermal and ocular effects.

Respiratory Effects. Pulmonary function tests were not affected in workers exposed to hexachloroethane for 5 weeks while wearing protective equipment (Selden et al. 1994). Acute exposure of rats to 5,900 ppm hexachloroethane (a combination of gaseous and microcrystalline material) resulted in interstitial pulmonary pneumonitis (Weeks et al. 1979). These pulmonary lesions were seen after a 14-day recovery period. The entrapment of solid hexachloroethane particles in the lungs could have contributed to the symptoms observed.

Excess mucus in the nasal turbinates, irritation of the epithelium, and increased incidence of a mycoplasma respiratory infection were seen in rats with inhalation exposure to 260 ppm for 6 weeks and in pregnant rats with inhalation exposure to 48 ppm for 11 days. Pulmonary irritation was also present in pregnant rats treated with an oral dose of 500 mg/kg/day for 11 days (Weeks et al. 1979). Effects on the respiratory

epithelium were not apparent in the tissue of the lungs, nasal cavity, nasal turbinates, larynx, trachea, or bronchi based on histopathological examination (NTP 1977, 1989; Weeks et al. 1979). Exposure to hexachloroethane, especially in its vaporous state, may weaken the effectiveness of respiratory tract mucus as an antimicrobial barrier and, thus, increase the incidence of pulmonary infections in exposed animals. Alternatively, it may weaken disease resistance by some other mechanism. Humans exposed to hexachloroethane vapors in the environment could experience an increased risk of respiratory tract infections.

Cardiovascular Effects. There were no histopathological effects on the heart after inhalation or oral exposure at any concentration tested (15-5,900 ppm for the inhalation route and l-750 mg/kg/day for the oral route) and with acute, intermediate, or chronic exposure durations (Gorzinski et al. 1985; NTP 1977, 1989; Weeks et al. 1979). The risk that humans will experience adverse effects on the cardiovascular system as the result of exposure to hexachloroethane through the environment seems to be relatively low.

Gastrointestinal Effects. There were no histopathological effects on the stomach, small intestines, or large intestines with inhalation or oral exposure to hexachloroethane at any concentration tested (15-5,900 ppm for the inhalation route and l-750 mg/kg/day for the oral route) and with acute, intermediate, or chronic exposure durations (Gorzinski et al. 1985; NTP 1977, 1989; Weeks et al. 1979). The risk that humans will experience adverse effects on the gastrointestinal system as the result of exposure to hexachloroethane in the environment seems to be relatively low.

Hematological Effects. Routine blood parameters (hemoglobin, erythrocyte, leukocyte and thrombocyte levels) measured in 11 hexachloroethane-exposed workers who wore protective clothing did not differ from those of the controls (Selden et al. 1994). Hexachloroethane plasma levels in these workers were 7.3 ± 6 μg/L (Selden et al. 1993).

The effects of acute exposures to hexachloroethane on hematological parameters were not evaluated in animals. Inhalation doses of 260 ppm for 6 weeks had no effect on erythrocyte counts in dogs (Weeks et al. 1979) and oral exposures of up to 62 mg/kg/day for 16 weeks had no effect on red cell counts, hemoglobin concentrations, or white cell counts in rats (Gorzinski et al. 1985). These results suggest that hexachloroethane does not affect hematological parameters, but there are relatively few data upon which to base this conclusion. On the basis of the existing data, the occurrence of hexachloroethane at hazardous waste sites should not pose a significant hematological risk for humans.

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Musculoskeletal Effects. Neither inhalation nor oral exposures to hexachloroethane were associated with histopathological changes in skeletal muscle or bone in rats following acute-, intermediate-, or chronic duration exposures with inhalation exposure concentrations of 15-5,900 ppm or oral exposure doses of l-750 mg/kg/day (Gorzinski et al. 1985; NTP 1977, 1989; Weeks et al. 1979). More comprehensive data pertaining to the musculoskeletal system were not identified. Based on the data available, there appears to be no risk for musculoskeletal effects for those who live or work near a hazardous waste site.

Hepatic Effects. Liver function tests (serum bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase) were not affected in 11 hexachloroethaneexposed workers who wore protective clothing (Selden et al. 1993).

Animal studies indicate that hepatic tissues are moderately vulnerable to exposure to hexachloroethane especially when exposure occurs by the oral route. With acute- and intermediate-duration inhalation exposures, the only effects noted were an increase in liver weight in rats and guinea pigs, but not dogs or quail, after 6 weeks of exposure to 260 ppm (Weeks et al. 1979). There were no observable histopathological changes in the tissues that accompanied the organ weight change and no histopathological changes with acute exposure to an even higher hexachloroethane concentration (5,900 ppm).

When exposures occurred by the oral route, increased liver weights, increases in serum liver enzyme levels, centrilobular necrosis, fatty degeneration, hemosiderin-laden macrophages, and hemorrhage were noted in animals following acute- and intermediate-duration exposures (Fowler 1969b; Gorzinski et al. 1985; NTP 1989; Weeks et al. 1979). The lowest LOAEL for these effects was a dietary dose of 15 mg/kg/day for 16 weeks which was associated with enlargement of the hepatocytes in males (Gorzinski et al. 1985). However, there were no observable adverse effects on tissue histopathology in male rats given 20 mg/kg/day for 2 years or in females given 160 mg/kg/day for the same period of time (NTP 1989). Organ weights were not determined for the chronic exposures. These data suggest that there is a potential for individuals who might be exposed to hexachloroethane from a contaminated diYnking water supply to experience hepatic effects. The risk from other exposure routes (inhalation or dermal) due to contaminated hazardous waste sites is probably minimal.

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Renal Effects. No effects on renal function tests (serum creatinine and urate, urinary hemoglobin, protein and glucose) were noted in 11 hexachloroethane-exposed workers who wore protective clothing (Selden et al. 1994).

Acute exposure to concentrations of 260-5900 ppm hexachloroethane had minimal effects on the kidney. There was an increase in kidney weights in male rats exposed to 260 ppm hexachloroethane for 6 weeks but no discernable effects on tissue histopathology (Weeks et al. 1979). This same exposure concentration had no effect on female rats or on male or female dogs, guinea pigs, or quail under parallel exposure conditions.

Acute-, intermediate-, and chronic-duration oral exposures of male rats to doses of 10 mg/kg/day or greater were associated with renal tubular nephropathy (Gorzinski et al. 1985; NTP 1977, 1989; Weeks et al. 1979). Affected animals displayed tubular necrosis, hyaline droplets in tubular epithelial cells, regenerative tubular epithelium, interstitial nephritis, and fibrosis. The severity of the renal lesions varied with the dose and the duration of exposure.

Hexachloroethane is a member of a family of compounds that bind to the male rat excretory protein α2μ-globulin and form hyaline droplets in the tubular epithelium leading to necrosis and repair hyperplasia (Borghoff 1993; Olson et al. 1990). The hexachloroethane metabolites tetrachloroethene and pentachloroethane are also members of this family of compounds (Borghoff 1993; Swenberg 1993). Female rats and laboratory animals from other species synthesize only minimal quantities of this protein and, thus, have a lower risk for renal effects. In male rats, α2μ-globulin accounts for 26% of the urinary protein, and chemicals that bind with it have a strong tendency to accumulate in the kidney causing cellular damage.

Mild to moderate nephropathy in female rats exposed to 80 or 160 mg/kg/day for 2 years, a high incidence of nephropathy in mice exposed to 590 or 1,179 mg/kg/day for 78 weeks, and nephrosis in rabbits exposed to 320 or 1,000 mg/kg/day for 12 days, indicate that hexachloroethane has an effect on the kidney that is independent of α2μ-globulin (NTP 1977, 1989; Weeks et al. 1979). Thus, the public health risk for renal effects should be considered when evaluating the possible effects of human exposure to hexachloroethane at hazardous waste sites.

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Endocrine Effects. Histological changes have not been observed in the pancreas or adrenal glands of rats, guinea pigs, dogs, or quail following inhalation exposure to hexachloroethane at concentrations up to 260 ppm for 6 weeks (Weeks et al. 1979). Intermediate-duration oral treatment of rats with hexachloroethane at doses up to 62 mg/kg/day also did not result in histological changes in the pancreas, adrenal glands, thyroid, or parathyroid glands (Gorzinski et al. 1985). Chronic gavage treatment of male rats with hexachloroethane at 10 or 20 mg/kg/day did result in an increased incidence of pheochromocytomas in the adrenal gland (NTP 1989). The relevance of this effect to humans is not clear.

Dermal Effects. Hexachloroethane-exposed workers reported a slightly higher prevalence of dry skin and dry mucous membranes as well as itching and other skin problems than the unexposed controls (Selden et al. 1994). Clinical examinations of the 11 exposed workers did not reveal signs of abnormal dermatological status. The investigators indicate that the dermal effects may also have been a result of a local trauma effect of the protective equipment.

There was no evidence that crystalline hexachloroethane affected the skin of animals with either inhalation or oral exposures of acute, intermediate, or chronic durations (Fowler 1969b; Gorzinski et al. 1985; NTP 1977, 1989; Weeks et al. 1979). When a water paste was placed on the shaved skin of rabbits for 24 hours, there was only a slight redness as the result of contact (Weeks et al. 1979).

The concentrations of hexachloroethane that might be found at hazardous waste sites are unlikely to act as skin irritants in humans.

Ocular Effects. Inhalation and oral exposure of animals to hexachloroethane caused lacrimation and reddening of the eyes after oral exposure (NTP 1977, 1989), or closing of the eyes as an avoidance mechanism during inhalation exposure (Weeks et al. 1979). Overnight, direct contact of the eyes with crystalline hexachloroethane resulted in cornea1 opacity and iritis in rabbits, but recovery was complete 3 days later (Weeks et al. 1979). Direct eye contact with hexachloroethane at hazardous waste sites may result in an eye irritation.

Body Weight Effects. Decreased weight gains occurred in rats in response to both acute inhalation exposure to a high concentration of hexachloroethane (5,900 ppm) and intermediate-duration exposures to a lower concentration (260 ppm) (Weeks et al. 1979). Oral exposures were also associated with decreased weight gains with doses of 320 mg/kg/day or greater for 12 days in rabbits (Weeks et al. 1979) and with

562 mg/kg/day or greater for 6-16 weeks in rats (NTP 1977, 1989). Female rats exposed to 750 mg/kg/day for 16 days actually lost 25% of their initial body weight (NTP 1989). Decreased weight gain occurred in mice at doses of 1,760 mg/kg/day (NTP 1977). In light of these findings, the concentrations of hexachloroethane found at hazardous waste sites are unlikely to be of great enough magnitude to have an effect on body weight in humans.

Immunological and Lymphoreticular Effects. No studies were located regarding immunological effects in humans after exposure to hexachloroethane. In addition, there were no data from comprehensive studies of immune response in animals for exposure by any route and for any duration. When the tissue histopathology of the spleen, thymus, and, in one case, lymph nodes were evaluated, no abnormalities were noted (Gorzinski et al. 1985; NTP 1989; Weeks et al. 1979). After 6-week inhalation exposures to 260 ppm hexachloroethane, the relative spleen weight was increased in young, but not in older, male rats. Data on dermal sensitization in guinea pigs indicate that exposure to low levels of hexachloroethane does not elicit antibody formation leading to an allergic dermatological response (Weeks et al. 1979).

An increased incidence in mycoplasma infections in rats exposed to 260 ppm hexachloroethane for 6 weeks suggests that hexachloroethane might weaken resistance to infection (Weeks et al. 1979). This could be the result of either a change in the quantity or consistency of the respiratory tract mucus or a systemic weakening of the immune system. The data are inadequate to formulate any hypothesis regarding the mechanism for diminished host resistance or to postulate whether hexachloroethane in the environment might lower the resistance of humans to respiratory infections.

Neurological Effects. No studies were located regarding neurological effects in humans after exposure to hexachloroethane. Inhalation, oral, and dermal exposure of animals to moderate or high doses (260 ppm, 5,900 ppm, 375 mg/kg/day, 750 mg/kg/day) resulted in hyperactivity, tremors, fasciculation of the facial muscles, ataxia, convulsions, and/or prostration (Fowler 1969b; NTP 1977, 1989; Southcott 1951; Weeks et al. 1979). Reduced motor activity has also been observed following oral exposure of pregnant rats (167 mg/kg/day) (Shimizu et al. 1992). Inhalation exposure of rats to 260 ppm for 6 weeks did not have any effect on spontaneous motor activity or shock avoidance behavior (Weeks et al. 1979).

Ataxia, tremors, and prostration in sheep given hexachloroethane (170 or 338 mg/kg) for a liver fluke infection were successfully ameliorated with calcium as calcium borogluconate. This suggests that the neurological action of hexachloroethane may be the result of interference with the availability of calcium

within excitable cells. This mechanism would explain the transient nature of the hexachloroethane neurotoxicity and is compatible with the low affinity that hexachloroethane shows for brain tissue (Fowler 1969b).

There were no effects at any of the doses tested on the histopathology of the brain for any duration or route of exposure (Gorzinski et al. 1985; NTP 1977, 1989; Weeks et al. 1979). This observation is consistent with tissue distribution studies which indicate that hexachloroethane has no particular affinity for the brain tissues (Fowler 1969b).

Based on the available data, the concentrations of hexachloroethane at hazardous waste sites are unlikely to reach levels that would elicit a neurological response in humans. However, there have not been any comprehensive studies of brain or nerve function after exposure to hexachloroethane.

Reproductive Effects. No studies of reproductive effects in humans were located. In animals, hexachloroethane adversely affected fertility following oral exposure, but no effects were reported following inhalation exposure (Weeks et al. 1979). The absence of quantitative data on reproductive parameters, as well as evaluation of parameters that are pertinent to the assessment of reproductive risk, precludes any meaningful determination of the potential for hexachloroethane to cause adverse effects on human reproduction.

Developmental Effects. No studies were located regarding the developmental effects of hexachloroethane in humans. Fetal body weights were reduced, late-gestation resorptions were increased, and the degree of ossification was reduced in offspring from pregnant rats treated orally with hexachloroethane at 500 mg/kg/day on gestation days 7-17 (Shimizu et al. 1992) or gestation days 6-16 (Weeks et al. 1979). The 500-mg/kg/day dose also caused a significant decrease in maternal body weights. No effect on the number of fetuses with anomalies was observed, and no fetal or maternal effects were observed at lower doses. These studies suggest that in the absence of maternal effects, developmental effects in humans are unlikely.

Genotoxic Effects. No studies were located regarding the genotoxic effects of hexachloroethane in humans after inhalation, oral, or dermal exposure. *In vitro* studies of hexachloroethane using microbial, fungal, and rodent cell assays are summarized in Table 2-4. Tests of prokaryotic cell systems failed to detect gene mutation (Haworth et al. 1983; Roldan-Arjona et al. 1991; Simmon and Kauhanen 1978;

TABLE 2-4. Genotoxicity of Hexachloroethane *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	Haworth et al. 1983
S. typhimurium (TA98, TA100, TA1535, TA1537, TA1538)	Gene mutation	–	–	Weeks et al. 1979
S. typhimurium (BA13)	Gene mutation	–	–	Roldan-Arijona et al. 1991
S. typhimurium (TA98, TA100, TA1535, TA1537, TA1538)	Gene mutation	–	–	Simmon and Kauhanen 1978
S. typhimurium (TA1535/psk1002)	DNA damage	–	–	Nakamura et al. 1987
Eukaryotic organisms:				
Fungi:				
Saccharomyces cerevisiae D_4	Gene mutation	–	–	Weeks et al. 1979
S. cerevisiae D_3	DNA damage/repair	–	–	Simmon and Kauhanen 1978
S. cerevisiae	Gene mutation	–	–	Bronzetti et al. 1989
Aspergillus nidulans diploid strains P1	Chromosomal abberation	–	Not tested	Crebelli et al. 1988
Mammalian cells:				
Chinese hamster ovary	Chromosomal aberration	–	–	Galloway et al. 1987
Chinese hamster ovary	Sister chromatid exchange	+	–	Galloway et al. 1987
Mouse (Balb/C-3T3)	Cell transformation	Not tested	–	Tu et al. 1985

– = negative result; + = positive result; DNA = deoxyribonucleic acid

Weeks et al. 1979) or DNA damage (Nakamura et al. 1987) following hexachloroethane treatment. Similar results were reported for eukaryotic cells. Hexachloroethane did not cause gene mutation in cells harvested from the stationary growth phase (Bronzetti et al. 1989) or DNA damage in yeast (*Succharomyces cerevisiue*) (Simmon and Kauhanen 1978), chromosomal aberrations in fungi *(Aspergillus nidulans)* (Crebelli et al. 1988), chromosomal aberrations in Chinese hamster ovary cells (Galloway et al. 1987), or cell transformations in mouse cells (Tu et al. 1985). Hexachloroethane did cause sister chromatid exchanges in Chinese hamster ovary cells in the presence of activation; however, the overall importance of this response is reduced since these effects occurred at doses that were cytotoxic (e.g., induced cell cycle delay) (Galloway et al. 1987). Similarly, hexachloroethane induced a significant ($p<0.01$) increase of gene conversion in *S. cerevisiae* cells harvested from the logarithmic growth phase. Similar effects were not seen in stationary growth phase cells, both with and without metabolic activation (Bronzetti et al. 1989). Because cells of this sort contain a high level of cytochrome P-450, it is plausible that the positive responses were due to metabolites rather than the parent compound.

Cancer. Only one report was located regarding an association between hexachloroethane and cancer in humans (Selden et al. 1989). In this study a liver tumor was found in an adult male who had used a product containing hexachloroethane at work for 6 years. However, under the conditions of use, the hexachloroethane reacted to form hexachlorobenzene and other chlorinated compounds which were as likely, or more likely, to have contributed to the tumorigenesis as the hexachloroethane.

Lifetime exposure of rats to hexachloroethane resulted in renal carcinomas and adenomas in Fischer-344 male rats (NTP 1989). The incidence of adenomas was l/50 for the controls, 2/50 for animals at a dose of 10 mg/kg/day, and 4/50 for animals at a dose of 20 mg/kg/day. In the animals from the high-dose group, there were also 3/50 renal carcinomas. The number of tumors (carcinomas and adenomas) was significantly greater in exposed rats than in both controls and historical controls using the Fisher Exact Test (NTP 1989). No tumors were seen in the female rats.

In an earlier study, there were renal tubular cell adenomas in 5/50 Osborne-Mendel rats receiving doses of 212 mg/kg/day but no tumors in 49 animals receiving 423 mg/kg/day or in 20 vehicle control rats (Weisburger 1977). Despite the lack of tumors, there was a high incidence of nephropathy (18-66%) in exposed male and female rats.

2. HEALTH EFFECTS

The male rat kidney is susceptible to the induction of tumors because of α2μ-globulin excretion (Borghoff 1993; Olson et al. 1990). This protein is not made by female rats, other laboratory species, or humans in significant quantities, but large amounts are synthesized and excreted by male rats. EPA (1991a) has concluded that renal tumors in male rats that are associated with α2μ-globulin should not be used in assessing the potential for any chemical to cause renal tumors in humans. Compounds that bind to α2μ-globulin lead to the formation of hyaline droplets in the kidney causing cell damage and regenerative hyperplasia (Borghoff 1993; Olson et al. 1990).

A statistically significant increase in hepatocellular carcinomas was seen in male and female mice that were dosed with 590 and 1,179 mg/kg/day hexachloroethane in corn oil by gavage for 78 continuous weeks (Weisburger 1977). The incidence of tumors in the exposed mice was greater than that in controls on the basis of both the Fisher Exact test and the Cochran-Armitage test. There were no hepatic tumors in male or female rats with chronic exposure to doses of 10423 mg/kg/day (NTP 1977, 1989; Weisburger 1977).

Hexachloroethane may function as a promoter rather than an inducer of hepatic tumors. When male rats were given a single dose of 497 mg/kg hexachloroethane followed by daily treatment with a known promotor (phenobarbital) for 7 weeks, there was no increase in the number of GGT+ foci in the liver (Milman et al. 1988). GGT+ foci are markers for precarcinogenic cell changes. When a single dose of a known initiator dimethylnitrosamine was followed by 7 weeks of dosing with 497 mg/kg/day hexachloroethane, the number of GGT+ foci was four times the number seen with a single dose of dimethylnitrosamine in the absence of hexachloroethane treatment. The fact that hexachloroethane does not appear to be mutagenic in short-term tests of genetic toxicity and that it has a low tendency to bind to DNA (Lattanzi et al. 1988) is consistent with classifying it as a promotor rather than a direct acting carcinogen.

NTP determined that there was clear evidence of carcinogenicity in male rats based on the increased incidence of renal neoplasms and no evidence of carcinogenic activity in female rats (NTP 1989). The EPA classified hexachloroethane as a possible human carcinogen (Group C). The slope factor calculated by EPA is 1.4×10^{-2} $(mg/kg/day)^{-1}$ for both the oral and inhalation routes of exposure (IRIS 1995). IARC has determined that hexachloroethane is not classifiable as to human carcinogenicity (Group 3).

2. HEALTH EFFECTS

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NCR 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 samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to hexachloroethane are discussed in Section 2.6.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical 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 not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by hexachloroethane are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the

biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8, "Populations That Are Unusually Susceptible."

2.6.1 Biomarkers Used to Identify or Quantify Exposure to Hexachloroethane

Based on results from animal studies, urinary and fecal excretion of hexachloroethane can be used to identify recent exposures (Fowler 1969b; Jondorf et al. 1957). Recent exposure to hexachloroethane can also be determined by measuring the amount of hexachloroethane in the blood, but this would be a more invasive procedure than analyzing urine or fecal matter (Fowler 1969b). The concentrations of hexachloroethane in fecal matter were higher than those in urine in sheep for the 24-hour period following exposure (Fowler 1969b). Thus, fecal matter might be better for analysis than urine.

Both hexachloroethane and its lipophilic metabolites can distribute to body fat. Only hexachloroethane can be used to confirm compound exposure by way of a fat biopsy, since some of its metabolites are also produced from other chlorinated hydrocarbons or are present as contaminants in the environment. Based on one worker occupationally exposed to hexachloroethane, Selden et al. (1993) estimated that the plasma half-life in humans was several days, but less than one week. A clearance half-life in rats of 2.5 days was reported for hexachloroethane absorbed from the diet (Gorzinski et al. 1985). Therefore, similar to measurement of hexachloroethane in blood, urine, and feces, hexachloroethane in body fat is representative of current exposures rather than exposures that occurred weeks or months before testing.

2.6.2 Biomarkers Used to Characterize Effects Caused by Hexachloroethane

No information was located regarding adverse health effects of hexachloroethane in humans; therefore, no judgment can be made concerning possible biomarkers of exposure in humans.

Animal data suggest that renal and liver effects may occur in humans exposed to high doses of hexachloroethane. Kidney and liver effects are not specific to hexachloroethane. Lesions ofthe kidney (nephropathy, linear mineralization, and hyperplasia) were reported at 10 mg/kg/day or greater in male rats (NTP 1989). Urinalysis also revealed granular and cellular casts in rats exposed to hexachloroethane (47 mg/kg/day or greater) for 13 weeks (NTP 1989). Because other compounds cause similar effects and because some of these effects are unique to male rats, they are not valuable as biomarkers for human hexachloroethane exposure.

The liver is also a target of hexachloroethane toxicity, but the effects are not as severe as for the kidneys. For the most part, effects in rats were confined to swelling of hepatocytes which occurred at dose levels of 15 mg/kg/day or greater following oral exposure (Gorzinski et al. 1985). Certain biochemical parameters that are commonly associated with chemically-induced liver damage were assessed in rabbits exposed to hexachloroethane by gavage for 12 days (Weeks et al. 1979) and in sheep given a single dose of 500 mg/kg (Fowler 1969b). There were no statistically significant alterations in serum enzymes (alanine amino transferase, aspartate aminotransferase, and alkaline phosphatase) or bilirubin in rabbits, but serum values were increased as compared to controls (Weeks et al. 1979). Plasma sorbitol dehydrogenase, glutamate dehydrogenase, and omithine carbamoyl transferase concentrations increased in sheep (Fowler 1969b). Because these effects can also be caused by other chemicals, they cannot be considered specific biomarkers for hexachloroethane.

2.7 INTERACTIONS WITH OTHER SUBSTANCES

Hexachloroethane is commonly used by the military for pyrotechnics and smoke screens. Hexachloroethane-containing, smoke-producing devices combine hexachloroethaue with zinc oxide (Gordon et al. 1991). Small quantities of other materials such as calcium silicide can also be present. Hexachloroethane is generally about 44-47% of the reaction mixture. When a smoke pot or grenade is ignited, hexachloroethane reacts with zinc oxide to produce zinc chloride. Only small amounts (0.3-5%) of hexachloroethane remain. Other products of the reaction are tetrachloroethylene, carbon tetrachloride, phosgene, and hexachlorobenzene (Gordon et al. 1991). The environmental residues from smoke generation vary with the configuration of the device and its position when it ignites (upright or prone) (Schaeffer et al. 1988).

A number of studies of the toxicity of zinc oxide/hexachloroethane smoke have been conducted (Brown et al. 1990; Karlsson et al. 1986; Mans et al. 1983). These studies demonstrate that smoke exposure results in pulmonary inflammation and irritation. When male Porton Wistar rats were exposed to hexachloroethane/zinc oxide smoke for 60 minutes, the lungs showed pulmonary edema, alveolitis, and areas of macrophage infiltration 3 days later. At 14 days, there was interstitial fibrosis and macrophage infiltration. At 28 days, increased fibrosis and macrophage infiltration were noted. However, these same symptoms occurred when the animals inhaled zinc chloride; there was no apparent synergism between the zinc chloride and residual hexachloroethane (Brown et al. 1990; Richard et al. 1989). This is consistent

with the fact that smoke contains little hexachloroethane and the observation that acute exposure to 260 ppm hexachloroethane had no effects on the lungs of rats (Weeks et al. 1979).

Environmental agents that influence microsomal reactions will influence hexachloroethane toxicity. The production of tetrachloroethene as a metabolite is increased by agents like phenobarbital that induce certain cytochrome P-450 isozymes (Nastainczyk et al. 1982a; Thompson et al. 1984). Exposure to food material or other xenobiotics that influence the availability of mixed function oxidase enzymes and/or cofactors will change the reaction rate and end products of hexachloroethane metabolism and thus influence its toxicity.

No other studies of interactions of hexachloroethane with other chemicals were identified in the published literature. However, the primary metabolites of hexachloroethane (tetrachloroethene and pentachloroethane) are themselves toxic and would be expected to exacerbate hexachloroethane toxicity if they were present in a mixture with hexachloroethane. Concurrent carbon tetrachloride exposure would also be expected to exacerbate hexachloroethane toxicity. Both hexachloroethane and carbon tetrachloride are processed by microsomes to generate free radicals, and carbon tetrachloride also forms endogenous hexachloroethane in the liver (Fowler 1969a).

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to hexachloroethane than will most persons exposed to the same level of hexachloroethane in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters may result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting end-product metabolites). For these reasons we expeet 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.”

2. HEALTH EFFECTS

No studies were located regarding populations that are unusually susceptible to hexachloroethane toxicity. Because the kidney and liver are the primary target tissues, individuals with compromised liver or kidney function would have an increased risk from exposure. Susceptibility to pulmonary infections could be increased by exposure to hexachloroetbane vapors and, thus, individuals that suffer from chronic respiratory problems could also have an increased risk from hexachloroethane exposure.

The risk to overweight individuals consuming a high fat diet is likely to be greater than that for lean individuals. Excess deposits of body fat increase physiological exposure durations due to the affinity of the adipose tissue for hexachloroethane. Hexachloroethane collects in the adipose deposits during exposure and is released slowly to circulatory fluids after the exposure has ceased. Individuals consuming a high fat diet are likely to absorb increased quantities of hexachloroethane when exposure occurs through the oral route; absorption from a lipid matrix is favored over absorption from an aqueous medium.

2.9 METHODS FOR REDUCING TOXIC EFFECTS

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

2.9.1 Reducing Peak Absorption Following Exposure

Humans can be exposed to hexachloroethane by inhalation, ingestion, or skin contact. There are no specific treatments for hexachloroethane overexposure. However, treatments available for halogenated hydrocarbons may be useful.

When individuals have been exposed to vapors of hexachloroethane, they should be moved-to fresh air. Additional treatment with oxygen may be beneficial.

If hexachloroethane has been ingested, treatments designed to minimize absorption of halogenated hydrocarbons are appropriate. If the victim is alert, can swallow, and appears to have a good gag reflex, water (l-2 glasses) may be administered after ingestion of small amounts of hexachloroethane (Bronstein

and Currance 1988; Stutz and Ulin 1992). Because many hydrocarbons may cause spontaneous vomiting, induced emesis is not recommended since it may result in aspiration of gastric contents. If large amounts of hexachloroethane have been ingested, gastric lavage may be useful if performed soon after exposure. Activated charcoal can be administered to bind hexachloroethane in the gastrointestinal tract and minimize absorption. Activated charcoal can be combined with cathartics to speed fecal excretion. Because hexachloroethane is lipid soluble, the administration of a fat-based substance or whole milk are not recommended as they may cause increased absorption.

In order to minimize absorption through the skin, all contaminated clothing should be removed and the skin should be washed with mild soap and water (Bronstein and Currance 1988; Stutz and Ulin 1992). In cases where the compound has been splashed into the eyes, irrigation with large amounts of water for 15-30 minutes has been recommended.

2.9.2 Reducing Body Burden

Hexachloroethane that is absorbed appears rapidly in the systemic circulation. It is distributed widely throughout the body, with the highest concentration in fat and kidney and the lowest in the muscle (Fowler 1969b; Gorzinski et al. 1985). There are no specific treatments available for reducing the body burden if hexachloroethane is absorbed. Because hexachloroethane causes renal injury, hemodialysis may be useful to reduce the plasma levels of hexachloroethane should renal failure occur in exposed persons.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

No information is available on the adverse health effects of hexachloroethane in humans. Animal studies revealed that hexachloroethane primarily causes liver and kidney toxicity. Effects on the nervous system and lungs have also been reported. The mechanism by which these effects are mediated is not well characterized. Reductive metabolism by cytochrome P-450 and production of a free radical intermediate have been suggested.as factors in hexachloroethane-induced hepatotoxicity (Nastainczyk et-al. 1982a; Thompson et al. 1984; Town and Leibman 1984). Accordingly, one possible approach may be to reduce free radical injury. To that end, oral administration of N-acetylcysteine can be used as a means of reducing free radical injury. Also, oral administration of vitamin E and vitamin C may be of value since they are free radical scavengers.

The mechanism of renal toxicity is not clear. Because the spectrum of kidney lesions observed in male rats (Gorzinski et al. 1985; NTP 1989) resembled those for $\alpha_{2\mu}$-globulin nephropathy, hexachloroethaneinduced kidney lesions may, in part, be due to hexachloroethane binding to this protein. On the other hand, renal toxicity was observed in female rats and did not present the same sequence of lesions. This suggests the effects in males may not be totally due to $\alpha 2\mu$-globulin. Specific methods to minimize renal toxicity, based on mechanism of action, cannot be proposed at this time.

2.10 ADEQUACY OF THE DATABASE

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

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

2.10.1 Existing Information on Health Effects of Hexachloroethane

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

2. HEALTH EFFECTS

As indicated by Figure 2-4, data available on the health effects of hexachloroethane in humans is extremely sparse. A study (Selden et al. 1994) of 11 workers who wore protective equipment while being exposed to hexachloroethane for 5 weeks showed no respiratory, hematological, liver or kidney effects at plasma levels of 7.3 ±6 μg/L (Selden et al. 1993). Because of skin irritation, the investigators suggest that the principal exposure route may have been dermal, although the dermal effects may also have been a result of trauma from the protective equipment. Because of the protective equipment it is not possible to determine exposure levels. There is one case study of a liver tumor in an individual who had used a hexachloroethane-containing degassing agent in his work for a period of 6 years (Selden et al 1989). However, during use the hexachloroethane reacted to form hexachlorobenzene and small amounts of other chlorinated compounds. Exposure to hexachloroethane was minimal compared to exposure to the reaction products.

There are more data available concerning the effects of hexachloroethane in animals, particularly for exposure by the inhalation and oral routes. These studies identify the liver and kidney as target organs for hexachloroethane. There have been no studies of chronic exposure by the inhalation route. Although there are some data on neurological and immunological effects, there have been no well-designed, comprehensive studies of these systems. This is also true for reproductive and developmental effects. The data are limited and there has been no comprehensive multigeneration study of reproductive processes and only two studies of developmental effects.

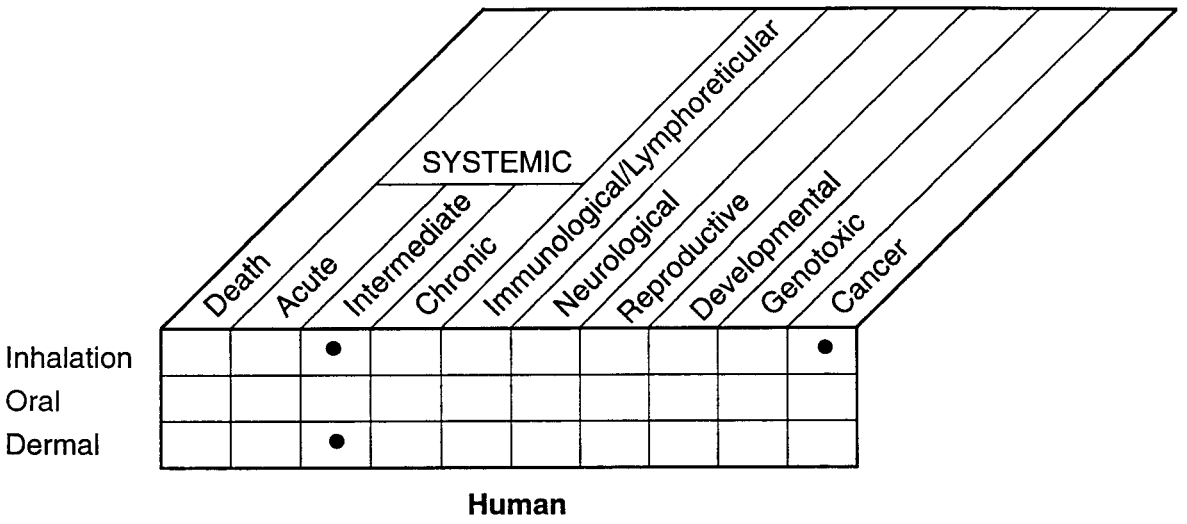
In vivo testing for mutagenic potential has also not been conducted. The carcinogenic potential for hexachloroethane has only been evaluated for the oral route.

Data for the dermal route are limited to an LD_{50} study and data on dermal/ocular effects. A theoretical estimation of dermal transport of hexachloroethane indicated that absorption is low.

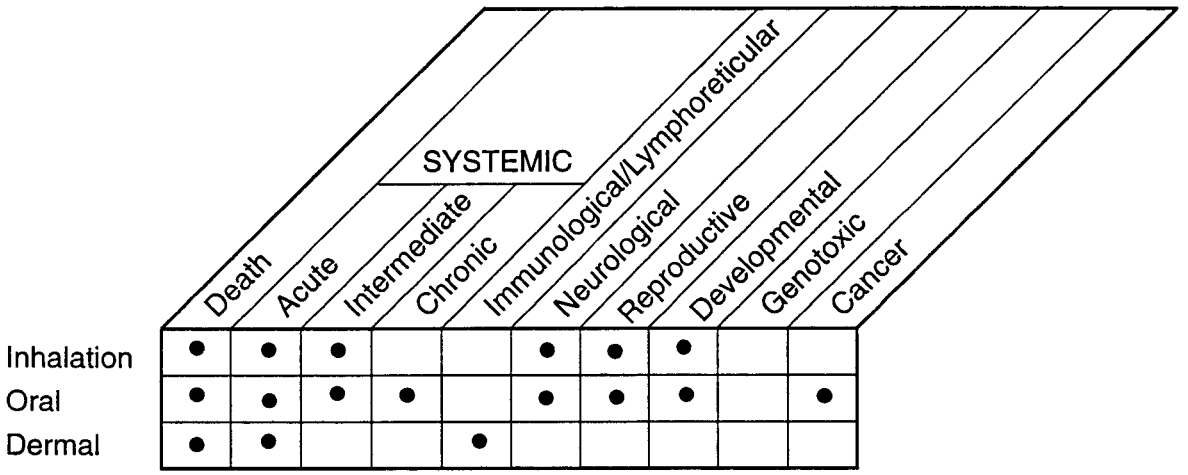
2.10.2 Identification of Data Needs

Acute-Duration Exposure. No studies were located on the effects of hexachloroethane in humans after acute exposure by any route. Acute inhalation exposure in animals caused respiratory effects, staggered gait, and reduced body weight gain, but these effects occurred at a concentration that was lethal (Weeks et al. 1979). There were no histological changes or changes in organ weights in the liver and kidneys after inhalation exposure to hexachloroethane (Weeks et al. 1979). Reproductive and

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



Human



Animal

● Existing Studies

developmental effects were not observed in rats exposed to hexachloroethane on gestation days 6-16 (Weeks et al. 1979). Tremors were observed at the high concentration in pregnant rats, and an acute inhalation MRL of 6 ppm was calculated based on the NOAEL for neurological effects observed in the developmental study (Weeks et al. 1979).

Acute oral exposure of animals was associated with tubular nephrosis and nephrocalcinosis in the kidneys (Weeks et al. 1979), hepatocellular degeneration, coagulation necrosis, hemorrhage in the liver (Weeks et al. 1979), and elevated liver enzymes in the serum (Fowler 1969b). An MRL of 1 mg/kg was derived for acute oral exposures based on a NOAEL for the absence of liver damage in rabbits (Weeks et al. 1979). Reduced body weight gain and neurological effects (tremor, decreased motor activity) have also been observed following acute oral exposure to hexachloroethane (Shimizu et al. 1992; Weeks et al. 1979). Increased fetal resorptions, decreases in fetal body weight, and an increase in skeletal anomalies have also been observed in rats treated orally with hexachloroethane during organogenesis (Shimizu et al. 1992; Weeks et al. 1979). As the dose following inhalation exposure is limited by the amount of hexachloroethane vapor that can be formed at standard temperatures (Weeks et al. 1979), oral studies may be more useful. Additional oral exposure studies to delineate the threshold for acute liver effects and to help clarify the indices that are predictive of liver damage would be especially useful. Studies of kidney effects in female rats and other laboratory animals using the oral route would also be helpful to differentiate between lesions associated with α2μglobulin and those produced by other mechanisms. Hexachloroethane caused reversible cornea1 injury in rabbits following ocular contact, but contact with the skin for 24 hours resulted in no dermal effects (Weeks et al. 1979). The physical properties of hexachloroethane suggest that absorption across human skin would be limited (Fiserova-Bergerova et al. 1990). Therefore, unless dermal absorption studies indicate that this prediction is incorrect, there is no need for additional studies of acute dermal toxicity.

Intermediate-Duration Exposure. A study (Selden et al. 1994) of 11 workers who wore protective equipment while-being exposed to hexachloroethane for 5 weeks showed no respiratory, hematological, liver, or kidney effects at plasma levels of 7.3 f 6 ug/L (Selden et al. 1993). Because mild dermal effects were noted, the principal exposure route may have been dermal. The dermal effects may also have been a result of trauma from the protective equipment. Because of the protective equipment, it is not possible to determine exposure levels.

2. HEALTH EFFECTS

Inhalation of 260 ppm hexachloroethane, but not 48 ppm, was associated with an increased incidence of a respiratory tract mycoplasma infection that was endemic in the rat colony (Weeks et al. 1979). Ocular irritation, reduced body weight gain, and tremors were also noted in rats at 260 ppm. Reduced body weight gain in guinea pigs and ocular irritation and tremors in dogs were noted at 260 ppm, but not 48 ppm (Weeks et al. 1979). Based on the 48 ppm concentration for the lack of neurological effects in rats (Weeks et al. 1979), an intermediate inhalation MRL of 6 ppm was calculated.

Following intermediate oral exposure to hexachloroethane, decreased body weight gain has been observed in rats and mice (NTP 1977) and kidney effects, including increased kidney weight, tubular atrophy and hypertrophy, and hyaline droplet formation (Gorzinski et al. 1985; NTP 1989), and post-treatment hyperactivity and convulsions have been observed in rats (NTP 1989). Following intermediate exposure, liver enlargement has also been observed in rats treated with hexachloroethane (Gorzinski et al. 1985; Milman et al. 1988; Story et al. 1986). Enlargement of hepatocytes in male rats following oral exposures to 15 mg/kg/day hexachloroethane, but not 1 mg/kg/day (Gorzinski et al. 1985), was used as the basis of an MRL of 0.01 mg/kg/day for intermediate-duration oral exposures. Because there is potential for persons living near hazardous waste sites to be exposed to hexachloroethane through contaminated drinking water, additional studies of liver damage in male and female rats and kidney damage in female rats by the oral route would be useful. Hexachloroethane appears to be less bioavailable in an aqueous medium than in a lipid medium (Weeks et al. 1979).

In an intermediate-duration study, dermal treatment of rats did not result in skin sensitization (Weeks et al. 1979). Additional intermediate-duration dermal studies were not available. The physical properties of hexachloroethane suggest that absorption across human skin would be limited (Fiserova-Bergerova et al. 1990). Therefore, unless dermal absorption studies indicate that this prediction is incorrect, there is no need for additional studies of intermediate dermal toxicity.

Chronic-Duration Exposure and Cancer. No studies were located in humans following chronicduration exposure to.hexachloroethane for any exposure route. No chronic animal studies were conducted using the inhalation route of exposure. In oral studies with rats, the kidney was identified as a primary target organ in males and females (NTP 1989). The kidney damage in male rats was the result of hyaline droplet nephropathy and, accordingly, was not suitable as the basis for an oral MRL. In contrast to acuteand intermediate-duration oral exposure, liver toxicity was not evident in rats following chronic oral exposure. There were no studies of chronic dermal exposure to hexachloroethane.

2. HEALTH EFFECTS

Studies using the inhalation route might be useful to determine the potential human health risk in populations that may be occupationally exposed to hexachloroethane vapors for long periods. Additional chronic oral studies may be useful to help further clarify the dose-response relationships and better characterize thresholds. Studies by the dermal route would not be useful until the rate and extent of absorption have been better characterized.

The carcinogenic potential of hexachloroethane has not been evaluated following chronic inhalation or dermal exposure. Hexachloroethane increased the incidence of renal tumors in male rats (NTP 1989) following chronic oral exposure. However, these tumors were associated with renal hyaline droplets and, thus, are unique to male rats. Although kidney damage was present in female rats after lifetime exposures to 80 and 160 ppm hexachloroethane, there was no increase in renal tumors. Liver lesions and liver tumors were found in mice following long-term oral exposure (NTP 1977).

A bioassay in mice (oral route) using current good laboratory practices may be useful in order to clarify whether or not hexachloroethane is a hepatic carcinogen. The suspected hepatic carcinogenicity of the hexachloroethane metabolites pentachloroethane and tetrachloroethene strengthens the justification for additional investigations of the carcinogenic potential of hexachloroethane. Studies of the mechanism of hexachloroethane carcinogenicity would also be useful to determine if effects observed in mice are applicable to humans. To further characterize risk to persons occupationally exposed to hexachloroethane, inhalation studies of the carcinogenic potential of hexachloroethane may be useful. The concentrations used in the inhalation studies would be limited to about 670-700 ppm, the saturated vapor concentration at 20°C (Weeks et al. 1979). The physical properties of hexachloroethane suggest that absorption across human skin would be limited (Fiserova-Bergerova et al. 1990). Therefore, unless dermal absorption studies indicate that this prediction is incorrect, there is no need for carcinogenic studies following dermal exposure.

Genotoxicity. Hexachloroethane did not exhibit mutagenic activity *in vitro* in prokaryotic cells (Haworth et al. 1983: Nakamura et al. 1987; Roldan-Arjona et al. 1991; Simmon and Kauhanen 1978; Weeks et al. 1979) or in eukaryotic cells (Galloway et al. 1987; Tu et al. 1985). In *vivo* data from animals, such as the results of a micronucleus assay, would be of value.

2. HEALTH EFFECTS

The mutagenic potential of hexachloroethane has not been evaluated in humans. Because hexachloroethane has been detected at hazardous waste sites, it would be useful to evaluate the potential for hexachloroethane to induce mutagenic effects in human cells (e.g., peripheral lymphocytes).

Reproductive Toxicity. The effects of hexachloroethane on human reproduction have not been evaluated for any route of exposure. Data were available from animal studies using the inhalation and oral routes of exposure, but there were no data from studies using the dermal route. Following inhalation exposure to 260 ppm hexachloroethane, signs of maternal toxicity (decreased weight gain and clinical signs of neurotoxicity) were noted, but there was no evidence of embryotoxicity or fetotoxicity (Weeks et al. 1979). Reduced fertility, as characterized by reduced gestation indices and the number of live fetuses, occurred in pregnant rats following oral exposure during gestation (Weeks et al. 1979). Increased late-stage fetal resorptions were observed in rats treated orally with hexachloroethane at doses that resulted in maternal body weight gain 35% less than the controls (Shimizu et al. 1992). A comprehensive onegeneration study focusing on a broad range of predictive parameters regarding reproductive success would be useful. Because inhalation exposure is limited by the properties of hexachloroethane, higher doses could be achieved using oral exposure. If an oral study is negative for reproductive effects at high doses, an inhalation study may not be necessary.

Developmental Toxicity. No studies on developmental effects in humans using any route of exposure were located. Rats were exposed to hexachloroethane during gestation using both the oral and inhalation routes and there were no soft tissue or skeletal effects in the pups (Weeks et al. 1979). Decreased fetal body weights and delayed ossification were observed in offspring of rats treated orally with hexachloroethane at doses that resulted in maternal body weight gain 35% less than the controls (Shimizu et al. 1992). Malformations were not observed in either control or hexachloroethane-treated fetuses. Confirmation of a lack of developmental effects in a second species following oral exposure would be useful. The inclusion of a developmental component to the suggested one-generation study would also provide useful data. As inhalation and dermal exposure are limited because of the physical properties of hexachloroethane that prevent exposure to high concentrations of vapor and that limit dermal absorption, studies by these routes of exposure may not be necessary.

2. HEALTH EFFECTS

Immunotoxicity. No studies are available for any exposure route on the potential for hexachloroethane to cause immunotoxic effects in humans. Data in animals are limited to studies that evaluated lymphoid organs (e.g., spleen and thymus) as part of a comprehensive histopathological examination following oral and inhalation exposure to hexachloroethane (Gorzinski et al. 1985; Weeks et al. 1979). Adverse effects were not reported for these organs.

Effects on immune function have not been evaluated in animals following any route of exposure. There was an increased frequency of pulmonary tract infections in animals following inhalation and oral exposures (Weeks et al. 1979). Responses of this sort may be due, in part, to compromised immune functions. Studies in animals, using a battery of *in vitro* and short-term *in vivo* studies of immunotoxicity following inhalation and oral exposure, may enhance our overall understanding of the effects of hexachloroethane on disease resistance.

Neurotoxicity. No information is available on neurotoxic effects of hexachloroethane in humans following any route of exposure. Acute inhalation exposure in rats caused staggering gait after exposure to high concentrations (5,900 ppm) (Weeks et al. 1979). The usefulness of this data is limited since this concentration was lethal. Tremors have been reported at 260 ppm but not 48 ppm following inhalation exposure of rats in a developmental study and in a study of 6-weeks duration (Weeks et al. 1979). The lack of tremors at 48 ppm in the developmental study serves as the basis for the acute inhalation MRL, and the lack of tremors at 48 ppm in the 6-week study serves as the basis for the intermediate inhalation MRL. One study that evaluated spontaneous motor activity and avoidance behavior in rats during 6 weeks of exposure to 260 ppm hexachloroethane vapors did not reveal adverse effects of hexachloroethane on these neurobehavioral functions (Weeks et al. 1979).

Acute oral doses (500 mg/kg) given to healthy sheep caused tremors of the facial muscles (Fowler 1969b); several liver-fluke-infected sheep experienced prostration with even lower doses (170 or 338 mg/kg) (Southcott 1951). Treatment of sheep with calcium relieved the clinical signs of neurotoxicity, suggesting that cellular availability of calcium ion may be related to the neuromuscular symptoms noted (Southcott 1951). Therefore, mechanistic studies of neuromuscular impulse transmission and cognitive function in animals would be useful. These neurological studies should examine the effects of different concentrations of hexachloroethane in several species.

2. HEALTH EFFECTS

Postgavage hyperactivity was noted in rats with an oral dose of 375 mg/kg/day (NTP 1989) and tremors occurred following a dose of 500 mg/kg/day (Weeks et al. 1979). Other available animal data are limited to the findings of histological examination of the brain and other nervous tissue following inhalation, oral, and dermal exposures (Gorzenski et al. 1985; NTP 1977, 1989; Weeks et al. 1979). No lesions were reported.

Epidemiological and Human Dosimetry Studies. No epidemiological studies of hexachloroethane exposure were identified. Epidemiological studies including endpoints such as immunotoxicity, neurotoxicity, liver enzymes, and kidney function in individuals who handle hexachloroethane in the production of military pyrotechnics and smoke-producing devices would be useful. Epidemiological studies of exposure to the hexachloroethane-generated smoke might be of little value because most of the hexachloroethane is consumed in the smoke-generating reaction. Epidemiological studies will be of greatest value when mixtures of other chlorinated hydrocarbons are not present with hexachloroethane in the occupational environment because there are similarities in metabolism and possible synergistic demands on microsomal enzymes.

Biomarkers of Exposure and Effect

Exposure. Hexachloroethane has been measured in the plasma of occupationally exposed humans (Selden et al. 1993). Because these workers were wearing protective equipment, it is not possible to relate exposure concentrations to plasma levels of hexachloroethane. Based on animal data, exposure to hexachloroethane can be determined by analyzing blood, urine, and fecal matter for the presence of hexachloroethane within 24 hours of exposure (Fowler 1969b). After 24 hours, most of the hexachloroethane has been metabolized to compounds that are not unique to hexachloroethane metabolism. Additional studies of biomarkers of exposure in animals are not needed at this time.

Effect. No data on biomarkers of effect in humans were identified. In animals, kidney and liver effects have been reported (Fowler 1969b; Gorzinski et al. 1985; NTP 1989; Weeks et al. 1979). Hyaline casts were present in urine but they can be caused by other chemicals as well as hexachloroethane (Borghoff 1993). Biochemical tests (e.g., blood urea nitrogen) to detect renal damage were negative (Weeks et al. 1979). However, the usual battery of urinary tests (i.e., glucose, protein, enzymes, creatinine, electrolytes, and urine output) has not been applied. Additional studies that monitor these indices would be useful and

could demonstrate whether or not hexachloroethane has an effect on glomerular filtration and/or tubular resorption.

In rabbits, biochemical indices commonly used to assess liver damage (e.g., aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, and protein) were elevated but within normal ranges (Weeks et al. 1979). On the other hand, plasma enzyme concentrations (sorbitol dehydrogenase, glutamate dehydrogenase, and ornithine carbamoyl transferase) increased in sheep (Fowler 1969b). Because people living near hazardous waste sites are likely to be exposed for long periods, it may be useful to evaluate these parameters in hexachloroethane-exposed animals to determine if there is consistent elevation of these biomarkers of liver damage with chronic exposure.

Absorption, Distribution, Metabolism, and Excretion. There are no mechanistic or quantitative studies of hexachloroethane absorption from the lungs or across the gastrointestinal tract or skin. However, absorption does occur following oral exposure based on the appearances of hexachloroethane and its metabolites in blood, urine, and exhaled air (Fowler 1969b; Gorzinski et al. 1985; Jondorf et al. 1957; Mitoma et al. 1985; Nolan and Karbowski 1978). The observation of toxic effects following inhalation exposure and dermal exposure (Weeks et al. 1979) indicates that hexachloroethane is absorbed through the respiratory tract. Quantitative studies that examine the absorption of hexachloroethane following inhalation and dermal exposure would be useful.

Oral kinetic studies in rats indicate that hexachloroethane distributes preferentially to the adipose tissue (Gorzinski et al. 1985; Nolan and Karbowski 1978). Relatively high concentrations are also found in male rat kidneys (Nolan and Karbowski 1978). Moderate concentrations of hexachloroethane are found in the liver, kidneys of female rats, and blood, and small amounts in muscle, lungs, and brain (Gorzinski et al. 1985).

The metabolism of hexachloroethane is relatively well defined and involves dehalogenation followed by oxidation (Fowler 1969b; Gorzinski et al. 1985; Jondorf et al. 1957; Nastainczyk et al. 1982a, 1982b; Nolan and Karbowski 1978; Salmon et al. 1981; Thompson et al. 1984; Town and Leibman 1984). Urinary by-products such as trichloroacetic acid and trichloroethanol are consistent with metabolism (Jondorf et al. 1975; Mitoma et al. 1985) and do not require additional evaluation at this time. A small portion of the exhaled radioactive label from hexachloroethane is exhaled as carbon dioxide (Mitoma et al. 1985). A more thorough investigation of the other hexachloroethane metabolites removed from the body

in exhaled air would be useful, along with quantification of biliary excretion and identification of the biliary metabolites.

Comparative Toxicokinetics. There are differences in the effects of hexachloroethane on different species and between sexes. Male rats are particularly susceptible to kidney damage following hexachloroethane exposure because of the binding of hexachloroethane to α2μ-globulin (NTP 1989). However, nephrotoxicity is also seen in female rats and in mice and rabbits (Gorzinski et al. 1985; NTP 1977, 1989; Weeks et al. 1979) and should be examined in greater detail to identify the mechanisms for the lesions observed. Additional information on hepatic lesions in species other than the rat and mouse would be useful in evaluating the risk to humans for both noncarcinogenic and carcinogenic effects from hexachloroethane exposure.

An increased risk of respiratory infections was seen in rats exposed to 260 ppm hexachloroethane for 6 weeks (Weeks et al. 1979). A similar occurrence was not noted in dogs or guinea pigs. Additional information on the susceptibility of species other than the rat to similar infections would be useful in determining the significance of this observation to human health. Comparative studies of the infection incidence should await elucidation of the mechanism for this effect.

Dogs were more susceptible to neurotoxicity from hexachloroethane vapors than rats, and both species were more sensitive than guinea pigs and quail (Weeks et al. 1979). Pregnant rats were more sensitive to tremors than nonpregnant rats (Weeks et al. 1979). Once the mechanism of neurotoxicity has been determined, the advisability of examining differences in species response can be evaluated.

Methods for Reducing Toxic Effects. There are no compound-specific methods for reducing the toxic effects of hexachloroethane. The mitigation procedures suggested (Bronstein and Currance 1988; Stutz and Ulin 1992) are applicable to exposure to volatile chlorinated hydrocarbons as a class and are not specific for hexachloroethane.

Neither the mechanism of absorption nor the mechanism of distribution for hexachloroethane has been established. There are indications that free radical reactions may be responsible for some of the toxic effects of hexachloroethane in the liver (Town and Leibman 1984), but the data are not conclusive. When additional data on absorption, distribution and mechanism are available, compound-specific studies on methods for mitigation of toxic effects can be designed.

2.10.3 On-going Studies

No on-going studies of the toxicity of hexachloroethane were identified.

3. CHEMICAL AND PHYSICAL INFORMATION

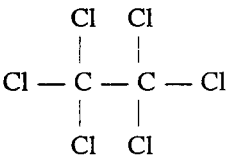
3.1 CHEMICAL IDENTITY

Table 3-l lists common synonyms, trade names, and other pertinent identification information for hexachloroethane.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 3-2 lists important physical and chemical properties of hexachloroethane.

TABLE 3-1. Chemical Identity of Hexachloroethane

Characteristic	Information	Reference
Chemical name	Hexachloroethane	HSDB 1995
Synonym(s)	Perchloroethane; carbon hexachloride; 1,1,1,2,2,2-hexachloroethane; hexachloroethylene; HCE; and others	ACGIH 1991; Gordon et al. 1991; HSDB 1995
Registered trade name(s)	Avlothane; Distokal; Distopan; Distopin; Egitol; Falkitol; Fasciolin; Mottenhexe; Phenohep	IARC 1979
Chemical formula	C_2Cl_6	HSDB 1995
Chemical structure		Howard 1989
Identification numbers:		
CAS registry	67-72-1	HSDB 1995
NIOSH RTECS	KI 4025000	HSDB 1995
EPA hazardous waste	U131	
OHM/TADS	No data	HSDB 1995
DOT/UN/NA/IMCO shipping	NA 9037	HSDB 1995
HSDB	2033	HSDB 1995
NCI	C04604	HSDB 1995

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 Chemical Substances

TABLE 3-2. Physical and Chemical Properties of Hexachloroethane

Property	Information	Reference
Molecular weight	236.74	Weast 1986
Color	Colorless	HSDB 1995
Physical state	Solid	HSDB 1995
Melting point	Sublimes	ACGIH 1991; Budavari et al. 1989
Boiling point	186.8°C (triple point)	Budavari et al. 1989
Density:		
at 20°C	2.091 g/mL	Weast 1986
Odor	Camphoraceous	Budavari et al. 1989
Odor threshold:		
Water	0.010 mg/L	Amoore and Hautala 1983
Air	0.15 ppm (1.5 mg/m^3)	Amoore and Hautala 1983
Solubility:		
Water at 22°C	50 mg/L	Verschueren 1983
Water at 25°C	14 mg/L	Spanggord et al. 1985
Organic solvent(s)	Soluble in alcohol, benzene, chloroform, ether, oils	Budavari et al. 1989
Partition coefficients:		
Log K_{ow}	3.82	Howard 1989
	3.34	Callahan et al. 1979
Log K_{oc}	4.3	Mabey et al. 1982
Vapor pressure:		
at 20°C	0.4 mmHg	Verschueren 1983
at 30°C	0.8 mmHg	Verschueren 1983
Henry's law constant:		
at 25°C:	2.237×10^{-2} atm·m^3/mole	Yaws et al. 1991
	6,100 L-torr/mol (8.0×10^{-3} atm·m^3/mol	Spanggord et al. 1985
	2.8×10^{-3} atm·m^3/mole	Howard 1989
Autoignition temperature	Nonflammable	IARC 1979
Flashpoint	Nonflammable	IARC 1979
Flammability limits	Nonflammable	IARC 1979
Conversion factors	1 ppm = 9.68 mg/m^3	Verschueren 1983
	1 mg/m^3 = 0.10 ppm	
Explosive limits	No data	

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Hexachloroethane is usually produced commercially by the chlorination of tetrachloroethylene in the presence of ferric chloride at l00-140°C. It may also be obtained as a co-product in the production of tetrachloroethylene by pyrolysis of carbon tetrachloride at 800-900°C or by passing a mixture of ethylene and chlorine over charcoal at 300-350°C. Small amounts of high purity hexachloroethane may be prepared by the action of chlorine on barium carbide (Dacre et al. 1979; Gordon et al. 1991; IARC 1979; Santodonato et al. 1985).

Hexachloroethane is not currently produced for commercial distribution in the United States. It is a by-product in the industrial chlorination of saturated and unsaturated C, hydrocarbons by several U.S. companies, including Dow Chemical, PPG Industries, and Occidental Petroleum Corporation. The product may be used captively in-house or recycled in feedstock to produce tetrachloroethylene or carbon tetrachloride. Estimates of current production volumes were not located (Gordon et al. 1991; Santodonato et al. 1985; TRI93 1995).

Hexachloroethane was produced in the United States for commercial distribution from 1921 to 1967. Hummel Chemical Company, Inc., South Plainfield, New Jersey, and the Nease Chemical Company (location not provided) produced hexachloroethane at one time. In the 1970s there were’14 producers and distributors of hexachloroethane in the United States. The producers reported that the product was not distributed; it was used in-house or recycled. The distributors were importers of hexachloroethane (see Section 4.2). Estimated production volume of hexachloroethane in 1977 was about 2-20 million pounds (Gordon et al. 1991; HSDB 1995; IARC 1979; Kitchens et al. 1978; Santodonato et al. 1985; SRI 1977).

Table 4-l lists information on U.S. companies that reported the manufacture and processingof hexachloroethane in 1993 (TRI93 1995). The Toxics Release Inventory (TRI) data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Table 4-1. Facilities That Manufacture or Process Hexachloroethane

State[a]	Number of facilities	Range of maximum amounts on site in thousands of pounds [b]	Activities and uses [c]
CA	2	0-100	1, 5, 6, 7, 11
IL	3	0-10000	2, 3, 4, 8, 9
IN	1	1-10	11
KS	1	100-1000	1, 5
LA	5	1-100	1, 3, 5, 6, 7, 11, 13
MI	1	10-100	7
MO	1	1-10	11
MS	1	10-100	12
NJ	2	10-100	2, 4, 9, 10
OH	3	1-1000	2, 3, 8, 9, 11
TX	4	0-100	1, 5, 6, 10, 12

Source: TRI93 1995

[a] Post office state abbreviations used
[b] Data in TRI are maximum amounts on site at each facility
[c] Activities/Uses:

1. Produce
2. Import
3. For on-site use/processing
4. For sale/distribution
5. As a by-product
6. As an impurity
7. As a reactant
8. As a formulation component
9. As a product component
10. For repackaging only
11. As a chemical processing aid
12. As a manufacturing aid
13. Ancillary or other uses

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.2 IMPORT/EXPORT

Quantities of hexachloroethane imported into the United States increased from the 1970s to the 1980s. Imports were about 1.6 million pounds (730,000 kg) in 1976 (mainly from France and the United Kingdom), more than 2 million pounds in 1977, approximately 2.5 million pounds (1,124,000 kg) in 1985, and approximately 4.5 million pounds in 1986. In 1978, all hexachloroethane distributed commercially in the United States was imported by Rhodia, Inc., Monmouth, New Jersey. Current information on importers and import quantities was not located (ACGIH 1991; Gordon et al. 1991; HSDB 1995; IARC 1979; Kitchens et al. 1978; Santodonato et al. 1985).

No data were located on export quantities, but exports are not expected, since hexachloroethane is not produced for commercial distribution.

4.3 USE

Prior to 1979, 50% of the hexachloroethane distributed was used by the military for hexachloroethane smoke pots and grenades, 30-40% for the manufacture of degassing pellets to force air bubbles out of molten ore in aluminum foundries, and 10-20% as an anthelminthic to control sheep flukes. It has also been used as a moth repellent, a plasticizer for cellulose esters in place of camphor, a polymer additive, a component of fungicidal and insecticidal formulations, in the formulation of extreme pressure lubricants, and in the manufacture of fire extinguishing fluids. Currently, large amounts of hexachloroethane are still used by the military for hexachloroethane smoke and pyrotechnic devices. Hexachloroethane is probably not used any longer as an anthelminthic, since approval of the Food and Drug Administration (FDA) for this use of hexachloroethane was withdrawn in 1971 (ACGIH 1991; HSDB 1995; IARC 1979; Kitchens et al. 1978; Santodonato et al. 1985).

Pine Bluff Arsenal in Arkansas was reported to be the major facility manufacturing smoke and pyrotechnic devices containing hexachloroethane for the military (Gordon et al. 1991). It was estimated that between 1966 and 1977 this facility used an average of 192,802 pounds of hexachloroethane annually (Kitchens et al. 1978). Data on quantities of hexachloroethane currently consumed for military and civilian uses were not located.

4.4 DISPOSAL

Hexachloroethane and waste containing hexachloroethane are classified as hazardous wastes by EPA. Generators of waste containing this contaminant must conform to EPA regulations for treatment, storage, and disposal (see Chapter 7). Rotary kiln or fluidized bed incineration methods are acceptable disposal methods for these wastes. Underground injection may also be used (HSDB 1995).

According to the TRI, approximately 92,755 pounds of hexachloroethane were transferred to landfills and/or treatment/disposal facilities by industrial manufacturers or processors in 1993 (see Section 5.2) (TRI93 1995). No hexachloroethane was discharged to publicly owned treatment works (POTW), but 1,081 pounds were disposed of by underground injection. These data do not include disposal of hexachloroethane-containing wastes by the military.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Hexachloroethane is an industrial chemical which is not known to occur naturally. It is not produced for commercial distribution in the United States, but is imported for use in military smoke and pyrotechnic devices and as an intermediate in the organic chemicals industry. It is released to the environment from these uses, primarily to the atmosphere.

Hexachloroethane is relatively persistent in the environment. It volatilizes readily from water to the atmosphere, with a half-life of less than one day in some waters. Hexachloroethane may also leach through soil to groundwater. Neither hydrolysis nor photolysis are expected to be important removal processes, but hexachloroethane may be reduced in aquatic systems in the presence of specific agents. Bioconcentration in fish has been reported, but biomagnification through the food chain is unlikely. Biodegradation may contribute to hexachloroethane removal from ambient waters, but there is conflicting evidence regarding the significance of this fate process for hexachloroethane.

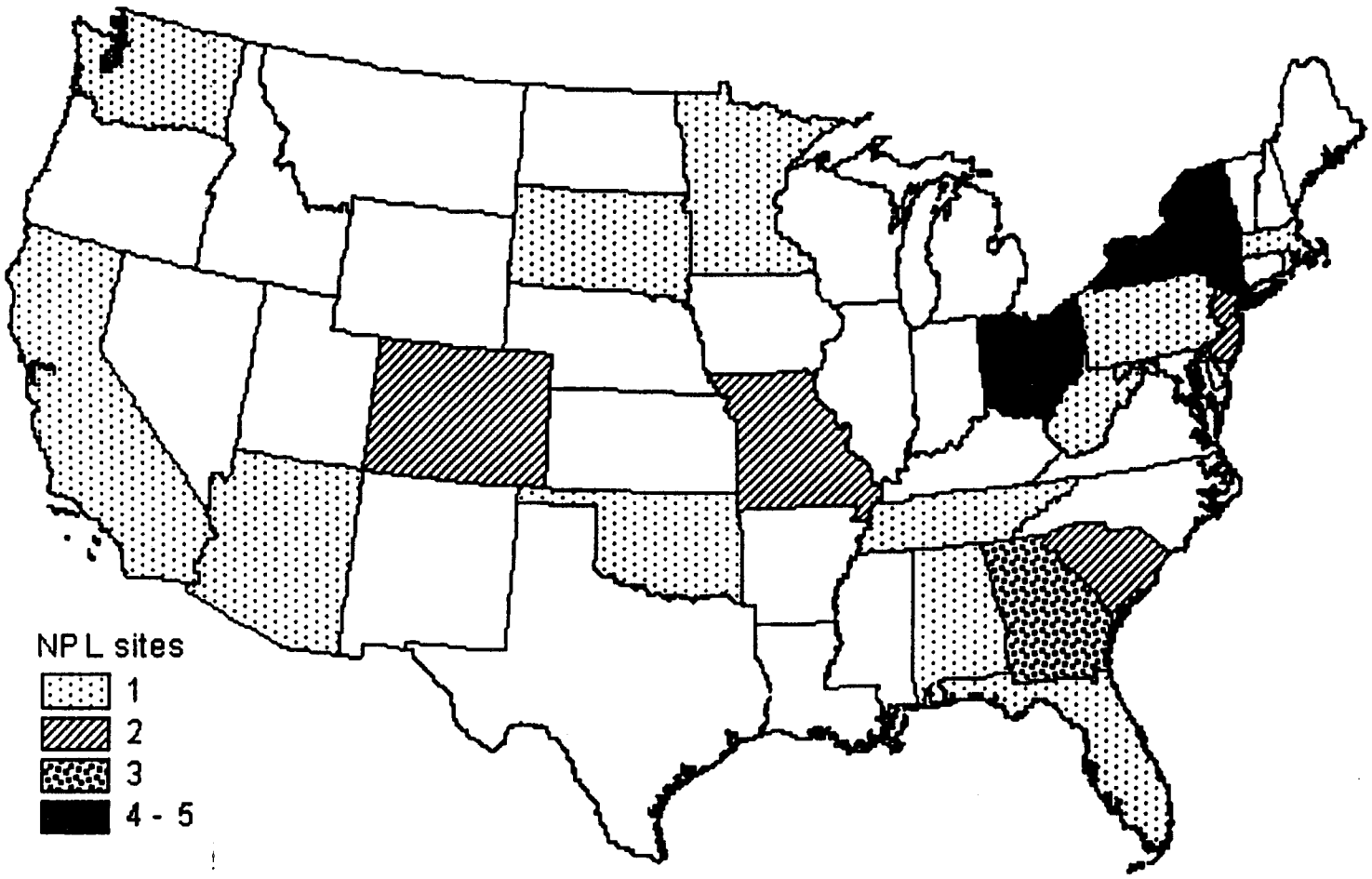
Hexachloroethane has been detected at low (ng/m^3) levels in the atmosphere and occasionally in drinking water systems. It is rarely detected in surface waters or biota, and has not been reported in ambient soil, sediments, or commercial food products.

Hexachloroethane has been identified in at least 45 of the 1,416 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 1995). However, the number of sites evaluated for hexachloroethane is not known. The frequency of these sites within the United States can be seen in Figure 5-l.

5.2 RELEASES TO THE ENVIRONMENT

Hexachloroethane is not known to occur naturally (IARC 1979). Most of the hexachloroethane entering environmental media is from releases during manufacture and use of the compound in smoke-producing and pyrotechnic devices and as an intermediate in the production of several other products (Gordon et al.

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



*Derived from HAZDAT 1996

1991). Treatment and disposal of hexachloroethane-containing wastes also contributes to the environmental concentrations of this chemical.

Recent data reported to the TRI indicate that environmental releases of hexachloroethane from manufacture and industrial processing total about 51,088 pounds (TRI93 1995). However, these data do not include releases from the manufacture and use of military smoke and pyrotechnic devices, since federal facilities are not required to report releases to the TRI.

5.2.1 Air

The major sources of hexachloroethane releases to air are from its production and use in the organic chemical industry. As shown in Table 5-1, an estimated total of 49,716 pounds of hexachloroethane, amounting to about 97% of the total industrial environmental release, was discharged to the air from manufacturing and processing facilities in the United States in 1993 (TRI93 1995). The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Releases may also occur from the use of this chemical in smoke and pyrotechnic devices. Hexachloroethane content of the smoke devices is about 44.5-46% of the total solid material. The smoke device burns, producing smoke which is mainly zinc chloride, but contains some hexachloroethane. It was estimated that about 0.3-5% of the mass of the reagents in the device is released to air as hexachloroethane in the smoke, assuming a 70% burn efficiency (Katz et al. 1980; Novak et al. 1987). On this basis, it was estimated that during 1982-1984, a maximum of about 6,683 kg (14,700 pounds) of hexachloroethane was released to the atmosphere at Fort Irwin, California, a major military training facility (Novak et al. 1987). Hexachloroethane in smoke (aerosol) was measured in a wind tunnel at concentrations ranging from 0.64-1.26 mg/m^3 (average 0.89 mg/m3) (Cataldo et al. 1989).

Hexachloroethane may also be released to air during combustion and incineration of chlorinated wastes, from hazardous waste sites, and in small amounts during chlorination of sewage effluent prior to discharge and chlorination of raw water during drinking water treatment (Gordon et al. 1991; Howard 1989).

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Hexachloroethane

State[b]	Number of facilities	Range of reported amounts released in pounds per year[a]						
		Air	Water	Land	Underground injection	Total environment[c]	POTW transfer	Off-site waste transfer
CA	2	0-5	0	0	0	0-5	0	0-1110
IL	3	0-7729	0	0	0	0-7729	0	0
IN	1	36005	0	0	0	36005	0	0
KS	1	10	0	0	1081	1091	0	645
LA	5	0-390	0-1	0	0	0-390	0	0-760
MI	1	2	0	0	0	2	0	41000
MO	1	500	0	0	0	500	0	0
MS	1	0	0	0	0	0	0	0
NJ	2	1-10	0	0	0	1-10	0	0
OH	3	0-738	0	0	0	0-738	0	0-46532
TX	4	0-110	0-290	0	0	0-400	0	0-2198

Source: TRI93 1995

[a] Data in TRI are maximum amounts released by each facility.
[b] Post office state abbreviations used
[c] The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility

POTW = publicly owned treatment works

5.2.2 Water

Releases of hexachloroethane to water may occur during production, processing, and disposal of the chemical. In the past, reported concentrations of hexachloroethane in manufacturing effluents and waste waters from industrial and POTW facilities ranged from 0.9 to 1,405.6 μg/L (Gordon et al. 1991). It is estimated that prior to 1979, about 117,000 gallons (443,000 liters) of waste water per day were released from the Pine Bluff Arsenal (Gordon et al. 1991). The average hexachloroethane concentration in the waste water was 168 mg/L, resulting in the release of about 165 pounds of hexachloroethane per day. Following installation of pollution abatement devices at the arsenal in 1979, hexachloroethane was not detected in several samples of waste water from the facility.

Hexachloroethane was detectable in 2.0% of 1,253 effluent samples reported in the storage and retrieval (STORET) database maintained by EPA from 1980 to 1982 (Staples et al. 1985). The median concentration for all samples, including nondetects, was <10 μg/L.

As shown in Table 5-1, an estimated total of 291 pounds of hexachloroethane, amounting to about 0.6% of the total industrial environmental release, was discharged to surface water from manufacturing and processing facilities in the United States in 1993 (TRI93 1995). An additional 1,081 pounds (2% of the total) was discharged to underground injection. The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

5.2.3 Soil

Hexachloroethane may be released to soil by industrial sources and from hazardous waste sites at which this chemical has been detected. It may be also be released to soil from the use of hexachloroethane smoke and pyrotechnic devices via deposition of airborne particulates (see Section 5.3.1) (Cataldo et al. 1989) or ejection of partially reacted compounds from the canister by the force of combustion (Schaeffer et al. 1988). Average hexachloroethane concentrations in deposited residues from several smoke pots, using different bum configurations, ranged from 1,900 to 54,700 mg/kg (Schaeffer et al. 1988). The authors estimated that the soil load of hexachloroethane from a single upright canister (smoke pot) could reach 6,054 mg hexachloroethane per kg soil in a semicircular area with a 5 m radius downwind of the burn.

5. POTENTIAL FOR HUMAN EXPOSURE

As shown in Table 5-1, no hexachloroethane was discharged to land from manufacturing and processing facilities in the United States in 1993 (TRI93 1995). The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Hexachloroethane released to water or soil may volatilize into air or adsorb onto soil and sediments. Volatilization appears to be the major removal mechanism for hexachloroethane in surface waters (Howard 1989). The volatilization rate from aquatic systems depends on specific conditions, including adsorption to sediments, temperature, agitation, and air flow rate. Volatilization is expected to be rapid from turbulent shallow water, with a half-life of about 70 hours in a 2 m deep water body (Spanggord et al. 1985). A volatilization half-life of 15 hours for hexachloroethane in a model river 1 m deep, flowing 1 m/set with a wind speed of 3 m/sec was calculated (Howard 1989). Measured half-lives of 40.7 and 45 minutes for hexachloroethane volatilization from dilute solutions at 25°C in a beaker 6.5 cm deep, stirred at 200 rpm, were reported (Dilling 1977; Dilling et al. 1975). Removal of 90% of the hexachloroethane required more than 120 minutes (Dilling et al. 1975). The relationship of these laboratory data to volatilization rates from natural waters is not clear (Callahan et al. 1979).

Atmospheric transport of hexachloroethane may occur, based on the stability of the compound in air (Class and Ballschmitter 1986; Singh et al. 1979). Hexachloroethane is expected to diffuse slowly into the stratosphere, with a half-life of about 30 years (Howard 1989). Deposition of hexachloroethane from air to water, plants, and soil has been reported (Cataldo et al. 1989).

Based on calculated soil adsorption factors (log K_{OC} of 2.24, 2.98, and 4.3), hexachloroethane is expected to have medium to low mobility in soil (Howard 1989). Thus, leaching to groundwater could occur. Results of studies with low organic carbon (0.02%) soil material indicate that sorption to aquifer materials retards hexachloroethane migration in groundwater (Curtis et al. 1986). In aquatic environments, moderate to slight adsorption to suspended solids and partitioning to sediments is likely (Howard 1989).

Bioconcentration of hexachloroethane is expected to occur to a moderate degree. A measured bioconcentration factor (BCF) of 139 was reported in bluegills (EPA 1980a). After adjustment of the BCF

for lipid content, the weighted average BCF calculated for the edible portion of freshwater and estuarine aquatic organisms was 86.9. However, hexachloroethane is rapidly metabolized in bluegill, with an estimated half-life of <l day (Howard 1989). The measured BCFs in rainbow trout were 510 and 1,200 at low (0.32 ng/L) and high (7.1 ng/L) exposure levels, respectively (Oliver and Niimi 1983). A BCF of 245 was calculated for hexachloroethane, based on the octanol water partition coefficient (K_{ow}) and the molar solubility in octanol (Banerjee and Baughman 1991). Since hexachloroethane is rarely detected in ambient waters (see Section 5.4.2) and appears to be rapidly metabolized, significant bioaccumulation or biomagnification in the food chain is not expected.

5.3.2 Transformation and Degradation

5.3.2.1 Air

Hexachloroethane is quite stable in air. It is not expected to react with hydroxyl radicals or ozone in the atmosphere or to photodegrade in the troposphere (Callahan et al. 1979; Howard 1989). Degradation by photolysis may occur in the stratosphere.

5.3.2.2 Water

Hexachloroethane is also relatively resistant to degradation in the aquatic environment. No hydrolysis of hexachloroethane in water was observed after 11 days at 85°C at 3 pH levels (3,7, and 11) (Ellington et al. 1987). However, hexachloroethane may be reduced in aquatic systems in the presence of sulfide and ferrous ions (Kriegman-King and Reinhard 1991). The transformation rate of hexachloroethane to tetrachloroethylene under simulated groundwater conditions at 50°C was evaluated without ferrous or sulfide ions, with minerals (biotite and vermiculite) providing ferrous ions, and with minerals and sulfide ions. Reported half-lives for hexachloroethane were 365 days for hexachloroethane alone, 57-190 days with minerals present, and 0.45-0.65 days in the presence of both minerals and sulfide.

Photolysis of hexachloroethane in water has been reported, but degradation to carbon dioxide occurred at a temperature of 90-95°C (Knoevenagel and Himmelreich 1976). The relevance of these results to ambient conditions are uncertain.

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Biodegradation may be an important removal process in ambient waters, but there is conflicting evidence regarding the significance of this fate process for hexachloroethane. In the presence of a mixed bacterial culture, hexachloroethane had no effect on the growth rate of the culture, was recovered quantitatively after incubation with the culture for 8 days, and hexachloroethane could not be used as a sole source of carbon after incubation for more than 6 weeks (Mrsny et al. 1978). The authors concluded that hexachloroethane was apparently not toxic to or metabolized by bacteria, and used hexachloroethane as an internal standard to monitor the bacterial degradation of crude oil. Results reported in another biodegradation screening study indicated that <30% degradation of hexachloroethane occurred after a 2-week incubation period in activated sludge under aerobic conditions (Howard 1989). However, other studies indicate that considerable biodegradation of hexachloroethane may occur. In a 7-day staticscreening- flask test at 25°C under aerobic conditions, 100% loss of hexachloroethane was reported, with no loss attributable to volatilization (Tabak et al. 1981). Other studies reported significant losses (38% loss in sterile control) resulting from volatilization under aerobic conditions (Spanggord et al. 1985). Under anaerobic conditions, loss of 90% of hexachloroethane was reported from pond water in 18 days, while no loss from sterile pond water was observed (Spanggord et al. 1985).

A half-life of about 40 days was reported for hexachloroethane in an unconfined sand aquifer (Criddle et al. 1986). Laboratory studies with wastewater microflora cultures and aquifer material provided evidence for microbial reduction of hexachloroethane to tetrachloroethylene under aerobic conditions in this aquifer system (Criddle et al. 1986). In anaerobic groundwater, hexachloroethane reduction to pentachloroethane and tetrachloroethylene was found to occur only when the water was not poisoned with mercury chloride (Roberts et al. 1994). Pentachloroethane reduction to tetrachloroethylene occurred at a similar rate in both poisoned and unpoisoned water. From these results, Roberts et al. (1994) suggested that the reduction of hexachloroethane to tetrachloroethylene occurred via pentachloroethane. The first step, the production of pentachloroethane, was microbially mediated, while the production of tetrachloroethylene from pentachloroethane was an abiotic process.

5.3.2.3 Sedimentand Soil

Hexachloroethane may biodegrade in soil, but abiotic degradation processes are not expected to be significant. Hexachloroethane is biotransformed in soil under both aerobic and anaerobic conditions, but proceeds more rapidly in anaerobic soils (Spanggord et al. 1985). Loss of 99% of hexachloroethane was

reported after 4 days of incubation anaerobically and after 4 weeks under aerobic conditions. Volatilization contributed to aerobic losses.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Since hexachloroethane is quite stable in air (see Section 5.3.2.1), it may tend to accumulate in the atmosphere. Based on limited data, typical background concentrations in the northern hemisphere were reported to range from 5 to 7 ppt (48-68 ng/m^3) (Singh et al. 1979). Data reported on the National Ambient Volatile Organic Compounds Database indicate that hexachloroethane was detected at an average concentration of 0.001 ppb (9.7 ng/m^3) in ambient air in the United States, based on 69 measurements (Shah and Heyerdahl 1988). The detected concentrations were in remote and rural areas (average 3.2 ppt (31 ng/m^3)), rather than in urban and industrial locations (Howard 1989; Shah and Heyerdahl 1988). Hexachloroethane was detected in the atmosphere in Portland, Oregon at concentrations ranging from 2.8 to 4.1 ng/m^3 (Ligocki et al. 1985) and in air over the Atlantic Ocean at an average concentration of 0.5 ppt (4.8 ng/m^3) in the northern hemisphere and 0.34 ppt (3.3 ng/m^3) in the southern hemisphere (Class and Ballschmiter 1986).

5.4.2 Water

Hexachloroethane is rarely detected in ambient water. Data reported in the STORET database indicate that the chemical was detectable in only 1 of 882 (0.1%) ambient water samples (Staples et al. 1985). The median concentration for all samples was <l0 µg/L. Hexachloroethane was detected in Lake Ontario water, but not in Lake Erie (International Joint Commission 1983). The concentration of hexachloroethane in Lake Ontario was reported at 0.02 ng/L (Oliver and Niimi 1983). It was also identified in leachate from a hazardous waste site in Niagara Falls, New York (Hauser and Bromberg 1982). Hexachloroethane was not detected in 86 samples of urban runoff from 15 cities analyzed for the National Urban Runoff Program (Cole et al. 1984).

Hexachloroethane has occasionally been reported in drinking water in the United States. Hexachloroethane was detected in drinking water from Cincinnati, Ohio and three water supplies in the New Orleans area at concentrations ranging from 0.03 to 4.3 µg/L (Keith et al. 1976); in the municipal

water supply in Evansville, Indiana (Kleopfer and Fairless 1972); and in 4 of 16 samples of Philadelphia drinking water (Suffet et al. 1980). It was also reported in 19 of 31 samples from private wells within 1 mile of a toxic waste dump in Hardeman County, Tennessee, at a median concentration of 0.26 μg/L (Clark et al. 1982).

5.4.3 Sediment and Soil

Data regarding hexachloroethane concentrations in soil or sediments are sparse. Hexachloroethane was not detectable in any of 356 sediment analyses reported in the STORET database (Staples et al. 1985). The median detection limit was 500 μkg.

5.4.4 Other Environmental Media

Hexachloroethane has not generally been reported in foods. Hexachloroethane was not detected in 116 fish samples reported in the STORET database (Staples et al. 1985), nor was it detected in 28 fish samples from 14 Lake Michigan tributaries (Camanzo et al. 1987). However, hexachloroethane was detected in 10 of 10 Lake Ontario rainbow trout at an average concentration of 0.03 ng/g (Oliver and Niimi 1983). No information was located regarding hexachloroethane in other foods.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure of the general population to hexachloroethane is expected to be low. Analysis of blood from 13 individuals, using a method with a detection limit of 0.028 ppb, did not identify hexachloroethane in any sample (Ashley et al. 1992). The chemical has not been frequently detected in any environmental medium. Ambient air is the most likely source of hexachloroethane for exposed individuals in the general population (Howard 1989). Due to the stability of hexachloroethane (see Section 5.3.2.1), it may remain in the atmosphere for extended periods.

Workers in industrial facilities manufacturing or using hexachloroethane as an intermediate in the manufacture of other products may be exposed to the chemical by inhalation or dermal absorption. In addition, military or civilian personnel working with smoke or pyrotechnic devices may be exposed. Based on information collected for the National Occupational Exposure Survey, the National Institute for

5. POTENTIAL FOR HUMAN EXPOSURE

Occupational Safety and Health (NIOSH) estimates that 8,515 workers were potentially exposed to hexachloroethane (NOES 1991).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Residents or workers near hazardous waste sites containing hexachloroetbane wastes or military training areas using smoke or pyrotechnic devices containing hexachloroethane may be exposed to higher than ambient levels.

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 hexachloroethane is available. Where adequate information is not available, ATSDR, in conjunction with the 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 hexachloroethane.

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

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of hexachloroethane are sufficiently wellcharacterized to allow estimation of its environmental fate (see Table 3-2) (EPA 1991a; Spanggord et al. 1985; Verschueren 1983; Weast 1986). On this basis, it does not appear that further research in this area is required at this time.

5. POTENTIAL FOR HUMAN EXPOSURE

Production, Import/Export, Use, Release, and Disposal. Hexachloroethane is not manufactured for commercial distribution in the United States (Gordon et al. 1991; IARC 1979; Santodonato et al. 1985). However, current production as a by-product and import information are not available. Current uses of this chemical and the amounts consumed by each use, including military uses, were not located. This information would be helpful in assessing potential exposure to workers and the general population. The amount of the chemical disposed of by industrial facilities was reported to EPA (TRI93 1995), but information on quantities of hexachloroethane-containing wastes disposed of by military facilities was not located. Rotary kiln or fluidized bed incineration are acceptable methods for disposal of waste containing hexachloroethane (HSDB 1995).

According to the Emergency Planning and Community Right-to-Know Act of 1986,42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1993, became available in 1995. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. The environmental fate of hexachloroethane has been characterized (Gordon et al. 1991; Howard 1989; Spanggord et al. 1985). The chemical is relatively unreactive and degrades slowly in environmental media. In groundwater the half-life of hexachloroethane may range from 365 days to less than a day when minerals and sulfide are present (Kriegman-King and Reinhard 1991). Because hexachloroethane appears to remain in the atmosphere for long periods (half-life not available) and may migrate to groundwater (Callahan et al. 1979; Curtis et al. 1986; Howard 1989), additional studies of adsorption and intermediate partitioning might be useful to assess the potential for emission and transport of this chemical from hazardous waste sites.

Bioavailability from Environmental Media. No data are available on the absorption of hexachloroethane following inhalation or dermal contact. However, systemic toxicity (though minimal) was observed and suggests that some absorption can occur by these routes (Weeks et al. 1979). Data from animal studies that used gavage in oil for exposure to hexachloroethane indicate that the compound can also be absorbed following oral exposure (Fowler 1969b; Mitoma et al. 1985). No data were located regarding the absorption of hexachloroethane from air, water, soil, or plant material. Hexachloroethane exists in the air almost entirely as a vapor and there are no known processes that would impair its bioavailability from this medium. Since there is some adsorption of hexachloroethane to suspended solids and sediments in water, bioavailability from water may be limited (Howard 1989). On the other hand,

hexachloroethane is not expected to adsorb to soil significantly (Howard 1989). Additional studies would be useful to determine the extent of bioavailability of hexachloroethane from contaminated air and drinking water near hazardous waste sites.

Food Chain Bioaccumulation. Hexachloroethane in water may bioconcentrate in aquatic organisms to a moderate degree (Howard 1989), with a BCF of 139 reported in bluegills (EPA 1980a). Due to its rapid metabolism (Howard 1989) and the low incidence of hexachloroethane in ambient waters (Staples et al. 1985), food chain bioaccumulation is unlikely. Additional research in this area does not appear to be necessary at this time.

Exposure Levels in Environmental Media. Hexachloroethane has been detected in smoke generated from smoke-producing devices during military training exercises (Katz et al. 1980; Novak et al. 1987). In the Northern hemisphere and the United States, hexachloroethane has been detected in air at concentrations in the parts per trillion (Howard 1989; Ligocki et al. 1985; Shah and Heyerdahl l988; Singh et al. 1979). In water, concentrations in the parts per billion are occasionally detected (Cole et al. 1984; International Joint Commission 1983; Staples et al. 1985). Hexachloroethane was not found in any of 356 sediment samples (Staples et al. 1985). Additional information regarding hexachloroethane in soil or sediments was not available. Since this chemical is not prevalent in the environment, monitoring of ambient environmental media does not appear to be required at this time. However, monitoring of workplace air, and environmental media at hazardous waste sites and military training areas at which hexachloroethane has been detected would help to determine potential sources of exposure.

Reliable monitoring data for the levels of hexachloroethane in contaminated media at hazardous waste sites are needed so that the information obtained on levels of hexachloroethane in the environment can be used in combination with the known body burden of hexachloroethane to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Hexachloroethane has not been detected in human tissuesas a result of exposure to this chemical from environmental media. Biological monitoring data were not located for populations surrounding hazardous waste sites. Hexachloroethane has been detected in the plasma of workers at concentrations of 7.3 ± 6 μg/L, despite the use of protective equipment including disposable overalls and compressed-air-fed visors or full-facepiece masks with filters (Selden et al. 1994). Because of

protective equipment, exposure concentrations could not be related to plasma levels of hexachloroethane. This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries. No exposure registries for hexachloroethane 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 exposure to this substance.

5.7.2 On-going Studies

No on-going studies regarding human exposure were located.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring hexachloroethane, its metabolites, and other biomarkers of exposure and effect to hexachloroethane. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and 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 modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

Analytical methods are available for measuring hexachloroethane in blood, urine, feces, liver, kidney, and adipose tissues, and breath (Ashley et al. 1992; Fowler 1969a; Nolan and Karbowski 1978; Pellizzari et al. 1985a, 1985b). Gas chromatography (GC) is the usual method for detecting and measuring hexachloroethane in biological materials (Pellizzari et al. 1985a, 1985b). The chromatograph separates complex mixtures of organics and allows individual compounds to be identified and quantified by a detector. An electron capture detector (ECD) is often used to identify hexachloroethane (Fowler 1969b; Nolan and Karbowski 1978). A mass spectrometer (MS) coupled to the GC column provides unequivocal identification.

Blood samples for analysis of volatile organic compounds (VOCs) including hexachloroethane should be collected into containers from which VOC contamination has been reduced (Ashley et al. 1992). Potassium oxalate/sodium fluoride is the recommended anti-coagulant. Blood samples should be placed on ice or refrigerated shortly after collection, and Ashley et al. (1992) recommend that analysis for VOCs be completed within 14 days.

Hexachloroethane can be detected in tissues at levels as low as 0.001 μg/g (Nolan and Karbowski 1978) and recoveries range from 50 to 130%. Prior to analysis, hexachloroethane must be separated from the

biological sample matrix and prepared for introduction into the analytical instrument. Separation may be effected by purging with an inert gas (helium), and trapping on an adsorbent cartridge (Tenax GC®, followed by thermal desorption directly to the GC column (Pellizzari et al. 1985a, 1985b). Alternatively, hexachloroethane may be extracted from the matrix with hexane (Fowler 1969b; Nolan and Karbowski 1978). Details of selected analytical methods for hexachloroethane in biological samples are summarized in Table 6-l.

6.2 ENVIRONMENTAL SAMPLES

Determination of hexachloroethane in air, water, soil, wastes, and food is usually by GC analysis (APHA 1992; EPA 1982, 1990a, 1990b, 1990c; NIOSH 1994; Yurawecz and Puma 1986). Several representative methods for quantifying hexachloroethane in each of these media are summarized in Table 6-2. NIOSH (1994) has developed an approved method for analysis of hexachloroethane in air and EPA has developed approved methods for analysis of hexachloroethane in drinking water (EPA 1989, 1991c), water/wastewater (EPA 1982, 1990c), and soil/sediment/waste (EPA 1990a, 1990b) samples. The APHA (1992) method is equivalent to an EPA approved method.

Separation of hexachloroethane from environmental samples is usually by extraction with an organic solvent such as methylene chloride or acetonitrile (EPA 1982,1990a, 1990b, 1990c; Yurawecz and Puma 1986). A supercritical fluid extraction protocol has been developed for extraction of organics from soils and sediments (Lopez-Avila et al. 1991), which may be applicable to hexachloroethane. Air samples are drawn through a solid sorbent material and desorbed with carbon disulfide (NIOSH 1994). Cleanup procedures, with Florisil, for example, may be required for some environmental matrices (Yurawecz and Puma 1986). In addition, co-eluting compounds may be eliminated from extracts of drinking water by high performance liquid chromatography (HPLC) prior to GC/MS analysis, thus improving the quality of analytical results (Thruston 1978).

The electron capture detector (ECD) is most frequently used to identify hexachloroethane. A flame ionization detector (FID) may also be used (NIOSH 1994). When unequivocal identification is required, an MS coupled to the GC column may be employed.

TABLE 6-1. Analytical Methods for Determining Hexachloroethane in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Purge and trap on Tenax GC cartridge; desorb thermally	GC/MS	≈3 ng/mL[a]	≈80[a]	Pellizzari et al. 1985a
Blood	Purge and trap on Tenax GC cartridge; desorb thermally	GC/MS	0.028 ppb	93–41	Ashley et al. 1992
Adipose tissue	Macerate tissue in water; tap on Tenax GC cartridge; desorb thermally	GC/MS	≈6 ng/g[a]	≈50[a]	Pellizzari et al. 1985a
Breath	Collect on Tenax GC cartridge; dry over calcium sulfate; desorb thermally	Capillary column GC/MS	No data	≈70–130	Pellizzari et al. 1985b
Urine	Extract with hexane; successively wash with water, sodium hydroxide, hydrochloric acid, and water	GLC/ECD	No data	>90	Fowler 1969b
Feces	Macerate under warm hexane; successively wash with water, sodium hydroxide, hydrochloric acid, and water	GLC/ECD	No data	>90	Fowler 1969b

TABLE 6-1. Analytical Methods for Determining Hexachloroethane in Biological Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood, liver, kidney, fat	Extract with hexane	GC/ECD	0.001 µg/g	No data	Nolan and Karbowski 1978

[a]Typical or expected values for halocarbons by this method. Data were not reported for hexachloroethane.

ECD = electron capture detector; GC = gas chromatography; GLC = gas liquid chromatography; MS = mass spectrometry

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collect on activated coconut shell charcoal in glass tube; desorb with carbon disulfide	GC/FID	0.01 mg/sample	98	NIOSH 1994
Water/waste water	Extract with methylene chloride; exchange to hexane; Florisil cleanup, if required	GC/ECD	0.03 µg/L	99	EPA 1982
Waste water	Extract continuously with methylene chloride under alkaline and then acidic conditions	Isotope dilution, capillary column GC/MS	10 µg/L	No data	EPA 1990c
Water/waste water	Extract with methylene chloride under alkaline and then acidic conditions	Packed column GC/MS	1.6 µg/L	40–113	APHA 1992
Water/soil/ wastes	Extract with methylene chloride; exchange to hexane; Florisil or GPC cleanup, if required	Capillary column GC/ECD	1.6 µg/L[a]	83–96	EPA 1990a
Water/soil/ wastes	Extract with methylene chloride; exchange to hexane; Florisil or GPC cleanup, if required	Packed column GC/ECD	0.03 µg/L[a]	≈74	EPA 1990b

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Food (fish, milk, butter, corn oil)	Extract with acetonitrile; cleanup with Florisil; elute with petroleum ether and ethyl ether/petroleum ether	GC/ECD	No data	≥80	Yurawecz and Puma 1986

[a]Method detection limit (MDL) in reagent water. Estimated quantitation limits for other matrices are: 10 MDL in groundwater, 670–10,000 MDL in soil, and 100,000 MDL in nonaqueous wastes.

ECD = electron capture detector; FID = flame ionization detector; GC = gas chromatography; GPC = gel permeation chromatography; MS = mass spectrometry

6. ANALYTICAL METHODS

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 hexachloroethane is available. Where adequate information is not available, ATSDR, in conjunction with the 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 hexachloroethane.

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

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect The presence of hexachloroethane in exhaled air, blood, and tissues can be determined using GC/MS (Ashley et al. 1992; Pellizzari et al. 1985a, 1985b). Separation by GC with electron capture detection and liquid chromatography have also been used to identify hexachloroethane in blood, tissues, urine, and/or fecal matter (Fowler 1969b; Gorzinski et al. 1985; Jondorf et al. 1957; Mitoma et al. 1985; Nolan and Karbowski 1978). These methods are sufficiently sensitive and selective to measure low levels of hexachloroethane and levels that may result in adverse effects. Since the metabolites of hexachloroethane are themselves xenobiotic compounds or are the metabolites of other xenobiotics, the parent compound serves as the only true biomarker of exposure. Endogenous production of hexachloroethane following carbon tetrachloride exposure necessitates the need for an exposure history even when hexachloroethane is detected in body tissues or fluids (Fowler 1969a). Additional studies correlating levels of hexachloroethane in various biological media with environmental exposures would be useful.

No data were located regarding methods that identify biomarkers of hexachloroethane's toxic effects. Although hexachloroethane-induced hepatic damage can cause increases in serum levels of liver enzymes,

these enzyme changes are not specific to hexachloroethane exposure (Fowler 1969b; Weeks et al. 1979). In male rats, exposure to hexachloroethane is associated with the presence of granular and cellular casts in the urine (NTP et al. 1989). These effects are related to the formation of hyaline droplets in the male rat kidney. The formation of hyaline droplets is unique in male rats and is not indicative of the toxic effect of hexachloroethane. Therefore, they are not useful as biomarkers of effect. There is a need to identify compound-specific biomarkers for the effects of hexachloroethane exposure at this time.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methods are available to detect and quantify hexachloroethane in air, water, soil, wastes, and food (APHA 1992; EPA 1982,1990a, 1990b, 1990c; NIOSH 1994; Yurawecz and Puma 1986). Air is the medium of most concern for human exposure to this chemical. Exposure may also occur from water, especially in the vicinity of hazardous waste sites or industrial sources. The existing analytical methods can provide determinations for hexachloroethane at levels sufficiently low to meet regulatory requirements and evaluate health effects (EPA 1982, 1990a, 1990b, 1990c; NIOSH 1994).

Methods are also available to measure degradation products of hexachloroethane in environmental samples, but these products (e.g., tetrachloroethylene) are released to the environment from many other sources and are therefore not useful determinants of the environmental impact of this chemical.

6.3.2 On-going Studies

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control, is developing methods for the analysis of hexachloroethane and other volatile organic compounds in blood. These methods use purge and trap methodology, high resolution gas chromatography, and magnetic sector mass spectrometry which gives detection limits in the low parts per trillion (ppt) range.

On-going studies to i,mprove analytical methods for hexachloroethane and related compounds include the EPA “Master Analytical Scheme” being developed for organic compounds in water (Michael et al. 1988) and the research in supercritical fluid extraction (Lopez-Avila et al. 1991; Wieboldt et al. 1988). Research continues on improving extraction, concentration, and elution techniques, and detection devices (Eichelberger et al. 1983,1990; Ho et al. 1993; Pankow and Rosen 1988; Valkenburg and Munslow

1989). These improvements are designed to overcome problems with sample preparation and increase sensitivity and reliability of the analyses.

7. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed people, numerous regulations, and advisories have been established for hexachloroethane by various international, national, and state agencies. Major regulations and advisories pertaining to hexachloroethane are summarized in Table 7-l.

ATSDR has calculated an MRL of 6 ppm for acute inhalation exposure to hexachloroethane based on a NOAEL of 48 ppm from a study in pregnant rats. The critical effect was tremors, which occurred during an 11 -day exposure period at a LOAEL of 260 ppm (Weeks et al. 1979). The intermediate inhalation MRL of 6 ppm was also calculated from a NOAEL of 48 ppm observed in a 6-week study in which tremors were observed in rats exposed intermittently at 260 ppm (Weeks et al. 1979).

An MRL of 1 mg/kg/day has been calculated for acute oral exposure to hexachloroethane based on a NOAEL of 100 mg/kg/day from a study in male rabbits (Weeks et al. 1979). Hepatic necrosis and degeneration were observed in the treated animals at doses of 320 and 1,000 mg/kg/day.

An intermediate-duration MRL of 0.01 mg/kg/day has been calculated for oral exposure to hexachloroethane in the diet based on a NOAEL of 1 mg/kg/day from a study in male and female rats (Gorzinski et al. 1985). Enlargement of the hepatocytes was seen in male rats at doses of 15 and 62 mg/kg/day. Relative liver weights were increased in males and females at the 62 mg/kg/day dose.

EPA has derived a chronic oral RfD of 0.001 mg/kg/day for hexachloroethane (IRIS 1995). This value is based on a NOAEL of 1 mg/kg/day for atrophy and degeneration of the renal tubules in rats exposed for 16 weeks (Gorzinski et al. 1985). The NOAEL was divided by an uncertainty factor of 1,000 to account for interspecies extrapolation, human variability, and the use of a subchronic study. EPA places medium confidence in this RfD (IRIS 1995).

TABLE 7-1. Regulations and Guidelines Applicable to Hexachloroethane

Agency	Description	Information	Reference
INTERNATIONAL			
IARC	Carcinogenic classification	Group 3[a]	IARC 1987
NATIONAL			
Regulations:			
a. Air:			
EPA OAQPS	Hazardous Air Pollutant	Yes	Public Law 101-549 Section 112
	NESHAP for Source Categories: Organic HAPs from Synthetic Organic Chemical Manufacturing Industry (proposed)	Yes	EPA 1992
OSHA	PEL TWA	1 ppm (10 mg/m^3), skin	OSHA 1993 (29 CFR 1910.1000)
b. Water:			
EPA OWRS	General permits under NPDES	Yes	40 CFR 122
	General Pretreatment Regulations for Existing and New Sources of Pollution	Yes	40 CFR 403
	Hazardous substance	Yes	40 CFR 116
	Reportable quantity	100 pounds	40 CFR 117.3
c. Other:			
EPA OERR	Reportable quantity	100 pounds	EPA 1989 (40 CFR 302.4)
EPA OSW	Hazardous Waste Constituent (Appendix VIII)	Yes	EPA 1980b (40 CFR 261)
	Groundwater Monitoring List (Appendix IX)	Yes	EPA 1987b (40 CFR 264)
	Land Disposal Restrictions	Yes	EPA 1990d, 1991b (40 CFR 268)
	Toxicity Characteristic Leaching Procedure Limit	3 mg/L	EPA 1995 (40 CFR 261.24)
	Burning of Hazardous Waste boilers and industrial furnaces-residue concentration limit	3×10^{-2} mg/kg	EPA 1991b
EPA OTS	Toxic Chemical Release Reporting Rule	Yes	EPA 1988b (40 CFR 372)
	Health and Safety Data Reporting Rule	Yes	EPA 1988b (40 CFR 716.120)
Guidelines:			
a. Air:			
ACGIH	TLV TWA	1 ppm (9.7 mg/m^3) A2 - suspect human carcinogen	ACGIH 1993
NIOSH	PEL TWA	1 ppm; occupational carcinogen	NIOSH 1990

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

Agency	Description	Information	Reference
NATIONAL (Cont.)			
b. Water:			
EPA ODW	Health Advisories		Gordon et al. 1991
	1-day (child)	5 mg/L	
	10-day (child)	5 mg/L	
	Longer term (child)	100 µg/L	
	Longer term (adult)	450 µg/L	
	Lifetime (adult)	1 µg/L	
EPA OWRS	Ambient Water Quality Criteria		EPA 1980a
	Ingesting water and organisms	1.9 µg/L[b]	
	Ingesting organisms only	8.74 µg/L[b]	
c. Other:			
EPA	RfD (oral)	1×10^{-3} mg/kg/day	IRIS 1995
	Carcinogenic classification	Group C[c]	IRIS 1995
	Cancer slope factor (q_1^*)		IRIS 1995
	q_1^* (oral)	1.4×10^{-2} (mg/kg/day)$^{-1}$	
	q_1^* (inhalation)	1.4×10^{-2} (mg/kg/day)$^{-1}$	
NTP	May reasonably be anticipated to be a carcinogen		NTP 1994
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient conditions		NATICH 1995
Connecticut	8-hour	50 µg/m^3	
Kansas	annual	2.5×10^{-1} µg/m^3	
Massachusetts	24-hour	5.3×10^{-1} µg/m^3	
	annual	2.5×10^{-1} µg/m^3	
Nevada	8-hour	2.38 mg/m^3	
North Dakota	8-hour	9.7×10^{-2} µg/m^3	
Oklahoma	24-hour	2.0×10^{2} µg/m^3	
Texas	30-minute	97 µg/m^3	
	annual	10 µg/m^3	
Vermont	annual	2.5×10^{-1} µg/m^3	
Virginia	24-hour	1.6×10^{2} µg/m^3	
b. Water:	Drinking water standards and guidelines		FSTRAC 1990
Kansas		1.9 µg/L	
Minnesota		0.7 µg/L	

[a]Group 3: Not classifiable as to human carcinogenicity
[b]Based on a lifetime incremental cancer risk of 1×10^{-6}
[c]Group C: Possible human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; HAP = Hazardous Air Pollutant; IARC = International Agency for Research on Cancer; NESHAP = National Emission Standards for Hazardous Air Pollutants; NIOSH = National Institute for Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; NTP = National Toxicology Program; OAQPS = Office of Air Quality Planning and Standards; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Waste; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; RfD = Reference Dose; TLV = Threshold Limit Value; TWA = Time-Weighted Average

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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 (Kd) -- 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.

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.

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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 Viva -- 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$_{(50)}$ (LC_{50}) -- 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$_{(50)}$ (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50}) -- 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.

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.

9. GLOSSARY

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 μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RID) -- 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. 3 11 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.

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 (TD_{50}) -- 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 fiopulation, (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.

APPENDIX A

ATSDR MINIMAL RISK LEVEL

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-4991, requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1-14 days), intermediate (15-364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

APPENDIX A

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEETS

Chemical Name: Hexachloroethane
CAS Number: 67-72-1
Date: September 1996
Profile Status: Draft 3 Post-public comments
Route: [x] Inhalation [ ] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 4
Species: Rat

Minimal Risk Level: 6 [ ] mg/kg/day [x] ppm

Reference: Weeks et al. 1979

Experimental design:

Groups of 22 pregnant Sprague-Dawley rats were exposed to vapors of hexachloroethane (0, 15, 48, or 260 ppm) 6 hours/day on gestation days 6-16. Specific details of methods and results are not reported in this paper.

Effects noted in study and corresponding doses:

Hexachloroethane resulted in tremors at 260 ppm, with no neurological effects at 48 ppm. Transient mucopurulent nasal exudate in 85% of the animals and an unspecified decrease in maternal weight gain were noted in animals at 48 ppm. This effect was considered a result of an endemic mycoplasma infection and was not observed at 48 ppm in the 6-week study (Weeks et al. 1979). The 260-ppm concentration is a serious LOAEL for neurological effects and the 48-ppm concentration is a NOAEL.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL

48 ppm

Uncertainty Factors used in MRL derivation:

[ ] 3 for use of a minimal LOAEL
[x] 3 for extrapolation from animals to humans
[x] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.
If so, explain:

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Human Equivalent Concentration was calculated using default values from EPA (1988a).
48 ppm [(0.22 m^3/day/0.204 kg) / (20 m^3/day/70 kg)] = 181 ppm

Other additional studies or pertinent information which lend support to this MRL:

Other than the study by Weeks et al. (1979), there are no inhalation studies useful for estimating an acute inhalation MRL.

APPENDIX A

Chemical Name: Hexachloroethane
CAS Number: 67-72-1
Date: September 1996
Profile Status: Draft 3 Post-public comments
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 14
Species: Rat

Minimal Risk Level: 6 [ ] mg/kg/day [x] ppm

Reference: Weeks et al. 1979

Experimental design:

Groups of 25 male and 25 female Sprague-Dawley rats were exposed to vapors of hexachloroethane (0, 15, 48 or 260 ppm) 6 hours/day, 5 days/week for 6 weeks. Half of the animals were sacrificed at the end of the exposure period while the remainder were sacrificed 12 weeks after the end of the study. Quantitative data are not reported in this paper.

Effects noted in study and corresponding doses:

One male and one female rat exposed at 260 ppm died. There was an increased incidence of mycoplasma infection at 260 ppm that the authors attributed to hexachloroethane-induced potentiation of an endemic infection. Histopathologic changes were not observed in the brain, lungs, heart, liver, kidneys, spleen, eyes, bone marrow, trachea, nasal turbinates, thymus, stomach, small intestines, large intestines, pancreas, adrenal glands, bladder, testes, skin, skeletal muscle, and bone. Body weights (quantitative data not given) were reduced, and eye irritation was noted at 260 ppm. The high concentration is a serious effect level associated with tremors and less serious effects, reduced resistance to infection, eye irritation, and reduced body weight. The 48-ppm concentration is a NOAEL.

Dose and end point used for MRL derivation:

[x] NOAEL [ ] LOAEL

48 ppm

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[x] 3 for extrapolation from animals to humans
[x] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.
If so, explain:

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Human Equivalent Concentration was calculated using default values from EPA (1988a).

Other additional studies or pertinent information which lend support to this MRL:

Other than the study by Weeks et al. (1979) there are no inhalation studies useful for estimating an intermediate inhalation MRL. Studies in guinea pigs and dogs confirm that 260 ppm hexachloroethane is a serious effect concentration; 4/10 guinea pigs, and 1/4 dogs died at this concentration. These studies do not clearly identify a less serious LOAEL that does not have some serious effects. The 48-ppm concentration is a NOAEL for the most sensitive toxicity endpoint in all three species.

APPENDIX A

Chemical Name: Hexachloroethane
CAS Number: 67-72-1
Date: September 1996
Profile Status: Draft 3 Post-public comments
Route: [] Inhalation [x] Oral
Duration: [x] Acute [] Intermediate [ ] Chronic
Graph Key: 8
Species: Rabbit

Minimal Risk Level: ___1__ [x] mg/kg/day [] ppm

Reference: Weeks et al. 1979

Experimental design:

Groups of five male New Zealand rabbits were treated by gavage with hexachloroethane in methyl cellulose for 12 days at 0, 100, 320, or 1,000 mg/kg/day. Body weights were recorded daily, clinical signs were monitored, and serum chemistry parameters were evaluated (alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, alkaline phosphatase, bilirubin, total protein, potassium, and sodium). Necropsies were performed 4 days after the last dose and organs (lungs, liver, kidneys, spleen, testes) were weighed. Histopathological examinations of selected tissues and organs (eye, brain, lung, kidney, liver, spleen, heart, stomach, pancreas, small intestine, large intestine, skeletal muscle, bone, urinary bladder, testes) were also conducted.

Effects noted in study and corresponding doses:

Liver degeneration and necrosis occurred in a dose-related manner at 320 and 1,000 mg/kg/day. Effects were characterized as fatty degeneration, coagulative necrosis, hemorrhage, ballooning degeneration, eosinophilic change, and hemosiderin-laden macrophages and giant cells. Comparable effects were not seen in the 100-mg/kg/day dose group (lowest dose tested). Also, liver weights increased at the highest dose tested; however, quantitative data were not provided for evaluation. For the most part, serum clinical chemistry parameters were not significantly affected, except that levels of potassium and glucose were decreased significantly at dose levels of 320 mg/kg/day or greater. No quantitative data were provided for evaluation. Toxic tubular nephrosis of the convoluted tubules was seen at dose levels of 320 and 1,000 mg/kg/day; however, comparable effects were not observed at the lowest dose tested (100 mg/kg/day). Effects observed among treatment groups did not occur in a dose-dependent manner. Minimal tubular nephrocalcinosis occurred in a dose-related manner at dose levels of 320 mg/kg/day or greater. Also, kidney weights increased significantly ($p<0.05$) at the highest dose tested. Quantitative data were not provided for evaluation. No treatment-related gross or histopathological lesions of the urinary bladder were reported. Body weights were reduced significantly ($p<0.05$) at exposure levels of 320 and 1,000 mg/kg/day. Effects were seen within 7 days after compound exposure in the highest dose group and within 10 days at the intermediate dose. No changes in body weight were found at 100 mg/kg/day, the lowest dose tested. Quantitative data were not provided for evaluation.

Dose and end point used for MRL derivation:

[x] NOAEL [ ] LOAEL

100 mg/kg/day for lack of liver effects

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[x] 10 for extrapolation from animals to humans
[x] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.
If so, explain:

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Other additional studies or pertinent information which lend support to this MRL:

There are no other acute oral studies of hexachloroethane which support this MRL. However, intermediate-duration oral studies of hexachloroethane in rats described further in the worksheet for the intermediate-duration oral MRL provide support that the liver is a target following oral exposure to hexachloroethane.

APPENDIX A

Chemical Name: Hexachloroethane
CAS Number: 67-72-1
Date: September 1996
Profile Status: Draft 3 Post-public comments
Route: [] Inhalation [x] Oral
Duration: [] Acute [x] Intermediate [ ] Chronic
Graph Key: 18
Species: Rat

Minimal Risk Level: 0.01 [x] mg/kg/day [] ppm

Reference: Gorzinski et al. 1985

Experimental design:

Groups of 10 male and 10 female Fischer-344 rats were fed hexachloroethane in the diet for 16 weeks at levels that provided doses of 0, 1, 15, or 62 mg/kg/day. Procedures were taken to minimize volatilization from food, and the doses are actual doses rather than target doses. Body weights were monitored weekly and food consumption biweekly. At 13 weeks, blood samples were collected and analyzed for red cell count, hemoglobin concentration, and leukocyte counts. Urine specimens (13-week) were analyzed for pH, glucose, protein, ketones, occult blood, and urobilinogen. Blood samples taken at 16 weeks were analyzed for serum urea nitrogen, creatine, glutamate-pyruvate transaminase, and alkaline phosphatase. After sacrifice, the weights of the brain, heart, liver, kidneys, and testes were determined. The tissues of the organs were preserved and examined histologically.

Effects noted in study and corresponding doses:

Liver weights were increased in male rats at the highest dose and there was swelling of the hepatocytes in males at the highest two doses. Differences were significant for absolute and relative liver weights at the highest dose. Increased relative liver weights were seen in females at the highest dose. The kidneys in the two highest male dose groups displayed tubular atrophy, hypertrophy, and dilation. At the highest dose, kidney weights were increased by 10% and relative kidney weight by 5.5%. These changes in the kidneys were not seen in females except at the highest dose. There were no differences in the urinalysis results for the controls and exposed animals. Histopathologic changes in other organs were not observed. The 15-mg/kg/day dose is considered a minimal LOAEL for swelling of hepatocytes, and the 1-mg/kg/day dose is a NOAEL.

Dose and end point used for MRL derivation:

[x] NOAEL [ ] LOAEL

1 mg/kg/day for lack of liver effects

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[x] 10 for extrapolation from animals to humans
[x] 10 for human variability

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Other additional studies or pertinent information which lend support to this MRL:

Increased liver weights and an increase in the number of gamma glutamyl transpeptidase positive foci (dimethylnitrosoamine was used as an initiator), were reported in rats treated by gavage with hexachloroethane in corn oil at 497 mg/kg/day 5 days/week for 7 weeks (Milman et al. 1988; Story et al. 1986). No other doses were used in this study. Centrilobular necrosis was observed in female Fischer-344 rats treated by gavage with hexachloroethane in corn oil 5 days/week for 13 weeks (NTP 1989). No liver effects were observed at 94 mg/kg/day, suggesting that the LOAEL identified in the Gorzinski et al. (1985) study may be conservative. No liver effects were observed in female rats treated by gavage with hexachloroethane in corn oil 5 days/week for 2 years (NTP 1989) providing further support that the 15-mg/kg/day LOAEL observed in the Gorzinski et al. (1985) study may be conservative.

APPENDIX B

USER'S GUIDE

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-l 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 end points, 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-l and Figure 2-l 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-l) 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.

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 tigures 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-l).

5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "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 1,1,2,2-tetrachloroethane 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.

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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-l

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/m' 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 (q_1*).

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

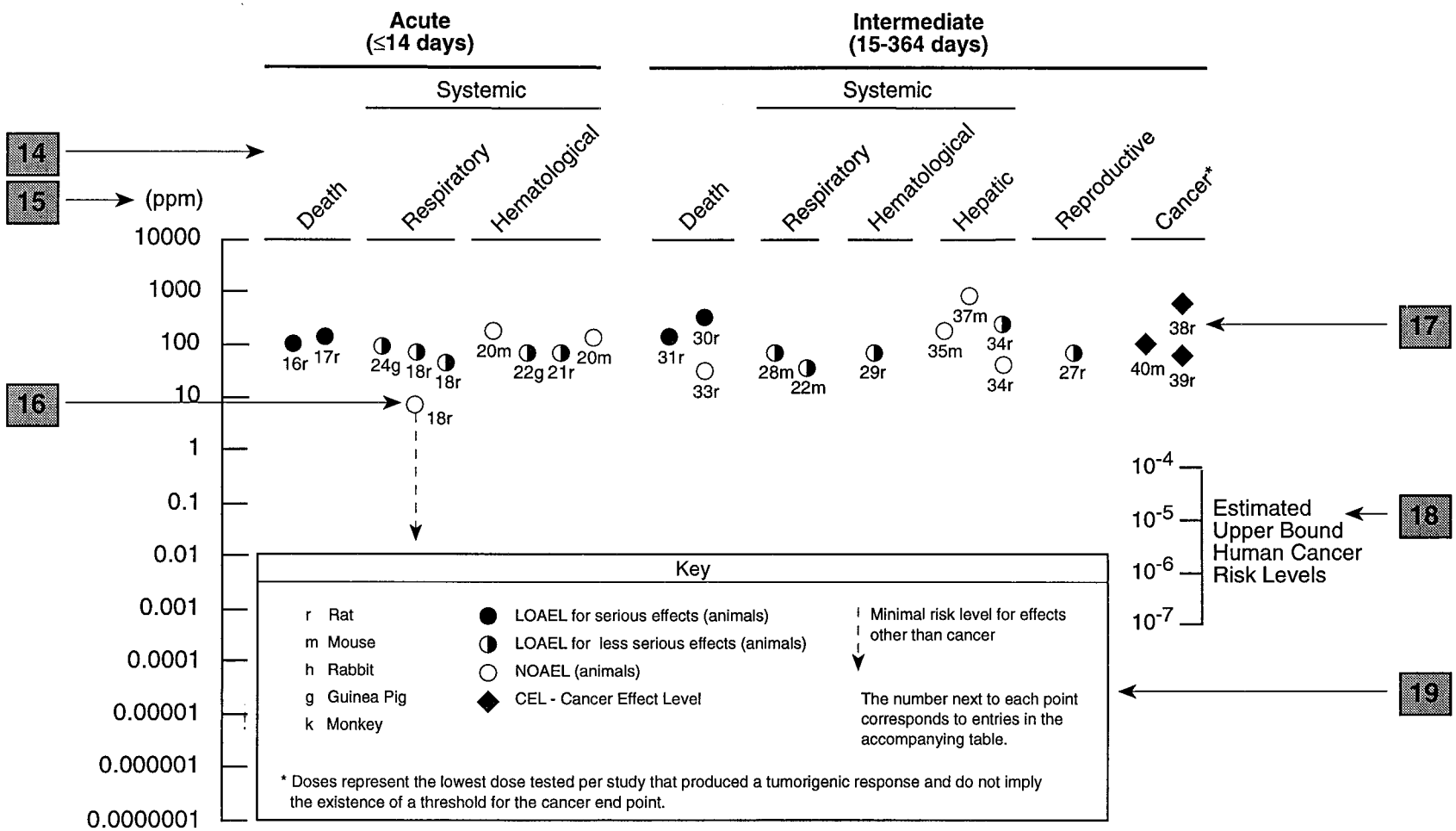
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE						
	5	6	7	8	9	10
3 → Systemic	↓	↓	↓	↓	↓	↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3 [b]	10 (hyperplasia)	Nitschke et al. 1981
CHRONIC EXPOSURE						
					11	
Cancer					↓	
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

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

12 → [b] ! 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)

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



APPENDIX B

Chapter 2 (Section 2.5)

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 end points 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 end points 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 end points (if derived) and the end points 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 2.5, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.7, “Interactions with Other Substances,” and 2.8, “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).

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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 C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
AML	acute myeloid leukemia
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BEI	Biological Exposure Index
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
Ci	curie
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
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
Kd	adsorption ratio

kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
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
MA	trans,trans-muconic acid
mCi	millicurie
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NCE	normochromatic erythrocytes
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
PCE	polychromatic erythrocytes
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
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
UMDNJ	University of Medicine and Dentistry New Jersey
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	micrometer
μg	microgram