CHEMICAL MANUFACTURERS ASSOCIATION

SEP - 7 1990

September 4, 1990

TO: Vinylidene Chloride Panel

RE: ATSDR Tox Profile on Vinylidene Chloride

I have enclosed a copy of the final ATSDR profile on Vinylidene Chloride (1,1-Dichloroethene). The profile does not have an ATSDR cover because I received the report directly from the prime contractor, Clement Associates. Also enclosed is a letter about the profile from Bruce Dickson, the Panel's legal counsel. Of particular interest to the Panel may be the profile sections on cancer (pp. 32-35, 46-49, 57-58) and data needs (pp. 73-78, 84, 93, 99). I will be in touch with each of you about whether or not the Panel wants to take any actions, particularly in response to the data need for additional information on chronic toxicity and carcinogenicity.

I look forward to working with each of you. If you have any questions, I can be reached at 202/887-1189. My staff assistant, Amy Kosko, can be reached at 202/887-1345.

Sincerely,

Jonathon T. Busch

Jonathon T. Busch
Manager, Vinylidene Chloride

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August 31, 1990

WRITER'S DIRECT DIAL NUMBER
202-457-9423

OUR FILE NO

MEMORANDUM TO THE CMA VINYLIDENE CHLORIDE PANEL

Re: ATSDR Tox Profile

ATSDR has issued the final version of its Toxicological Profit for 1,1-Dichloroethene (vinylidene chloride). The Tox Profile contains the following evaluation of data needs:

> "Chronic Exposure and Carcinogenicity. Data from animal studies on the chronic toxicity and carcinogenicity of DCE are sparse, and limited in their usefulness because of experimental design flaws. The data presented do not sufficiently characterize the carcinogenic or chronic toxic effects of DCE. However, the available information does suggest that DCE is carcinogenic in animals. Additional information on the chronic toxicity and carcinogenicity of DCE from well-conducted animal bioassays and human epidemiological studies using various routes of exposure would be useful in predicting the likelihood that such effects occur in humans."

You will recall that at a meeting with the Panel on May 19, 1989, Richard Troast stated that EPA was awaiting the Tox Profile before deciding whether to withdraw the test

rule. We have discussed this development with Jon Busch, who agrees that a conference call or meeting of the Panel should be held in the near future to discuss whether any further action should be taken by the Panel.

R. Bruce Dickson

Enclosure

cc: Zeb Bell, Ph.D., Chairman
James Barter, Ph.D.
Stanley Dombrowksi
William Hayes
Jon Busch
Marilyn Browning, Esq.

TOXICOLOGICAL PROFILE FOR
1,1-DICHLOROETHENE

Prepared by:

Clement Associates
Under Contract No. 205-88-0608

Prepared for:

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

In collaboration with:

U.S. Environmental Protection Agency

December 1989

DISCLAIMER

Mention of company name or product does not constitute endorsement by the Agency for Toxic Substances and Disease Registry.

FOREWORD

The Superfund Amendments and Reauthorization Act of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law (also known as SARA) directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The list of the 100 most significant hazardous substances was published in the Federal Register on April 17, 1987.

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

> "(A) An examination, summary and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects,
>
> (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, or chronic health effects, and
>
> (C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans."

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by SARA.

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

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the statement is material that presents 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. Research gaps that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the front of the document.

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. We plan to revise these documents in response to public comments and as additional data become available; therefore, we encourage comment that will make the toxicological profile series of the greatest use.

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

Walter R. Dowdle, Ph.D.
Acting Administrator
Agency for Toxic Substances
and Disease Registry

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1. PUBLIC HEALTH STATEMENT

1.1 WHAT IS 1,1-DICHLOROETHENE (DCE)?

1,1-Dichloroethylene (DCE) also known as vinylidene chloride is a chemical used to make certain plastics such as packaging materials (flexible films [SARAN™ wrap]) and flame-retardant fabrics. DCE is also used to make other chemicals. It is a clear, colorless liquid that evaporates quickly at room temperature and has a mild, sweet smell like chloroform. DCE also burns.

DCE is a man-made chemical that is not found naturally in the environment. It is released into the environment mostly in the air and water coming from factories where it is made, at hazardous waste sites where it has been disposed, and from accidental spills. DCE can also be found as a breakdown product of other chemicals in the environment. Although high amounts of DCE in soil and water will quickly escape to the air, small amounts will stay and be broken down. We do not known how long DCE will stay in soil and water. DCE quickly breaks down in the air. DCE released into the atmosphere is estimated to last for only about 2 days. The physical and chemical properties of DCE are explained in Chapter 3, production and use information can be found in Chapter 4, and more information on environmental fate is given in Chapter 5.

1.2 HOW MIGHT I BE EXPOSED TO DCE?

Besides the high exposures in plants where DCE is made, low-level exposures to DCE may occur in the environment. DCE is found at very low amounts in indoor and outdoor air (estimated as less than one part per trillion). Therefore, the potential for exposure in the environment is extremely low. Somewhat higher amounts are found in the air near some factories that make or use DCE (as in the making of plastic food-packaging films, adhesives, flame-retardant coatings for fiber and carpet backing, in piping, and in coating for steel pipes), hazardous waste sites, and areas near accidental spills. The amount of DCE in the air near these factories is not known exactly. In air around waste sites DCE amounts range from 0.39 to 36.4 parts DCE in one billion parts of air (ppb). The levels of DCE in air around waste sites are usually much lower than those that affect the health of laboratory animals. The plants that make DCE are located in Texas and Louisiana. DCE is now estimated to be in the air around 97 factories throughout the United States. Air levels inside manufacturing plants have recently been measured to range from less than 5 parts DCE in 1 million parts of air (ppm) to 25 ppm. The Occupational Health and Safety Administration (OSHA) has recently established a limit for air contaminants of 1 ppm for an 8-hour work day which should significantly reduce worker exposure in the future.

DCE was found at approximately 16% of all hazardous waste sites tested through the U.S. Environmental Protection Agency (EPA) Contract Laboratory Program and is found at 175 of the 1177 National Priorities List (NPL)

hazardous waste sites. DCE has been found in the soil at a small number of these hazardous waste sites, but the amounts were not reported.

A small percentage (3%) of the drinking water sources in the United States has been found to contain low amounts of DCE (0.2-0.5 ppb with an estimated average of 0.3 ppb). Again, the amounts are very low when compared with levels that are expected to affect human health. Levels in groundwater samples taken from hazardous waste sites where DCE was found average 1.38 ppm.

Finally, because DCE is used in making some consumer products, exposure might occur during the making and use of these products. For example, DCE has been estimated at less than 1.26 ppm in plastic food-packaging films, and DCE measured in foodstuffs wrapped in these films is less than 0.01 ppm. These numbers represent the levels found only in food samples that had DCE in them as not every food sample tested was found to contain DCE. However, the Food and Drug Administration (FDA) regulates the use of plastic packaging films, and the low levels of DCE found in foods wrapped in these films are considered by the FDA to present no health risk to the consumer. More information on human exposure can be found in Chapter 5.

1.3 HOW CAN DCE ENTER AND LEAVE MY BODY?

DCE can easily enter the body through the lungs as an air pollutant or through the digestive tract as a contaminant of food or water. DCE can probably also enter the body through the skin. This assumption is based on the physical and chemical properties of DCE, the fact that chemicals similar to DCE are known to be absorbed through the skin, and the occurrence of t xic effects in animals after DCE was applied to their skin. The most common means of exposure in the workplace, in the general population, and in areas around hazardous waste sites is breathing contaminated air. However, some DCE can be taken in by drinking contaminated ground water, particularly around hazardous waste sites.

Research using animals has led to the following information. Within hours of exposure, DCE begins to leave the body through the lungs. Remaining DCE in the body is broken down into other substances and removed through the kidneys within 1 to 2 days. The way DCE and its breakdown products leave th body depends on the level of exposure to DCE. Low or moderate levels breathed in (25-200 ppm) or taken by mouth (up to 50 mg DCE/kg body weight), leave the body mainly as breakdown products in the urine. As the levels of exposure increase, more and more DCE leaves the body in the exhaled breath. DCE breathed in and taken by mouth both leave the body about the same way. DCE is not stored very much in the body after exposure to moderate (up to 300 ppm) levels. More information is given in Chapter 2.

1. PUBLIC HEALTH STATEMENT

1.4 HOW CAN DCE AFFECT MY HEALTH?

The health effects of DCE in humans are not known. High amounts of DCE in animal studies have caused liver, kidney, heart, and lung damage and have also caused nervous system disorders and death after short exposures. Liver damage has also been seen when exposure was long (weeks to years). The amount of damage depends on the level of exposure and the length of time exposed. Exposure by breathing DCE appears to be more harmful in animals than exposure through food or water. After short exposures to high levels of DCE, the same kinds of effects can be expected to occur in humans.

An increased risk for cancer has been shown in one study in which animals were exposed to DCE. Although most studies have shown that DCE does not cause cancer in animals, it is wise to consider the possibility that DCE may cause cancer in humans because of this one suggestive study. Harmful effects on the developing fetus have been seen in the offspring of pregnant animals inhaling this chemical. Sickness of the mothers was also seen. The health effects of DCE in both humans and animals are explained in Chapter 2.

1.5 IS THERE A MEDICAL TEST TO DETERMINE IF I HAVE BEEN EXPOSED TO DCE?

DCE can be measured in the breath, blood, urine, and body of exposed individuals. However, only relatively high levels of DCE can be detected in body tissues and fluids using currently available analytical techniques. Because breath samples are easily collected, tests of exhaled air are now the most common way to tell whether a person has been exposed to high levels of DCE. Other medical tests can measure breakdown products of the chemical in the blood and urine. None of these tests is regularly available at a doctor's office, because they need special equipment for sampling and measuring the compound. Although these tests can prove that a person has been exposed to DCE, they can not yet tell how severe any health effects might be. Because DCE leaves the body fairly quickly, these methods are best for finding exposures that have occurred within the last several days. Levels of DCE measured in the body with these types of medical tests may not reflect exposure to DCE alone, because exposure to DCE at hazardous waste sites is likely to include exposure to other organic compounds at the same time that result in similar breakdown products as DCE. Other methods of measuring the effects associated with exposure to DCE (such as reduced enzyme levels) are not sufficiently specific to detect effects caused by exposure to DCE alone. Information on tests to find DCE in the body is given in Chapter 6.

1.6 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

Except for loss of breath, fainting, and nervous system disorders like drunkenness that result from exposure to high amounts of DCE in a closed space, there are few medical reports to prove that human exposure to DCE affects health. However, human exposure has not been studied very much. The available information on DCE exposure in humans is not very useful for telling how DCE affects human health and at what levels and kinds of exposure. The

information is mainly reports about small numbers of people, without the level and time of exposure to DCE given, and with the possibility of exposure to other harmful chemicals. So, levels of exposure that may affect human health must be estimated from animal studies.

Studies in animals indicate that the normal actions of the liver, kidney, lungs, heart, and blood can be affected by exposure to DCE. These effects began to occur at air amounts of 15 ppm after 5 days of exposure. Animals exposed to DCE at 98 ppm DCE in the air for 7 days have died. Exposure of animals to 24 ppm DCE in air for 6 hours a day, 5 days a week, for months to years, can cause liver damage.

When animals had 200 milligrams of DCE per kilogram of body weight per day (mg/kg/day) (4,000 ppm) placed in their stomachs experimentally, they developed liver disease, and some even died. Animals fed amounts of 7 mg DCE/kg/day (50 ppm) in their drinking water over a period of months to years also developed liver disease.

Tables 1-1 through 1-4 show the relationship between exposure to DCE and known health effects. Minimal Risk Levels (MRLs) are also included in Tables 1-1 and 1-3. These MRLs were derived from animal data for both sh rt-term or longer-term exposure, as described in Chapter 2 and in Tables 2-1 and 2-2. The MRLs provide a basis for hazard in humans, based upon all known experimental data on the chemical. Should a person be exposed to DCE at an amount below the MRL, it is not expected that harmful (noncancer) health effects will occur. Since these levels are based on information that is currently available from animal studies; there is always some uncertainty associated with them. Also, since the method for deriving MRLs does not use any information about cancer, a MRL does not imply anything about the presence, absence, or level of risk to cancer.

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

The Federal Government has developed regulatory guidelines and standards to protect individuals from the possible health effects of DCE. EPA has ruled that the highest level of DCE in drinking water be less than 7 μg/L and any release of more than 5,000 lb to the environment be reported. However, EPA has recently suggested that this level should be no more than 100 lb.

For short-term exposures EPA has decided that drinking water levels should not be more than 2 mg/L (2 ppm) for one day or 1 mg/L (1 ppm) for 10 days.

The National Institute for Occupational Safety and Health (NIOSH) has decided that the highest level of DCE in workplace air should not be more than 4 mg/m^3 (1 ppm). OSHA recently established a limit for air contaminants of

1. PUBLIC HEALTH STATEMENT

TABLE 1-1. Human Health Effects from Breathing DCE*

Short-term Exposure (less than or equal to 14 days)		
Levels in air (ppm)	**Duration of Exposure**	**Description of Effects****
0.9		Estimated minimal risk level (based on animal studies, see section 1.6 for discussion)
500		Odor threshold
4,000	< 1 day	Temporary nervous system disorders
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	**Duration of Exposure**	**Description of Effects****
0.02		Estimated minimal risk level (based on animal studies, see section 1.6 for discussion)

* See Section 1.2 for a discussion of exposures encountered in daily life.

** These effects are listed at the level at which they were first observed. They may also be seen at higher levels.

TABLE 1-2. Animal Health Effects from Breathing DCE

Short-term Exposure (less than or equal to 14 days)		
Levels in air (ppm)	Duration of Exposure	Description of Effects**
10	4 hr.	Kidney disease in fasted mice
15	8 days	Changes in the appearance of the liver in mice
15	11 days	Toxicity to developing fetus in mice
40	4 hr.	Death in fasted male mice
50	6 hr.	More severe kidney disease in fasted male mice
60	5 days	Severe liver disease in male mice.
Long-term Exposure (greater than 14 days)		
Levels in air (ppm)	Duration of Exposure	Description of Effects**
4	6 months	Changes in the appearance of the liver in rats
4	18 months	Liver disease in rats
25	1 year	Kidney disease in mice
48	3 months	Changes in the appearance of the lungs and kidneys in rats

** These effects are listed at the level at which they were first observed. They may also be seen at higher levels.

1. PUBLIC HEALTH STATEMENT

TABLE 1-3. Human Health Effects from Eating or Drinking DCE*

Short-term Exposure (less than or equal to 14 days)		
Levels in food (ppm)	Duration of Exposure	Description of Effects**
		The health effects of short-term human exposure resulting from DCE in food containing specific levels of DCE are not known
Levels in water (ppm)		The health effects of short-term human exposure resulting from DCE in water containing specific levels of DCE are not known
Long-term Exposure (greater than 14 days)		
Levels in food (ppm)	Duration of Exposure	Description of Effects**
0.32		Estimated minimal risk level (based on animal studies, see section 1.6 for discussion)
Levels in water (ppm)		The health effects of long-term human exposure resulting from DCE in water containing specific levels of DCE are not known

* See Section 1.2 for a discussion of exposures encountered in daily life.

** These effects are listed at the level at which they were first observed. They may also be seen at higher levels.

TABLE 1-4. Animal Health Effects from Eating or Drinking DCE

Short-term Exposure (less than or equal to 14 days)		
Levels in food (ppm)	**Duration of Exposure**	**Description of Effects****
500	1 day	Changes in the appearance of liver in rats
1,000	1 day	Death in rats
1,540	1 day	Changes in the appearance of of the lung in mice
4,000	1 day	Changes in the appearance of the kidney and stomach in fasted rats
4,000	1 day	Liver disease in fasted rats
Levels in water (ppm)		The health effects resulting from short-term animal exposure to DCE in water containing specific levels of DCE are not known
Long-term Exposure (greater than 14 days)		
Levels in food (ppm)	**Duration of Exposure**	**Description of Effects****
		The health effects resulting from long-term animal exposure to DCE in food containing specific levels of DCE are not known.
Levels in water (ppm)		
50		Changes in the appearance of the liver in rats

** These effects are listed at the level at which they were first observed. They may also be seen at higher levels.

1 ppm. Employers must be in compliance with this standard by September 1, 1989. This new Permissible Exposure Limit (PEL) should significantly reduce future workplace exposure to DCE.

EPA estimates that for an average-weight adult, an exposure of 0.63 mg of DCE or less per day will probably not cause harmful health effects (not including cancer).Work is now being done by EPA to measure the levels of DCE found at abandoned waste sites.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have further questions or concerns, please contact your state health or environmental department or:

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

1. PUBLIC HEALTH STATEMENT

2. HEALTH EFFECTS

2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to DCE. Its purpose is to present levels of significant exposure for DCE based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of DCE and (2) a depiction of significant exposure levels associated with various adverse health effects.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

Levels of significant exposure for each exposure route and duration (for which data exist) are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear, determine whether or not the intensity of the effects varies 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 on the tables and graphs may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (minimal risk levels, MRLs) are of interest to health professionals and citizens alike.

For certain chemicals, levels of exposure associated with carcinogenic effects may be indicated in the figures. These levels reflect the actual doses associated with the tumor incidences reported in the studies cited. Because cancer effects could occur at lower exposure levels, the figures also

show estimated excess risks, ranging from a risk of one in 10,000 to one in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer endpoint for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1980c), uncertainties are associated with the techniques.

2.2.1 Inhalation Exposure

Figure 2-1 and Table 2-1 describe the health effects observed in laboratory animals associated with exposure level and exposure duration. The minimal risk levels to humans for adverse effects other than cancer are presented in Figure 2-1 for the inhalation route of exposure.

2.2.1.1 Death

No studies were found regarding death in humans following inhalation exposure to DCE. However, studies in rats, mice, and hamsters provide evidence that inhalation exposure to DCE can be lethal.

The lethality of DCE in animals following inhalation exposure has been found to vary considerably and is influenced by such factors as species, strain, sex, and nutritional status. Differences between strains could account for the range of reported 4-hour LC_{50}s in fed rats (approximately 6,000-8,000 ppm in males, and a value of 10,000 ppm has been reported in females) (Henderler 1979; Siegel et al. 1971; Zeller et al. 1979a,b). High r 4-hour LC_{50}s (10,000-15,000 ppm) have been reported for fed rats (sex not specified) but the animals were observed only for 24 hours (Jaeger et al. 1973b).

The LC_{50}s reported for 16-hour fasted rats are generally orders of magnitude lower than those reported for fed rats. For instance, a 4-hour LC_{50} of 400 ppm was reported for fasted male rats (Zeller et al. 1979b). Female rats appear to be more resistant to the detrimental effects of starvation; a 4-hour LC_{50} of 6,545 ppm was reported by the same author for fasted female rats. Finally, Jaeger et al. (1974) compared the effects of nutritional status on lethality in male rats exposed to DCE for 24 hours and found that the LC_{50} for fasted animals was almost 30 times lower than that for fed animals. The proposed mechanism by which fasting increases the toxicity of DCE will be discussed in Sections 2.3 and 2.6.

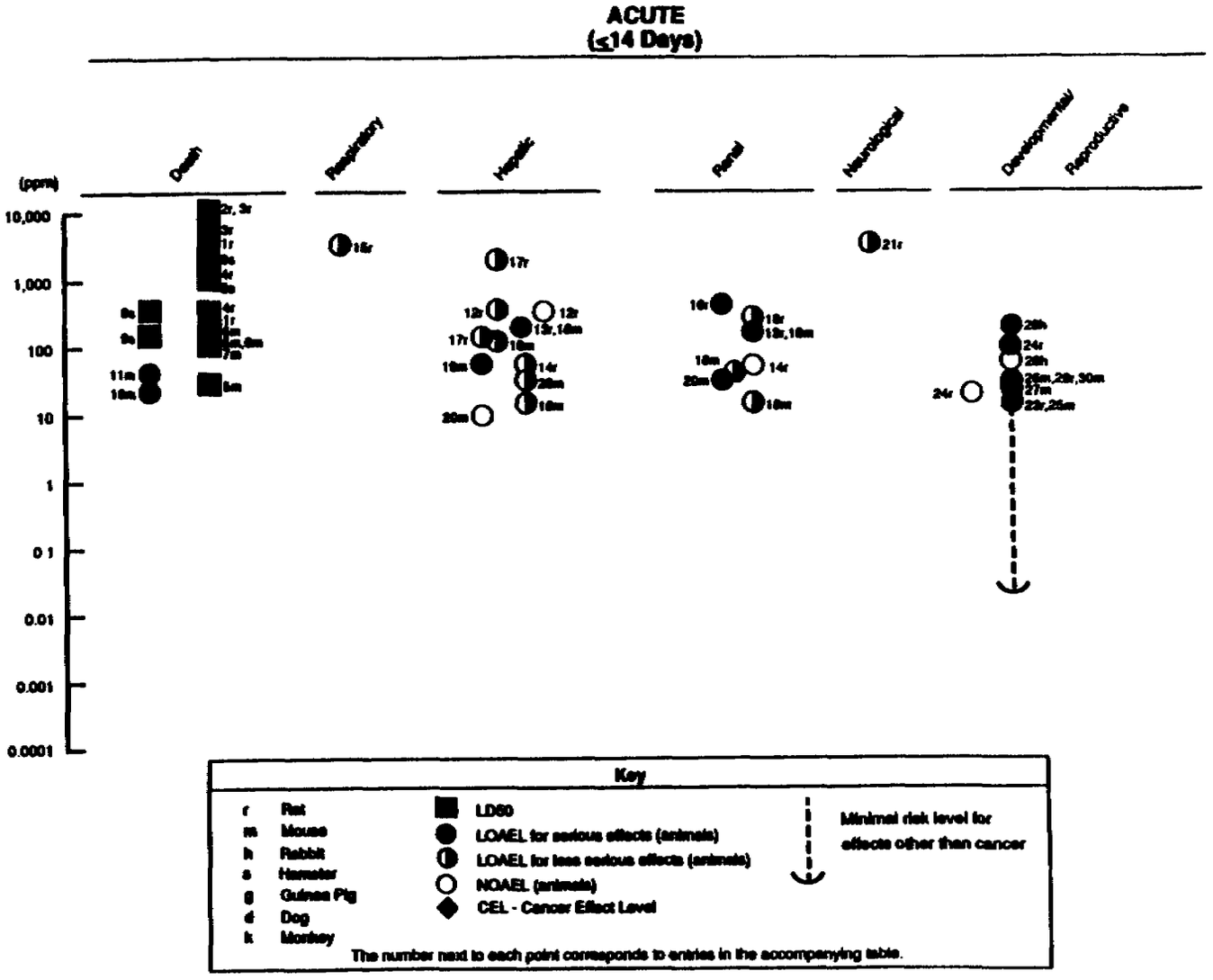

FIGURE 2-1. Levels of Significant Exposure To DCE - Inhalation

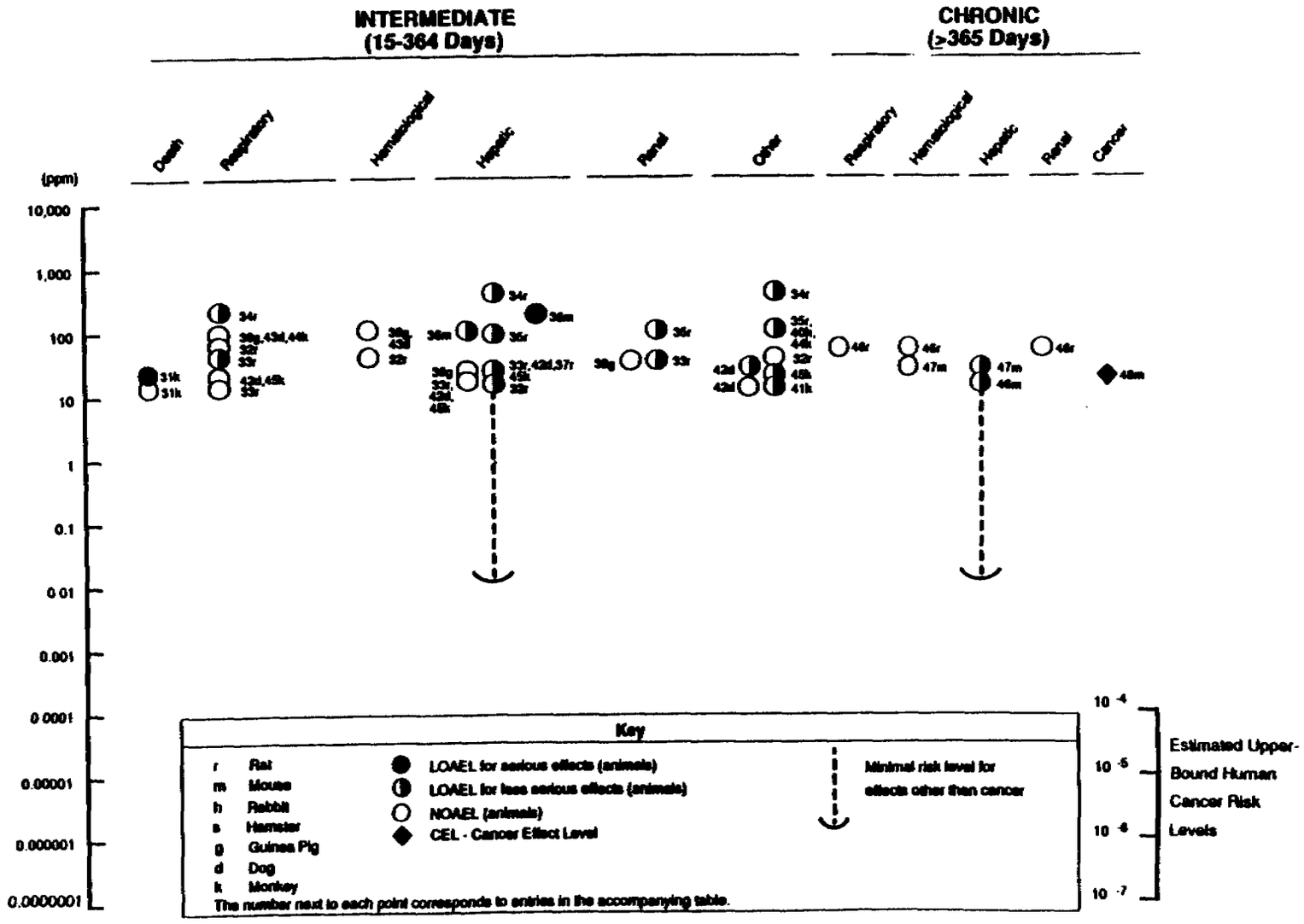

FIGURE 2-1. Levels of Significant Exposure To DCE - Inhalation (Continued)

TABLE 2-1. Levels of Significant Exposure to 1,1-Dichloroethene - Inhalation

Graph Key	Species	Exposure Duration/ Frequency	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious	LOAEL (Effect) Serious	Reference
ACUTE EXPOSURE							
Death							
1	rat	4 hr 1 x				2,010 (LC50-M&F)** 415 (LC50 - M)** 6,545 (LC50 - F)**	Zeller et al. 1979b (as cited in Fielder at al. 1985)
2	rat	4 hr 1 x				10,000 -(LC50) 15,000	Jaeger et al. 1973b
3	rat	4 hr 1 x				8,600 (LC50-M&F) 7,100 (LC50 - M) 10,300 (LC50 - F)	Henschler 1979 (as cited in Fielder et al. 1985)
4	rat	4 hr 1 x				500- (LC50)** 2,500	Jaeger et al. 1973a
5	mouse	4 hr 1 x				40 (LC50 - M)** 115 (LC50 - F)**	Henschler 1979 (as cited in Fielder et al. 1985)
6	mouse	4 hr 1 x				115 (LC50 - M) 205 (LC50 - F)	Henschler 1979 (as cited in Fielder et al. 1985)
7	mouse	1 d 23 hr/d				98 (LC50 - M) 105 (LC50 - F)	Short et al. 1977c

TABLE 2-1 (Continued)

Graph Key	Species	Exposure Duration/ Frequency	Effect	NOAEL	LOAEL (Effect) Less Serious	LOAEL (Effect) Serious	Reference
				(ppm)			
8	hamster	4 hr 1 x				1,660 (LC50 - M) 2,945 (LC50 - F)	Klimisch and Freisbierg 1979a (as cited in Fielder et al. 1985)
9	hamster	4 hr 1 x				150 (LC50 - M)** 455 (LC50 - F)**	Klimisch and Freisbierg 1979a (as cited in Fielder et al. 1985)
10	mouse	7 d 22-23hr/d				40 (M-70% mort)	Short et al. 1977c
11	mouse	1-8 d 6hr/d		10		50 (M-69% mort)	Oesch et al. 1983
Systemic							
12	rat	4 hr 1 x	Hepatic	250	250** (>serum SDH, orn car tr)		Jaeger 1977
13	rat	6 hr 1 x	Hepatic Renal	200 200		200** (necrosis) 200** (hemoglob) (deg tub ep)	McKenna et al. 1978a
14	rat	1-3d 23hr/d	Renal Hepatic	60	60 (degen lesn)		Short et al. 1977
15	rat	4 hr 1 x	Resp		5,000 (histo)		Henschler 1979 (as cited in Fielder et al. 1985)

TABLE 2-1 (Continued)

Graph Key	Species	Exposure Duration/ Frequency	Effect	NOAEL	LOAEL (Effect) Less Serious	LOAEL (Effect) Serious	Reference
				(ppm)			
16	rat	4 hr 1 x	Renal		250** (swelling)	300** (necrosis)	Jackson and Conolly 1985
17	rat	4 hr 1 x	Hepatic		2,000 (>ser AKT, no histo) 150** (>ser AKT)		Jaeger et al. 1974
18	mouse	10 d 5d/wk 6hr/d	Hepatic Renal		100 (F-histo) 55 (F-histo)	200 (F-histo) 200 (M-renal failure)	Henck et al. 1979
19	mouse	5 d 23hr/d	Hepatic Renal		15 (degen) 15 (tub neph)	60 (degen)	Short et al. 1977
20	mouse	6 hr 1 x	Hepatic Renal	10	50 (histo) 10 (histo)	50 (necrosis)	Reitz et al. 1980
Neurological							
21	rat	4 hr 1 x			5,000 (CS)		Henschler 1979 (as cited in Fielder et al. 1985)
22	rat	10 min 1 x			25,600 (cardiac arrythmias)		Siletchnik and Carlson 1974
Developmental							
23	rat	11 d g6-16 23hr/d				15[a] (fetl anom)	Short et al. 1977a

TABLE 2-1 (Continued)

Graph Key	Species	Exposure Duration/ Frequency	Effect	NOAEL	LOAEL (Effect) Less Serious	LOAEL (Effect) Serious	Reference
				(ppm)			
24	rat	10 d g6-15 7h/d		20		80 (skel alt)	Murray et al. 1979
25	mouse	11 d g6-16 23hr/d				15 (skel anom)	Short et al. 1977a
26	mouse	4d g12-15 23hr/d				54 (resorb)	Short et al. 1977a
27	mouse	8 d g8-15 23hr/d				41 (skel anom)	Short et al. 1977a
28	rabbit	[illegible] g6-18 7h/d		80		160 (skel alt)	Murray et al. 1979
Reproductive							
29	rat	11 wk 5d/wk 6hr/d		55			Short et al. 1977b
30	mouse	5 d 6hr/d		50			Anderson et al. 1977
INTERMEDIATE EXPOSURE							
Death							
31	monkey	90 d cont.		15		25	Prendergast et al. 1967

TABLE 2-1 (Continued)

Graph Key	Species	Exposure Duration/ Frequency	Effect	NOAEL	LOAEL (Effect) Less Serious	LOAEL (Effect) Serious	Reference
				(ppm)			
Systemic							
32	rat	6 mo 5d/wk 6hr/d	Resp Hemato Hepatic Derm/Oc	66 66 66	 21[b](fatty)		Quast et al. 1986
33	rat	90 d cont.	Hepatic Renal Resp	25 15	48 (fatty) 48 (Nuc Hyp Tu Ep) 48 (inflamatn)		Prendergast et al. 1967
34	rat	3 wk 5d/wk 6hr/d	Hepatic Resp Other		500 (Deg LivCel) 200 (irritation) 500 (< bw)		Gage 1970
35	rat	5 wk 5d/wk 6hr/d	Hepatic Renal Other		100 (> wt) 100 (histo,> wt) 100 (biochem)		Klimisch et al. 1979 (as cited in Fielder et al. 1985)
36	rat	30 d 5d/wk 6hr/d	Hepatic		125 (histo)	200 (histo)	Quast 1976
37	rat	90 d 5d/wk 6hr/d	Hepatic		200 (histo)		Balmer et al. 1976
38	gn pig	90 d cont.	Hepatic Renal	48 48	 		Prendergast et al. 1967

TABLE 2-1 (Continued)

Graph Key	Species	Exposure Duration/ Frequency	Effect	NOAEL	LOAEL (Effect) Less Serious	LOAEL (Effect) Serious	Reference
				(ppm)			
39	gn pig	6 wk 5d/wk 8hr/d	Resp Hemato	100 100			Prendergast et al. 1967
40	rabbit	6 wk 5d/wk 8hr/d	Other		100 (< bw)		Prendergast et al. 1967
41	rabbit	90 d cont.	Other		25 (< bw)		Prendergast et al. 1967
42	dog	90 d cont.	Resp Hepatic Other	25 25 25	 48 (fatty) 48 (adenoma)		Prendergast et al. 1967
43	dog	6 wk 5d/wk 8hr/d	Resp Hemato	100 100			Prendergast et al. 1967
44	monkey	6 wk 5d/wk 8hr/d	Resp Other	100	 100 (< bw)		Prendergast et al. 1967
45	monkey	90 d cont.	Resp Hepatic Other	25 25 5	 48 (histo) 15 (< bw)		Prendergast et al. 1967
CHRONIC EXPOSURE							
Systemic							
46	rat	18 mo 5d/wk 6hr/d	Resp Hemato Hepatic Renal Other	72 72 72 72	 24[c](<wt, fatty)		Quast et al. 1986
47	mouse	1 yr 5d/wk 6hr/d	Hemato Hepatic	55	 55 (necrosis)		Lee et al. 1977

TABLE 2-1 (Continued)

Graph Key	Species	Exposure Duration/ Frequency	Effect	NOAEL	LOAEL (Effect) Less Serious	LOAEL (Effect) Serious	Reference
				(ppm)			
Cancer							
48	mouse	52 wk 5d/wk 4hr/d				10 (CEL)	Maltoni et al. 1985

[a]Used to derive acute inhalation MRL; divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans and 10 for human variability) resulting in an MRL of 0.9 ppm. This MRL is presented in Table 1-1.

[b]Used to derive an intermediate inhalation MRL; adjusted for intermittent exposure and human breathing rate and divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) resulting in an MRL of 0.02 ppm. This MRL is presented in Table 1-1..

cUsed to derive a chronic inhalation MRL; adjusted for intermittent exposure and human breathing rate divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans and 10 for human variability) resulting in an MRL of 0.03 ppm.

**Fasted prior to exposure

TABLE 2-1 (continued)

Legend for Levels of Significant Exposure Tables for Toxicity Studies for 1,1-Dichloroethene

Header

NOAEL	no-observed-adverse-effect-level		
LOAEL	lowest-observed-adverse-effect-level		
mg	milligram	m^3	cubic meter
kg	kilogram	cm^2	centimeter squared

Duration/Frequency of Exposure

1x	one time	d	day
hr	hour	gen	generation
mo	month	min	minutes
wk	week	yr	year
g	gestation	PG	post-gestation

Route

(C)	capsule	(F)	feed
(G)	gavage	(W)	water

No/Sex/Group

F	female	M	male
NS	not specified		

Species

gn pig	guinea pig

Effect

Cardio	cardiovascular	Hemato	hematological
Derm/Oc	dermal/ocular	Musc/Skel	musculoskeletal
Gastro	gastrointestinal	Resp	respiratory

Results

>	increased		
<	decreased		
aden	adenoma	lesn	lesions
adrenalectmy	adrenalectomy	midzon nec	mid-zonal necrosis
bil sec	biliary secretion	mort	mortality
biochem	biochemical	Nuc Hyp Tu Ep	nuclear hypertrophy of tubular epithelium
CEL	cancer effect level	nr	next
degen	degeneration	orn car tr	ornithine carbamoyl transferase
Deg LivCel	degraded liver cells	path chg	pathological change
deg tub ep	degraded tubular epithelium	resorp	resorption
developmt	development	SD	sorbitol dehydrogenase
dispos	disposition	sens	sensitivity
enz act	enzyme activity	ser AKT	serum AKT
fetl anom	fetal anomalies	ser creat	serum creatinine
GSH	glutathione transferase	skel anom	skeletal anomalies
hemoglob	hemoglobin	skel alt	skeletal alterations
histo	histopathology	tub neph	tubular nephrosis
implnt los	implantation loss	TWA	time weighted average
inflt	infiltration	vacuolatn	vacuolation
inflamatn	inflammation	wt	weight

These same trends are seen in mice and hamsters, i.e., nutritional status and sex influence the lethality of DCE following inhalation exposure. However, mice are considerably more susceptible to the lethal effects of DCE than rats. Reported 4-hour LC_{50}s in fed mice range from 100 (males) to 200 ppm (females) (Henschler 1979), and in fasted mice from 40 (males) to 115 ppm (females) (Henschler 1979). The concentration of 40 ppm in air (Henschler 1979) is presented in Table 1-2. Similarly, fasted male Chinese hamsters are more susceptible to the lethal effects of inhaled DCE than fasted females (Henschler 1979; Klimisch and Freisberg 1979a,b).

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

2.2.1.2 **Systemic Effects**

Limited information is available on the systemic effects of inhaled DCE in humans. This information comes primarily from case reports and/or insufficiently detailed mortality studies wherein the concentration and duration of exposure to DCE has not been quantified. Concurrent exposure to other toxic substances cannot be ruled out in most of these cases. Given these limitations, the information available indicates that inhaled DCE can induce neurotoxicity after short-term exposure (Henschler et al. 1970; Tierney et al. 1979) and that DCE is possibly associated with hepato- and nephrotoxicity after repeated, low-level exposure in humans (e.g., Tierney et al. 1979).

Considerable information is also available on the systemic effects of DCE following both short- and long-term exposure in laboratory animals. The target organs or systems of DCE toxicity are reported to be the central nervous system, liver, kidney, and lungs, with adverse effects occasionally being noted in the heart. No studies were located regarding gastrointestinal or musculoskeletal effects in laboratory animals following inhalation exposure to DCE.

One trend that is observed in these studies is that animals are much less tolerant to continuous exposure to DCE than to intermittent exposure. This is because continuous exposure does not allow the animal time to clear the chemical from the body; this will be discussed in detail in the sections on hepatic and renal effects. Another trend observed is that fasting tends to exacerbate the acute toxic effects of DCE in male animals to a greater extent than in female rats.

The level of glutathione (GSH) present in the liver appears to modulate the toxic effects of DCE in animals. GSH is believed to be actively involved in the biotransformation and detoxification of DCE (Andersen et al. 1980; Liebler et al. 1985, 1988--see Section 2.3). Furthermore, the level of binding of reactive intermediate(s) to cellular macromolecules may be reduced

by elevated levels of GSH (Andersen et al. 1978, 1980; Moslen and Reynolds 1985; Okine et al. 1985; Reynolds et al. 1984), which has been proposed to chemically inactivate the reactive intermediate and thereby decrease the toxicity of the chemical. Also, acute inhalation exposure to DCE results in a decrease in hepatic GSH concentration in rats with concomitant manifestation of toxic effects (Jaeger et al. 1974). The role of GSH in DCE-induced toxicity will be explored further in the discussion of hepatic and renal toxicity and in Section 2.3.

Respiratory Effects. Aside from some reports of upper airway irritation in acutely exposed humans (ITII 1982), no studies were located regarding respiratory effects in humans following inhalation exposure to DCE.

Irritation of the mucous membranes and pulmonary edema/congestion and hyperemia are consistently seen at necropsy in rodents acutely exposed to high levels of DCE (500-15,000 ppm) via inhalation (Henschler 1979; Klimisch and Freisberg 1979a; Rylova 1953 and Zeller et al. 1979b). The severity of these effects is increased in fasted rats (Zeller et al. 1979b)

Chronic inhalation exposure to DCE is also associated with adverse respiratory effects as evidenced by irritation of the upper respiratory tract. For example, nasal irritation was observed in rats exposed to 200 ppm for 4 weeks (Gage 1970). Quast et al. (1986) reported inflammation of the trachea in rats exposed to 72 ppm of DCE for 6 months. Other pulmonary effects seen in rats, guinea pigs, and dogs exposed to similar concentrations (189 mg/m^3 or 48 ppm) of DCE for 90 days include discoloration and morphologic changes in the lungs (Prendergast et al. 1967). The concentration of 48 ppm in air (Prendergast et al. 1967) is presented in Table 1-2. These effects appear to be rather nonspecific and are due to DCE's local irritating properties. Therefore, these data suggest that any possible respiratory effects associated with inhalation exposure to DCE (particularly acute) in humans are likely to be just a consequence of local, nonspecific irritation.

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

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following inhalation exposure to DCE. Few studies are available that describe adverse cardiovascular effects of DCE following inhalation exposure in laboratory animals. In one experiment conducted in rats, acute administration of extreme concentrations (25,600 ppm for 10 minutes) produced arrhythmias mediated by the sympathetic nervous system (Siletchnik and Carlson 1974). These authors also found that DCE at 26,500 ppm increased the sensitivity of the myocardium to epinephrine, thereby providing a mechanism for the electrocardiographic changes.

Cardiac effects such as contraction of the main vessels, dilation of the right side (most likely secondary to pulmonary congestion) and hyperemia are

seen following acute, high-level exposure (500-15,000 ppm) to DCE in rodents (Klimisch and Freisberg 1979a,b; Zeller et al. 1979b). Cardiovascular toxicity is generally not seen following more prolonged lower-level exposure, and is, therefore, most likely not a concern for prolonged low-level exposure in humans.

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

Hematological Effects. In several inhalation studies using animals where hematological parameters have been monitored, no statistically significant effects were seen in rats (72 ppm/18 months) (Quast et al. 1986) or mice (55 ppm/1 year) (Lee et al. 1977) as compared to controls. No studies were located regarding hematological effects in humans following inhalation exposure to DCE. However, given the lack of effect noted in animals in two species in well-conducted long-term studies, it is unlikely that DCE adversely affects hematological parameters in humans.

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

Hepatic Effects. Hepatotoxicity has been observed in humans following repeated exposure to DCE, presumably by the inhalation route. Preliminary clinical findings on workers exposed to DCE for up to 6 years in a DCE polymerization plant revealed a high incidence of hepatotoxicity. Liver scans and measurements of liver enzymes revealed marked dysfunction in 27 (59%) of the 47 exposed workers (EPA 1985a; Tierney et al. 1979). These data were presented briefly with little detail, and no follow-up study has been reported. Therefore, these findings must be considered only to be qualitative in nature.

The liver is a major target organ of DCE toxicity following both acute and longer-term inhalation in laboratory animals. Hepatotoxicity is evident by the appearance of both biochemical changes (alterations in serum enzyme levels, indicative of liver dysfunction and induction of hepatic enzymes) and marked histological changes (e.g., midzonal and centrilobular swelling, degeneration, and necrosis). These effects appear to follow a dose-response relationship that may also be influenced by duration of exposure. Mice inhaling 50 ppm DCE for 6 hours exhibited only slight centrilobular swelling (Reitz et al. 1980; Watanabe et al. 1980), whereas continuous inhalation exposure of mice to 15 ppm DCE for 23 hours/day for 5 days resulted in an increase in serum enzymes indicative of liver dysfunction, and hepatic degeneration was seen at 60 ppm under the same exposure regimen (Short et al. 1977c). The concentrations of 15 and 60 ppm in air (Short et al. 1977c) are presented in Table 1-2. Similar results were obtained in four strains of mice that were exposed to DCE by inhalation at concentrations of 55, 150 and 200 ppm 6 hours/day, 5 days/week for 10 days. Hepatotoxic effects (characterized by hepatocellular degeneration and necrosis with centrilobular

hepatocellular swelling and pleomorphism at 100 and 200 ppm) were observed in all strains, with the effects being more severe in the females (Henck et al. 1979). Severe effects are seen at higher doses in rats at even shorter duration exposures. Four-hour inhalation exposure to 200-250 ppm of DCE resulted in increased liver weight, induction of certain liver enzymes (Jackson and Conolly 1985; Jaeger 1977) and massive histologic injury (Reynolds et al. 1980).

The degree of DCE-induced hepatotoxicity is influenced by the nutritional status of the organism, with more severe effects displayed by animals fasted overnight prior to exposure. This suggests that a relationship exists between chemical toxicity and depletion of GSH (Reynolds et al. 1980). For exampl , results from acute studies in both fed and fasted male rats demonstrate that inhalation exposures to low levels (60 to 200 ppm) of DCE for periods ranging from 75 minutes to 23 hours induced increases in serum enzyme levels indicative of liver dysfunction--aspartate aminotransferase (AST) and alanine aminotransferase (ALT)--in fasted animals, but not in fed animals (Andersen et al. 1979; Jaeger et al. 1974; Jaeger et al. 1975b). Only a slight increase in these serum enzymes was seen in fed rats exposed to DCE at levels of 2,000 ppm or above (Jaeger et al. 1974). Gross, histological and biochemical evidence of hepatotoxicity is seen earlier and is more extensive in fasted rats following short-term inhalation exposure to DCE. Inhalation of 200 ppm of DCE by fasted rats for up to 4 hours resulted in aberrations in hepatic sodium, potassium, calcium, and GSH levels which preceded and/or accompanied major histologic changes (Jaeger et al. 1975b; McKenna et al. 1978a; Reynolds et al. 1980). As mentioned above, the increased hepatotoxic effects of DCE following inhalation exposure seen in fasted vs. fed animals may be related to depletion of hepatic GSH levels in the fasted animals. GSH is known to be involved in the metabolism of DCE (see Section 2.3). Jaeger et al. (1973a) reported that GSH levels in rats fed ad libitum exhibited a marked diurnal rhythm with levels being minimal at 1900-2200 hr and maximal at 0700-1300 hr. This increase was prevented in fasted rats, with maximal levels reduced by 50%. They further demonstrated that DCE-induced hepatotoxicity coincided with the reduction in liver GSH levels. Fed rats exposed to DCE via inhalation during the period 1000-1400 hours exhibited no signs of hepatotoxicity whereas 40% mortality and a marked increase in serum enzyme markers was seen in fed rats exposed to similar levels of DCE during the period of minimal GSH levels.

The hepatotoxic effects of DCE following intermediate or chronic exposure in animals resemble those described above for acute exposure (e.g., Gage 1970; Lee et al. 1977; Quast et al. 1986). Many of the studies that describe the longer-term effects of DCE in animals are limited in that there is often a lack of experimental detail reported or only one or two doses are studied. This often prevents a full assessment of the quality of the results. Male and female rats exposed 6 hours/day, 5 days/week over a 30-day period to 125 or 200 ppm DCE exhibited liver changes. These changes were more severe in females, and were characterized by a minimal degree of centrilobular fatty degeneration or hepatocellular necrosis (Quast 1976). Mild dose-related

hepatotoxic effects consisting of cytoplasmic vacuolation were observed in male and female rats exposed to 25 or 75 ppm DCE 6 hours/day, 5 days/week for either 30 or 90 days (Balmer et al. 1976). The authors considered these changes to be reversible. Quast et al. (1986) reported that rats exposed to 25 ppm DCE 6 hours/day, 5 days/week for six months exhibited fatty infiltration of the liver. Based on this value, an intermediate inhalation MRL of 0.02 ppm was calculated, as described in the footnote in Table 2-1. This MRL has been adjusted for intermittent exposure and human breathing rate and is presented in Table 1-1. The concentration of 4 ppm (Quast et al. (1986) in air is presented in Table 1-2.

Animals appear to be much less tolerant to continuous exposure (23-24 hours per day) than to intermittent exposure to DCE. There was no evidence of toxicity in beagles exposed to 100 ppm of DCE for 8 hours/day, 5 days/week for 43 days, but continuous exposure to 48 ppm of DCE for 90 days resulted in marked liver damage (Prendergast et al. 1967). Similarly, marked evidence f liver damage was exhibited by squirrel monkeys continuously exposed to 48 ppm f DCE for 90 days, whereas no liver toxicity was apparent following 42 days of intermittent exposure to 100 ppm DCE (Prendergast et al. 1967). It would appear that when animals are exposed to DCE on an intermittent basis, they are better able to compensate for the toxic effects induced by this chemical. This observation supports the involvement of depletable stores of liver GSH as a possible mediator of DCE-induced hepatotoxicity.

Hepatotoxic effects similar to those discussed above are seen following chronic inhalation exposure to DCE in laboratory animals (e.g., Lee et al. 1977, Quast et al. 1986). Quast et al. (1986) observed that rats exposed to DCE via inhalation at a time-weighted average concentration of 24 ppm 6 hours/day, 5 days/week for 18 months exhibited fatty changes in the liver. Based on this value, a chronic inhalation MRL of 0.03 ppm was calculated, as described in the footnote in Table 2-1. This MRL has been adjusted for intermittent exposure, and human breathing rate and this value is presented in Table 1-1. The concentration of 4 ppm (Quast et al. 1986) in air is presented in Table 1-2. The information available on chronic inhalation exposure to DCE in animals is generally limited, and the quality of reporting is generally poor.

In conclusion, hepatotoxic effects have been observed in experimental animals following inhalation exposure to DCE. The reversibility of the hepatotoxic effects of DCE has not been studied. The limited information available on human exposure indicate that DCE is hepatotoxic. Thus, one may assume, based on the studies in several species of animals, that humans are at risk for DCE-induced liver toxicity following inhalation exposure to this chemical at high levels and/or for prolonged periods.

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

2. HEALTH EFFECTS

Renal Effects. No studies were found regarding renal effects in humans following inhalation exposure to DCE. However, adverse effects have been observed in the kidneys of laboratory animals following acute, intermediate, and chronic inhalation exposure to DCE. These effects are manifested as enzyme changes (decreases in kidney monooxygenase and epoxide hydrolase levels) (Oesch et al. 1983), functional changes (hemoglobinuria) (McKenna et al. 1978a), gross changes (increase in organ weight) (Henck et al. 1979; Quast et al. 1986), and histological changes (tubular swelling, degeneration and necrosis) (Henck et al. 1979; Jackson and Conolly 1985; Lee et al. 1977; McKenna et al. 1978a; Prendergast et al. 1967; Reitz et al. 1980; Short et al. 1977c; and Watanabe et al. 1980). Following acute exposure, the range of DCE concentrations that produced the aforementioned effects in rats is 50-300 ppm, with the severity of the kidney lesions increasing with increasing dose and duration of exposure. Male mice appear to be more susceptible to the acute nephrotoxic effects of inhaled DCE than female mice or rats of both sexes. Severe histological lesions of the kidney are often seen in mice following acute inhalation exposure to 10-50 ppm of DCE (Reitz et al. 1980; Short et al. 1977c; Watanabe et al. 1980). The concentrations of 10 ppm and 50 ppm (Reitz et al. 1980; Short et al. 1977c; Watanabe et al. 1980) in air and the renal histological changes resulting from the exposure in mice are presented in Table 1-2. Similar results were obtained in four strains of mice that were exposed to DCE by inhalation at concentrations of 55, 150 and 200 ppm 6 hours/day, 5 days/week for 10 days. Adverse renal effects (characterized by moderate to severe nephrosis) were observed in all strains, with the effects observed predominantly in the males. (Henck et al. 1979). There is evidence that the kidney damage produced by acutely inhaled DCE in animals is reversible, though this may depend on the dose level and duration of exposure. Reitz et al. (1980) reported that tubular regeneration was evident in mice 48 hours after a single 6-hour exposure to 50 ppm DCE. However, reversibility of kidney damage at higher concentrations of exposure has not been demonstrated.

As was seen with hepatotoxicity, the nutritional status of the animal appears to be an important determinant of DCE-induced nephrotoxicity. McKenna et al. (1978a) observed that fasted male rats exposed once to 200 ppm DCE for 6 hours exhibited delayed hemoglobinuria and marked tubular degeneration, while fed male rats similarly exposed displayed no treatment-related toxic effects. GSH depletion may play an indirect role in the exacerbation of DCE-induced nephrotoxicity.

Though the bulk of the information on DCE-induced nephrotoxicity in animals comes from acute experiments, there is limited evidence that nephrotoxicity is also seen following intermediate exposure. Prendergast et al. (1967) reported that continuous inhalation exposure of rats to 189 mg/m^3 (48 ppm) of DCE for 90 days resulted in nuclear hypertrophy of the renal tubular epithelium in all rats examined. Maltoni et al. (1985) reported that severe nephrotoxicity occurred in male mice exposed to 25 ppm DCE 4 hours/day, 4-5 days/wk for one year. The concentrations of 25 and 48 ppm in air (Maltoni et al. 1985; Prendergast et al. 1967) are presented in Table 1-2. The

reversibility of this effect was not determined. No treatment-related effects were noted in the kidneys of rats chronically exposed to DCE at a time-weighted average concentration of 24 or 72 ppm for 6 hours/day, 5 days/week for 18 months (Quast et al. 1986).

Though data on kidney toxicity following inhalation exposure to DCE in humans are lacking, evidence from animal studies in two species suggest that DCE may also exhibit a toxic effect on the kidney of humans, particularly following acute DCE exposure. The limited animal data on the kidney effects of inhaled DCE following more prolonged exposure at lower concentrations coupled with the observation that the nephrotoxic effects are reversible after acute exposure is terminated suggest that repair mechanisms may be operating. DCE-induced nephrotoxicity may be transient and reversible; the effects in humans exposed to low levels over a long period of time are not known.

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

Dermal/Ocular Effects. Limited information was found regarding the dermal/ocular effects of inhaled DCE in humans or animals. No eye irritation was observed in rats exposed to a time-weighted-average (TWA) concentration of 72 ppm DCE for 18 months (Quast et al. 1986). This LOAEL is recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.3 Immunological Effects

No studies were found regarding immunological effects in humans or animals following inhalation exposure to DCE.

2.2.1.4 Neurological Effects

Central nervous system depression with accompanying symptoms of inebriation, which may progress to convulsions, spasms, and unconsciousness have been observed in humans acutely exposed to high concentrations (approximately 4,000 ppm) of inhaled DCE (Tierney et al. 1979). Complete recovery occurs if exposure is not prolonged. In addition, two cases of persistent cranial nerve disorders were observed involving primarily the trigeminal nerve and, to a lesser extent, the hypoglossal, occipital, auricular, and cervical cutaneous nerves, as well as the innervation of muscles of mastication, and the eye muscles (Henschler et al. 1970). These two patients were involved in the manual cleaning of tanks used in the transport of an aqueous dispersion of DCE copolymers. The effects were most likely a result of dichloroacetylene formation from DCE as a result of heat and the presence of alkali from the soaps used. Chloroacetylenes are highly neurotoxic (Fielder et al. 1985). Although this does not provide direct evidence that DCE can produce adverse neurological effects, it is possible that similar conditions may occur (i.e. heat and an alkali environment) which generate chloroacetylenes at hazardous waste sites where DCE is present.

Signs of central nervous system toxicity are the predominant effect observed in animals acutely exposed to high concentrations of DCE via the inhalation route. The toxic signs are similar across species and consist primarily of central nervous system depression, lacrimation, dyspnea, tremor, convulsions, uncoordinated motor response, and narcosis, finally resulting in death (e.g., Henschler 1979; Klimisch and Freisberg 1979a,b; Zeller et al. 1979a,b). These symptoms can also be accompanied by lethargy, stark coats and a hunched appearance (Zeller et al. 1979b).

No studies were found regarding neurolo cal effects in humans or animals following intermediate or chronic exposure.

All reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-1 and Figure 2-1.

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans following acute inhalation exposure to DCE.

Based upon studies by Short et al. (1977a), DCE has weak teratogenic effects in laboratory animals. Prenatal exposure resulted in soft tissue anomalies in rats and skeletal defects in rats, mice, and rabbits. Maternal toxicity, as evidenced by decreased body weight and death, was also observed at developmentally toxic doses. Doses of DCE used in these studies ranged from 15 ppm to 449 ppm. Increased mortality was observed in both pregnant and nonpregnant mice at exposure concentrations of 144 ppm and above and in pregnant rats at 57 ppm and above. Skeletal anomalies were seen at 15 ppm in mice. In the interest of public health, an acute inhalation MRL of 0.9 ppm was calculated based on this value, as described in the footnote in Table 2-1. This value, adjusted for human breathing rate is presented in Table 1-1 (Short et al. 1977a). Though it is not optimal to base an MRL on a serious effect, developmental effects appear to be the most sensitive endpoint of DCE-induced toxicity for this duration of exposure. Thus, an MRL calculated from this value would be most protective of human health. The concentration of 15 ppm (Short et al. 1977a) in air is presented in Table 1-2. Because a high incidence of resorption was observed in these initial experiments, Short et al. (1977a) conducted additional studies in mice. Pregnant animals were exposed via inhalation to various concentrations of DCE ranging from 41 to 112 ppm. These experiments were carried out over different exposure durations that covered various phases of fetal development. The statistical analysis by two sample rank tests demonstrated that the treatment-induced increases in resorption frequency were significantly reduced at the shorter exposure periods, although the treatment-related weight loss was still evident in the dams. The viable pups demonstrated a variety of soft tissue anomalies, such as hydrocephalus, microphthalmia, cleft palate, and hydronephrosis. Skeletal anomalies were also present.

Murray et al. (1979) reported a statistically significant increase in the incidence of skeletal anomalies following inhalation of DCE in rats at 80 and 160 ppm and in rabbits at 160 ppm. Developmental toxicity was evidenced by wavy ribs and delayed ossification in rat fetuses, and by increased resorption and skeletal alterations in rabbit fetuses. A statistically significant decrease in maternal body weight gain was also noted at these concentrations. In this study, no statistically significant adverse effects were noted in rats at 20 ppm or in rabbits at 80 ppm.

Thus, among all these developmental studies discussed above, the most sensitive indicators of hazard were maternal and developmental toxicity. The LOAEL in rats for these end points was 15 ppm (Short et al. 1977a). A NOAEL for developmental toxicity following continuous inhalation exposure was not identified. Based upon these studies in laboratory animals, it would be prudent to consider that potential adverse maternal and developmental effects from exposure to DCE could occur in humans.

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

2.2.1.6 Reproductive Effects

No studies were located regarding reproductive effects in humans following acute inhalation exposure to DCE.

Studies by Short et al. (1977a) demonstrated that inhalation exposure of pregnant dams to DCE produced a statistically significant increase in the incidence of early embryo resorptions in rats at 57 and 449 ppm (49% and 64% resorptions, respectively) and in mice exposed at 57 ppm (100% resorption), but a dose-response was not observed. In another study by Short et al. (1977b), pre-mating exposure of male rats to DCE at 55 ppm did not affect their fertility. This was evidenced by the lack of pre- and post-implantation losses in untreated pregnant females resulting from the matings with treated males. Anderson et al. (1977) found that inhalation exposure of male mice to 10 and 30 ppm of DCE 6 hours/day for 5 days had no adverse effect on fertility. Decreased fertility was observed at inhalation concentrations of 50 ppm, but the authors attributed this to infertility in males that ordinarily might not have been used, but had to be included in the study in order to establish a group of sufficient size. The biological significance of these findings in animals with regard to potential reproductive effects in humans is not known.

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

2.2.1.7 Genetic Effects

No studies were located regarding genotoxic effects in humans following inhalation exposure to DCE. Inhalation of DCE vapors in animals has not been shown to result in dominant lethal gene mutations (Anderson et al. 1977; Short et al. 1977b), but it has been observed to produce DNA damage as indicated by slightly increased DNA repair rates in cells of mouse kidney (in which normal replicative DNA synthesis had been inhibited) (Reitz et al. 1980). Inhalation of DCE has been associated with minimal rates of DNA alkylation in mouse and rat kidney and liver cells (Reitz et al. 1980). These data suggest that inhalation exposure to DCE does not lead to significant levels of unrepaired DNA damage in the germ cells of the testes at the doses tested (as shown by the lack of a dominant lethal effect). However, these same doses are capable of inducing low levels of DNA damage in kidney cells of mice and minimal alkylation in liver and kidney.

2.2.1.8 Cancer

No relationship between the occurrence of cancer in humans and occupational exposure (primarily chronic inhalation exposure) to DCE has been demonstrated. However, only three studies are currently available for analysis.

Chronic occupational exposure to DCE was not associated with the occurrence of angiosarcoma in rubber-plant workers (Waxweiler 1981). Similarly, no association was found between morbidity and mortality and occupational exposure to DCE in DCE production and polymerization plant workers (Ott et al. 1976). Thiess et al. (1979) also studied workers in a DCE production and polymerization plant and found no association between exposure and cancer mortality. Both the Ott et al. (1976) and Thiess et al. (1979) studies are limited in their usefulness in assessing the cancer risk to humans exposed to DCE. In both studies the cohort size was limited, the observation period was too short, and there was a small number of deaths from specific causes. No allowance was made for a latency period, thus resulting in an overestimation of risk. Despite these limitations, the results of the Ott et al. (1976) study are of some value. These authors intended to conduct only a mortality study and not a carcinogenicity study and they recognized the need to do additional research before any definitive conclusions could be drawn.

The carcinogenicity of DCE in laboratory animals following inhalation exposure has been evaluated in intermediate and chronic studies with rats, mice, and Chinese hamsters (Hong et al. 1981; Lee et al. 1977, 1978; Maltoni et al. 1982, 1985; Quast et al. 1986; Rampy et al. 1977; Viola and Caputo 1977). Exposure concentrations of DCE in these studies ranged from 10 ppm to 150 ppm. Of the long-term inhalation bioassays conducted in laboratory animals to date, only the results of a study by Maltoni et al. (1985) in mice have provided some suggestive evidence of a carcinogenic effect associated with DCE exposure.

In a study reported by Maltoni et al. (1985), male and female Swiss mice were exposed by inhalation to DCE for 4 hours/day, 4-5 days/week at concentrations of 0, 10, or 25 ppm for 1 year, and then observed until spontaneous death occurred. Increases in both malignant and nonmalignant tumors were observed. In female mice of both treatment groups (10 and 25 ppm), carcinomas of the mammary gland were increased. Lung tumors (most of which were benign pulmonary adenomas) were increased in males at 10 ppm, and in both males and females at 25 ppm. Although the authors stated that these increases were statistically significant, no statistical analyses were presented. The authors concluded that no dose-response relationship could be established for either increased tumor incidence. Of the 150 high-dose males in the 25 ppm groups examined, 28 had renal adenocarcinomas, but no such tumors were found in either the 30 males in the low-dose (10 ppm) group nor in the 186 control males. Renal adenocarcinomas are rare tumors in the Swiss mouse. The kidney tumors were accompanied by severe nephrotoxic effects including nephrosis. Indeed, an increased incidence of renal tumors in the male mice was only observed at doses that induced toxicity and were near the acutely lethal concentration. Only one female developed kidney tumors, whereas there appeared to be no difference between the sexes with regard to the incidence of regressive changes in the kidney. Thus, it is difficult t assess whether the occurrence of nephrosis predisposes the animal to the development of kidney tumors. However, this study can only be used to provide suggestive evidence of DCE-induced carcinogenicity in animals because the maximum tolerated dose (MTD) appeared to have been exceeded.

Maltoni et al. (1985) reported an increased incidence of malignant mammary tumors and leukemias in rats exposed to 100 ppm of DCE by inhalation 7 hours/day, 5 days/week. Inhalation exposure commenced on pregnant females on gestation day 12, and continued in mothers and approximately half of the offspring of both sexes (in 12-day and older embryos via transplacental exposure followed by inhalation exposure for all exposed animals in this group) for 104 weeks. The other half were exposed for 15 weeks only. The highest tumorigenic response was seen in offspring treated for 104 weeks. The authors concluded that under conditions of exposure to high doses during embryonal development and later, DCE is carcinogenic in rats. However, there are several flaws that limit the usefulness of this study; no statistical analyses were presented, and ambiguous terminology (i.e., "total malignant tumors") was employed to present the results.

Results of other inhalation studies with laboratory animals have provided negative results with respect to the carcinogenicity of DCE (e.g., Hong et al. 1981; Lee et al. 1977, 1978; Maltoni et al. 1982, 1985; Quast et al. 1986; Rampy et al. 1977; Viola and Caputo 1977). In studies by Lee et al. (1977, 1978), mice and rats were exposed by inhalation to DCE at concentrations of 0 or 55 ppm for 1 year. Few hepatic hemangiosarcomas, hepatomas, bronchioalveolar adenomas, and skin keratoacanthomas were observed in experimentally treated mice, whereas some of the rats exposed to 55 ppm DCE had hemangiosarcoma of the mesenteric lymph nodes and of the subcutaneous tissue. These incidences were not statistically significant. Carcinogenicity

was examined in rats and mice during a 12-month period subsequent to the exposures described in Lee et al. (1977, 1978) in a follow-up study conducted by Hong et al. (1981). Except for mammary tumors in female mice, no significant increase in cumulative tumor incidence was observed in either species at 55 ppm DCE, regardless of duration of exposure. Though the increased tumor incidences observed in the Lee et al. (1977, 1978) and Hong et al. (1981) studies were not statistically significant, these studies provide evidence of the differences in species and strain sensitivity to the effects of DCE exposure.

Quast et al. (1986) administered DCE by inhalation to male and female rats at concentrations of 0, 25, or 75 ppm for 18 months. A statistically significant increase ($p<0.05$) in adenocarcinomas of the mammary gland was noted in the low-dose females (25 ppm). This increase was not considered by the authors to be related to inhalation of DCE because the incidences of mammary gland adenocarcinomas were within the range of historical control data and were not dose-related.

Maltoni et al. (1985) exposed female and male rats to DCE at concentrations of 0, 10, 25, 50, 100, or 150 ppm for 1 year. An increase in the incidence of total mammary tumors (fibroadenomas, carcinomas, sarcomas, carcinosarcomas) was observed in females of the 10 and 100 ppm exposure groups. However, evidence for a carcinogenic effect from inhalation exposure of DCE in this study was inconclusive because (a) there was no clear dose-related increase in total mammary tumor incidence, (b) the latency time for mammary tumor incidence was similar in all treated and control groups, (c) there was a high (62%) incidence of spontaneous mammary tumors in controls, and (d) the incidence of mammary gland carcinomas in treated groups was lower than that of controls (Maltoni et al. 1985).

The effects of chronic inhalation exposure of CD-1 mice and CD rats to 55 ppm DCE for 12 months was studied by Lee et al. (1978, 1979). There was no statistically significant increase in tumors at any of the sites examined compared to the respective control animals. However, two treated male rats and three mice exhibited hemangiosarcomas, an uncommon tumor type, while n ne were found in the controls. The authors claimed that rats were more resistant to the carcinogenic effects of DCE, but the data do not support this since there was no significant increase in the incidence of tumors in either species, and the incidence of hemangiosarcomas was practically the same across the two species. The short duration of this study may have precluded observing tumors that have a long latency period.

In a follow-up study, CD-1 mice and CD rats were exposed to 55 ppm DCE by inhalation for 1, 3, or 6 months (mice) or 1, 3, 6, or 10 months (rats) followed by a 12 month observation period (Hong et al. 1981). There was a high incidence of mortality; in the groups that were exposed the longest, 18% and 21% of the control mice, 50% and 42% of the treated mice, 38% and 44% of the control rats, and 79% and 56% of the treated rats died before terminal sacrifice. There was no statistically significant increase in the incidence

of tumors in any of the treated animals, though tumors were observed in some treated and control animals. The small number of animals in each group weakens the ability of this study to detect a tumorigenic response, and the exposure durations were considerably less than lifetime.

The negative findings of various inhalation studies may be partially explained by inadequate test conditions (EPA 1985a). Study limitations for many of these investigations included less than lifetime exposure, use of concentrations below or above the maximum tolerated dose, use of single exposure concentrations, small numbers of animals, and/or limited gross or microscopic examinations (Hong et al. 1981; Lee et al. 1977, 1978; Maltoni et al. 1982, 1985; Quast et al. 1986; Rampy et al. 1977; Viola and Caputo 1977). Such limitations reduce the sensitivity of a test to detect a carcinogenic response.

EPA has derived a q_1^* of 1.2 $(mg/kg/day)^{-1}$ for cancer risk associated with inhalation exposure to DCE based on the study by Maltoni et al. (1985) in mice. This value is plotted in Figure 2-1.

2.2.2 Oral Exposure

Figure 2-2 and Table 2-2 describe the health effects observed in laboratory animals associated with oral exposure level at varying time and exposure durations. The MRL to humans for adverse effects (other than cancer effects) is also presented for the oral route of exposure.

2.2.2.1 Death

No studies were located regarding lethality in humans following oral exposure to DCE. Death has been observed in laboratory animals following the ingestion of DCE. The database on the lethality of ingested DCE in animals consists primarily of gavage studies in fasted rats. Few data were found on lethality in mice or other species.

Reported oral LD_{50}s in rats are approximately 1,500 mg DCE/kg body weight (Jenkins et al. 1972; Jones and Hathway 1978a). The threshold for mortality 10 percent mortality in male rats is 50 DCE mg/kg in corn oil (Andersen and Jenkins 1977). No short-term studies of DCE administered in food were located; therefore, the dose level of 50 mg/kg/day, which was administered by gavage in corn oil, was converted to an equivalent concentration of 1,000 ppm in food for presentation in Table 1-4. The limited data available for mice indicate that this species is considerably more sensitive than rats to the lethal effects of ingested DCE. Reported LD_{50} values in mice are approximately 200 mg DCE/kg body weight (Jones and Hathway 1978a).

Since all available data are from fasted animals, it is difficult to assess if the nutritional status of the animal influences the lethality of ingested DCE, as was the case for inhalation exposure. Jenkins et al. (1972) demonstrated that adrenalectomy exacerbates the lethal effects of ingested DCE

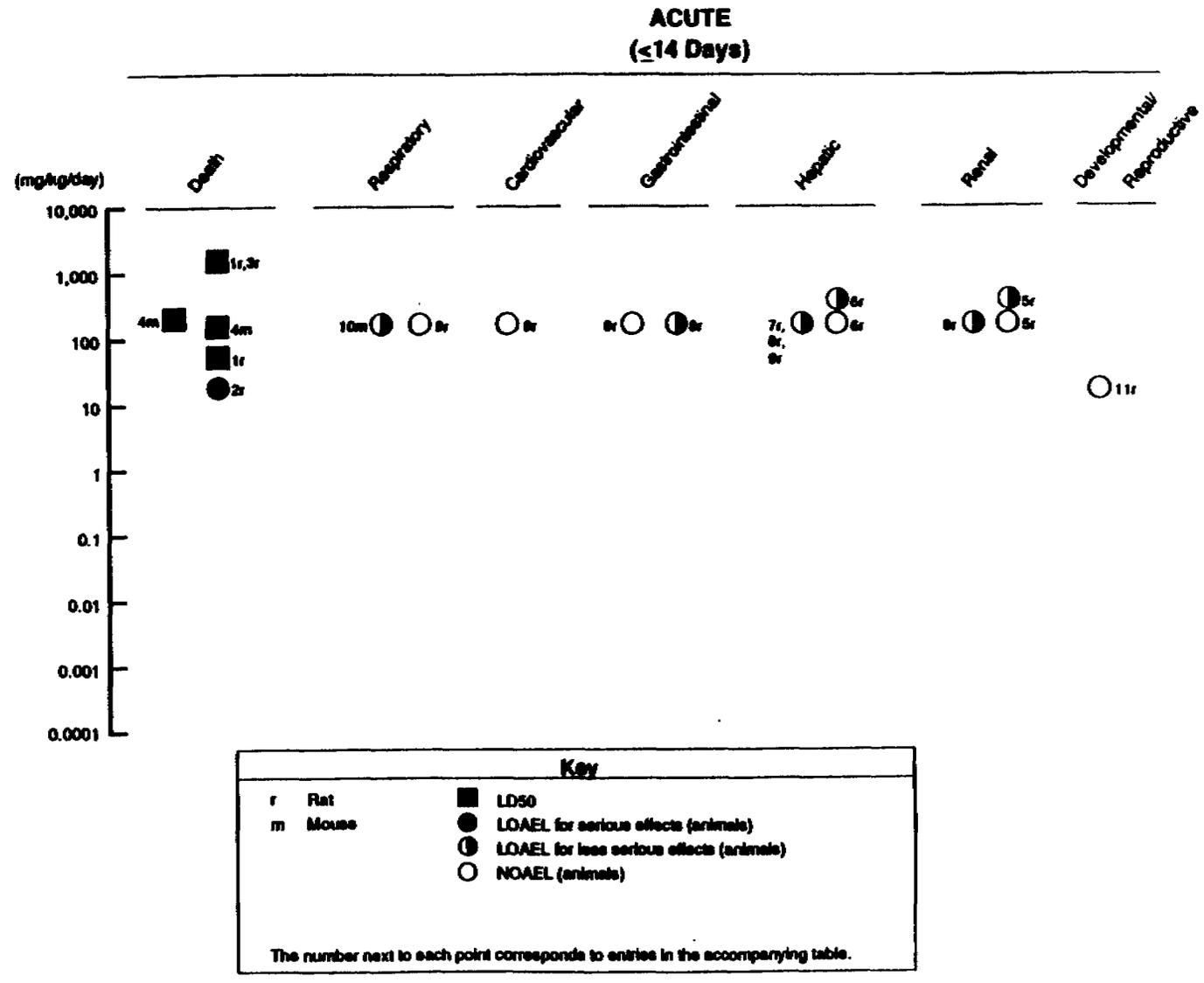

FIGURE 2-2. Levels of Significant Exposure To DCE - Oral

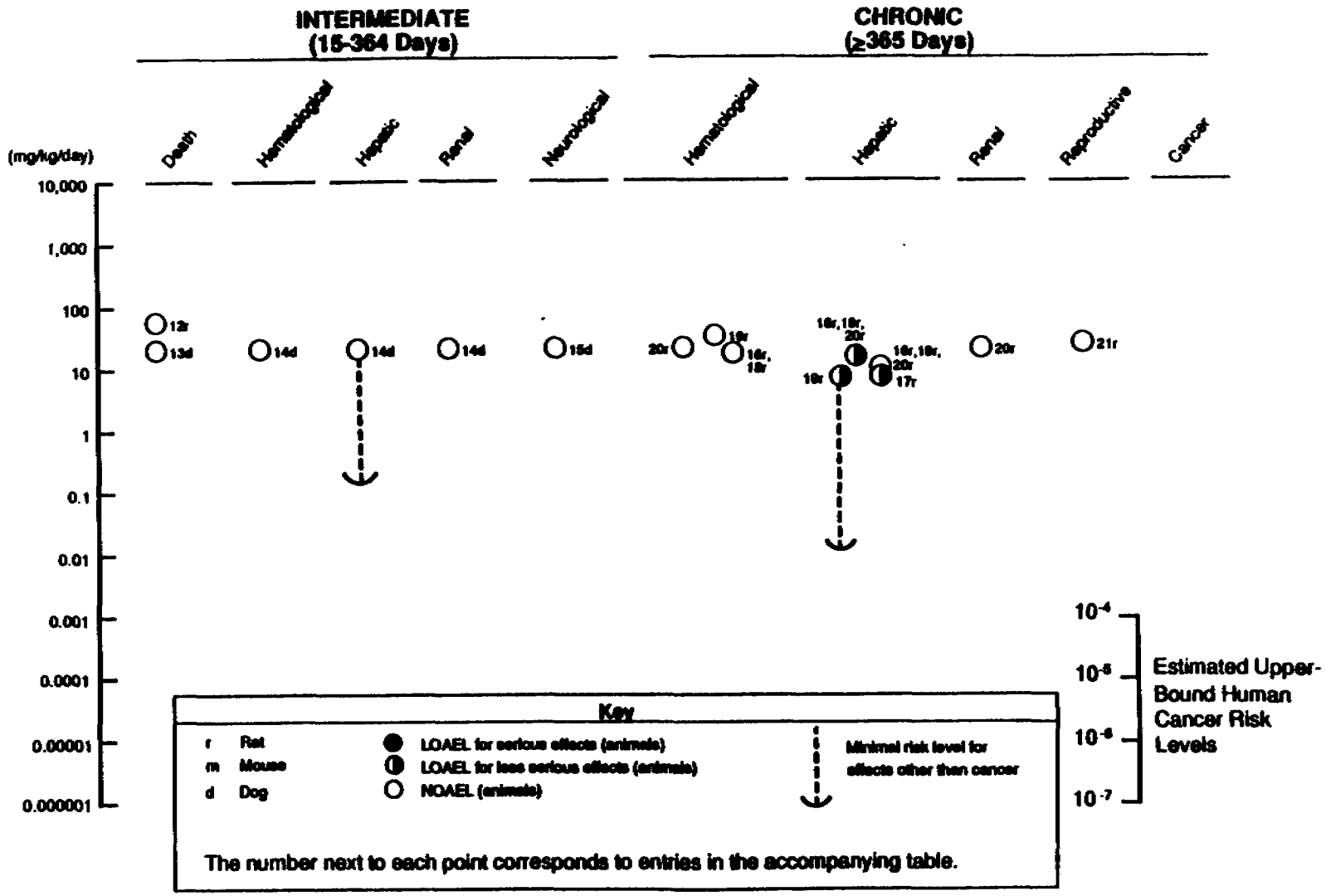

FIGURE 2-2. Levels of Significant Exposure To DCE - Oral (Continued)

TABLE 2-2. Levels of Significant Exposure to 1,1-Dichloroethene - Oral

Graph Key	Species	Route	Exposure Duration/ Frequency	Effect	NOAEL	LOAEL (Effect) Less Serious	LOAEL (Effect) Serious	Reference
					(mg/kg/day)			
ACUTE EXPOSURE								
Death								
1	rat		NS				1,500 **(LD50) 80 **(LD50 - adrenalect)	Jenkins et al. 1972
2	rat	(G)	1 d 1 x				50 **(M)	Andersen and Jenkins 1977
3	rat	(G)	1 d 1 x				1,550 (LD50)	Jones and Bathway 1978a
4	mouse	(G)	1 d 1 x				194 (LD50 - F) 217 (LD50 - M)	Jones and Bathway 1978a
Systemic								
5	rat	(G)	1 d 1 x	Renal	200**	400** (histo, > ser. creat.)		Jenkins and Andersen 1978
6	rat	(G)	1 d 1 x	Hepatic	200	400 (fatty)		Jaeger et al. 1973b
7	rat	(G)	1 d 1 x	Hepatic		200 (< bil sec)		Moslen et al. 1985
8	rat	(G)	1 d 1 x	Gastro Hepatic Renal		200 (histo) 200 (histo) 200 (histo)	200 (histo)**	Chieco et al. 1981

TABLE 2-2 (Continued)

Graph Key	Species	Route	Exposure Duration/ Frequency	Effect	NOAEL	LOAEL (Effect) Less Serious	LOAEL (Effect) Serious	Reference
					(mg/kg/day)			
9	rat	(G)	1 d 1 x	Resp Cardio Gastro Hepatic	200 200 200		200 (histo)**	Chieco et al. 1981
10	mouse	(G)	1 d 1 x	Resp		200 (histo)		Forkert et al. 1985
Developmental								
11	rat	(W)	10 d g6-15 ad lib		40			Murray et al. 1979
INTERMEDIATE EXPOSURE								
Death								
12	rat	(W)	90 d 7d/wk		60			Moore 1980
13	dog	(C)	97 d 1x/d		25			Quast et al. 1983
Systemic								
14	dog	(C)	97 d 1x/d	Hepatic Hemato Renal	25[a] 25 25			Quast et al. 1983
Neurological								
15	dog	(C)	97 d 1x/d		25			Quast et al. 1983
CHRONIC EXPOSURE								
Systemic								
16	rat	(W)	2 yr ad lib	Hepatic Hemato	10 19.3	19.3 (histo - M)		Rampy et al. 1977

TABLE 2-2 (Continued)

Graph Key	Species	Route	Exposure Duration/ Frequency	Effect	NOAEL	LOAEL (Effect) Less Serious	LOAEL (Effect) Serious	Reference
					(mg/kg/day)			
17	rat	(W)	3 gen cont.	Hepatic		7 (fatty infilt)		Nitschke et al. 1983
18	rat	(W)	2 yr ad lib	Hepatic Hemato	10 20	20 (histo - M)		Quast et al. 1983
19	rat	(W)	2 yr ad lib	Hemato Hepatic	30	9[b] (swelling midzon fatty changes-F)		Quast et al. 1983
20	rat	(W)	2 yr ad lib	Hemato Hepatic Renal	25.6 10.0 25.6	19.3 (>vacuolatn)		Rampy et al. 1977
Reproductive								
21	rat	(W)	3 gen ad lib		28			Nitschke et al. 1983

[a]Used to derive an intermediate oral MRL; divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) resulting in an MRL of 0.25 mg/kg/day.

[b]Used to derive a chronic oral MRL; divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans and 10 for human variability) resulting in an MRL of 0.009 mg/kg/day. This MRL has been converted to an equivalent concentration in food (0.32) for presentation in Table 1-3.

**Fasted prior to exposure

TABLE 2-2 (Continued)

Legend for Levels of Significant Exposure Tables for Toxicity Studies for 1,1-Dichloroethene

Header

NOAEL	no-observed-adverse-effect-level		
LOAEL	lowest-observed-adverse-effect-level		
mg	milligram	m^3	cubic meter
kg	kilogram	cm^2	centimeter squared

Duration/Frequency of Exposure

1x	one time	d	day
hr	hour	gen	generation
mo	month	min	minutes
wk	week	yr	year
g	gestation	PS	post-gestation

Route

(C)	capsule	(F)	feed
(G)	gavage	(W)	water

No/Sex/Group

F	female	M	male
NS	not specified		

Species

gn pig	guinea pig

Effect

Cardio	cardiovascular	Hemato	hematological
Derm/Oc	dermal/ocular	Musc/Skel	musculoskeletal
Gastro	gastrointestinal	Resp	respiratory

Results

>	increased		
<	decreased		
aden	adenoma	lesn	lesions
adrenalectmy	adrenalectomy	midzon nec	mid-zonal necrosis
bil sec	biliary secretion	mort	mortality
biochem	biochemical	Nuc Hyp Tu Ep	nuclear hypertrophy of tubular epithelium
CEL	cancer effect level	nr	next
degen	degeneration	orn car tr	ornithine carbamoyl transferase
Deg LivCel	degraded liver cells	path chg	pathological change
deg tub ep	degraded tubular epithelium	resorp	resorption
developmt	development	SD	sorbitol dehydrogenase
dispos	disposition	sens	sensitivity
enz act	enzyme activity	ser AKT	serum AKT
fetl anom	fetal anomalies	ser creat	serum creatinine
GSH	glutathione transferase	skel anom	skeletal anomalies
hemoglob	hemoglobin	skel alt	skeletal alterations
histo	histopathology	tub neph	tubular nephrosis
implnt los	implantation loss	TWA	time weighted average
infilt	infiltration	vacuolatn	vacuolation
inflamatn	inflammation	wt	weight

in rats. They reported that the oral LD_{50} for DCE in adrenalectomized animals is 80 mg DCE/kg body weight. The mechanism and significance of this effect is unclear, but may involve a compromise in the animal's response to stress.

Oral administration of a single dose of DCE to fasted rats revealed that young male rats (100-200 g) appeared to be more susceptible to the lethal effects of this chemical (Andersen and Jenkins 1977). This age-dependent differential toxicity was not seen in females, although male rats exhibited enhanced toxicity upon fasting prior to inhalation exposure.

In summary, ingested DCE is moderately toxic in at least two species of laboratory animals. Young animals and those with compromised stress responses appear to be most susceptible to these effects. Therefore, orally-ingested DCE at high doses is likely to cause death in humans, and younger members (particularly males) of the population may be at higher risk.

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

2.2.2.2 Systemic Effects

No studies were located regarding systemic effects in humans following oral exposure to DCE. However, DCE has been shown to adversely affect several organ systems in laboratory animals. The major target organs of DCE toxicity following oral administration to laboratory animals are the liver and kidney. In addition, some evidence exists for DCE-induced adverse effects on the respiratory system (lungs), digestive tract (rat forestomach) and kidney following oral administration. No reports were identified that discussed adverse cardiovascular, hematological, dermal, or ocular consequences of acute, intermediate, or chronic oral treatment with DCE.

Respiratory Effects. No studies were located regarding respiratory effects in humans following oral exposure to DCE. Pulmonary injury has been reported in mice following the oral administration of a single dose of 200 mg DCE/kg body weight (Forkert et al. 1985). Histopathological changes were observed in Clara cells within 24 hours, and these were accompanied by pulmonary edema, hemorrhage, and focal lung collapse. This damage appeared to be reversible as cellular regeneration was evident within 5 days of treatment. No short-term studies of DCE administered in food were located; therefore, the dose level of 200 mg DCE/kg body weight/day (Forkert et al. 1985), which was administered by gavage in corn oil, was converted to an equivalent concentration of 4,000 ppm in food for presentation in Table 1-4. The relevance of these findings to human exposure is not understood.

No studies were located regarding respiratory effects in animals following intermediate or chronic exposure to DCE.

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

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following oral exposure to DCE. Minor effects on the gastrointestinal system have been reported in laboratory animals following a single oral administration of 200 mg DCE/kg body weight to fasted rats. Chieco et al. (1981) observed forestomach edema in these animals. However, this alteration was not associated with any discernible degenerative changes, and its relevance to human exposure is therefore unknown. No short-term studies of DCE administered in food were located; therefore, the dose level of 200 mg DCE/kg body weight/day, (Chieco et al. 1981) which was administered by gavage in corn oil, was converted to an equivalent concentration of 4,000 ppm in food for presentation in Table 1-4.

No studies were located regarding gastrointestinal effects in animals following intermediate or chronic oral exposure to DCE. The highest NOAEL values and all reliable LOAEL values in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Hepatic Effects. No studies were located regarding hepatic effects in humans following oral exposure to DCE. This chemical is hepatotoxic in laboratory animals, particularly after ingestion of an acute dose. A whole spectrum of effects indicative of liver toxicity has been observed in animals following acute oral administration of DCE, and their incidence and severity tend to follow a dose-response relationship. Significant increases in serum enzyme markers of liver dysfunction (AlT and AsT) have been noted in fasted rats after the ingestion of a single dose of 50 mg DCE/kg body weight or higher (Andersen et al. 1980; Andersen and Jenkins 1977; Jenkins and Andersen 1978). Increases in liver weight have been observed in acutely exposed rats at doses of 50 mg DCE/kg body weight and above (Chieco et al. 1981), and severe histological evidence of liver damage (i.e., necrosis, hemorrhage) was noted following the oral administration of 200 mg DCE/kg body weight to rats (Chieco et al. 1981). No short-term studies of DCE administered in food were located; therefore, the dose level of 200 mg DCE/kg body weight/day (Chieco et al. 1981), which was administered by gavage in corn oil, was converted to an equivalent concentration of 4,000 ppm in food for presentation in Table 1-4. Ultrastructural changes in hepatocellular organelles have also been noted in rats after a single dose of 25 mg DCE/kg body weight (Kanz and Reynolds 1986). No short-term studies of DCE administered in food were located; therefore, the dose level of 25 mg DCE/kg body weight/day (Kanz and Reynolds 1986), which was administered by gavage in oil was converted to an equivalent concentration of 500 ppm in food for presentation in Table 1-4.

The hepatotoxicity of orally administered DCE in animals has been shown to be influenced by the nutritional status of animals, and also on the dosing vehicle. Fasting exacerbates DCE-induced hepatotoxicity; fed animals exhibit only mild effects at comparable doses (i.e., increases in organ weight) (Andersen and Jenkins 1977; Andersen et al. 1980; Chieco et al. 1981; Jenkins

and Andersen 1978). The hepatotoxic effects of DCE in rats tend to be more severe when administered in mineral or corn oil than when Tween 80 is used as the vehicle (Chieco et al. 1981). These authors have suggested that an aqueous solution of Tween 80 facilitates the clearance of DCE from the body. This observation has important implications with regard to humans, since oral exposure to DCE, particularly in individuals in close proximity to Superfund sites, will most likely be via groundwater.

Little information was obtained relevant to effects of intermediate treatment regimens with DCE. However, a subchronic study in beagles (97 days) given up to 25 mg DCE/kg body weight/day in the drinking water revealed no exposure-related gross or histopathological changes in the liver (Quast et al. 1983). An intermediate oral MRL of 0.25 mg DCE/kg body weight/day (Quast et al. 1983) was calculated for DCE as described in the footnote in Table 2-2.

Chronic studies have been performed in rats ingesting low levels (10-20 mg DCE/kg body weight/day) of DCE for 2 years. The results indicated few treatment-related changes. After 1 year of treatment, only a minimal increas in cytoplasmic vacuolation of hepatocytes was noted (Rampy et al. 1977). After 2 years, only a minimal amount of hepatocellular swelling with midzonal fatty change was reported (Quast et al. 1983). Nitschke et al. (1983) observed slight hepatocellular changes in rats exposed to DCE in the drinking water at levels equivalent to 7 mg DCE/kg body weight/day in utero, during lactation, and through weaning into adulthood. The dose level of 9 mg DCE/kg body weight/day (Quast et al. 1983) was calculated from the administered concentration of 50 ppm in water. This concentration in water is presented in Table 1-4. A chronic oral MRL of 0.009 mg DCE/kg body weight (Quast et al. 1983) was calculated for DCE as described in the footnote in Table 2-2. This MRL has been converted to an equivalent concentration in food (0.32 ppm) for presentation in Table 1-3.

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

Renal Effects. No studies were located regarding renal effects in humans following oral exposure to DCE. Evidence for DCE-induced kidney dysfunction has been observed in laboratory animals following acute oral exposure. Jenkins and Andersen (1978) found that fasted rats given single gavage doses of 200 mg DCE/kg body weight and above exhibited increased plasma urea levels and creatinine levels (at 400 mg DCE/kg body weight). Histopathological changes (vacuolization, pigmentation, tubular dilation, and necrosis) were observed at 400 mg DCE/kg body weight. These changes were more severe in females though some recovery was evident in females 96 hours post-exposure. Chieco et al. (1981) noted histological changes in the kidneys of rats administered single doses of 200 mg DCE/kg body weight by gavage. No short-term studies of DCE administered in food were located; therefore the dose level of 200 mg DCE/kg body weight/day (Chieco et al. 1981), which was administered by gavage in corn oil, was converted to an equivalent

concentration of 4,000 ppm in food for presentation in Table 1-4. As has been noted previously for hepatic effects, DCE-induced nephrotoxicity is exacerbated in fasted animals; no renal effects were observed in fed animals administered single doses of 400 mg DCE/kg body weight in the study described above.

No renal effects were noted in animals following intermediate or chronic oral exposure to DCE at doses of 25-200 mg DCE/kg body weight/day. An intermediate MRL of 0.25 mg DCE/kg body weight (Quast et al. 1983) was calculated as described in the footnote in Table 2-2. This MRL has been converted to an equivalent concentration in food (10 ppm) for presentation in Table 1-3.

Given the relative scarcity of data on DCE-induced renal effects in animals, particularly following prolonged exposures, and the possibility that the effects that have been observed are reversible, the potential for nephrotoxic effects in humans via ingestion of DCE cannot be evaluated.

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

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals following oral exposure to DCE.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans following oral exposure to DCE. No adverse effects on neurological parameters were identified subsequent to oral administration of DCE under any duration of exposure in animals. No effects were seen on either appearance or demeanor of the test animals in either an intermediate feeding study in dogs (25 mg DCE/kg body weight/day for 97 days) or a chronic study in rats (up to 30 mg DCE/kg b dy weight/day for 2 years) (Quast et al. 1983). These NOAELs for neurological effects in each species are listed in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans following oral exposure to DCE.

Murray et al. (1979) reported that ingestion by pregnant rats of 40 mg DCE/kg body weight/day in drinking water resulted in an increased mean fetal crown-rump length in the pups. No skeletal alterations occurred. There was no evidence of toxicity to the dams.

The highest NOAELs for developmental effects in each duration category are listed in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to DCE.

DCE (99.5% purity) was administered in the drinking water of rats at dosages up to 28 mg DCE/kg body weight/day for three generations. Histopathological examination of treated adult rats revealed mild dose-related hepatotoxic effects. No dose-related changes were seen in reproduction or neonatal development (Nitschke et al. 1983). The NOAEL for reproductive effects is listed in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genetic Effects

No studies were located regarding genetic effects in humans or animals following oral exposure to DCE.

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans following oral exposure to DCE.

The carcinogenicity of DCE by the oral route has been evaluated in a number of chronic studies in rats and mice (Maltoni et al. 1982, 1985; Ponomarkov and Tomatis 1980; Quast et al. 1983; Rampy et al. 1977). Dosages of DCE in these studies ranged from 0.5 mg DCE/kg body weight/day to 30 mg DCE/kg body weight/day. Administration was by gavage with the exception of two studies in which DCE was administered daily in the drinking water (Quast et al. 1983; Rampy et al. 1977). Major organs and tissues of treated and control animals in these investigations were subjected to both gross and microscopic examination. Under conditions of the oral bioassays performed to date, DCE has not demonstrated carcinogenic activity.

No statistically significant changes in tumor incidence in treated animals have been noted when DCE is administered orally. However, a trend toward increased incidence of malignant and nonmalignant tumors in DCE-treated animals has been reported in several studies (Ponomarkov and Tomatis 1980; Quast et al. 1983). However, relative to controls, the incidence of these and other tumors were not statistically significant. Ponomarkov and Tomatis (1980) reported an increased incidence of meningiomas and liver cell carcinomas and adenomas in rats given weekly gavage doses of 50 mg DCE/kg body weight from weaning until 120 weeks of age. The mothers of these animals received a single oral dose of 150 mg DCE/kg body weight by gavage in corn oil

on day 17 of gestation. The incidence of the hepatocellular tumors were statistically significant ($p=0.04$). Increases in hyperplastic nodules of the liver were seen in these animals. These hepatic lesions were not observed in controls.

Statistically significant increases in certain types of tumors and cancers have been reported in bioassays in which rats and beagles were orally exposed to DCE (Quast et al. 1983); however, these results have been discounted by the investigators. In a 2-year study by Quast et al. (1983), DCE doses of 7, 10, and 20 mg DCE/kg body weight/day and 9, 14, and 30 mg DCE/kg body weight/day were administered in the drinking water of male and female rats, respectively. A statistically significant increase ($p<0.05$) in the incidence of combined mammary gland fibroadenomas and adenofibromas was noted in low-dose females. Because the incidence of these types of tumors were within the normal range of historical control data and because these tumors were not observed in higher-dose females or in treated males, these increases were not considered by the authors to be related to ingestion of DCE, and thus are of questionable biological significance.

Clinical signs of toxicity were not generally observed in the various oral carcinogenicity studies on DCE; consequently, maximum tolerated doses may not have been achieved (Ponomarkov and Tomatis 1980; Quast et al. 1983; Rampy et al. 1977). Long-term animal studies at or near the maximum tolerated dose are necessary to ensure an adequate power for the detection of carcinogenic activity (EPA 1986). Two of the oral carcinogenicity studies also used exposure periods that were less than lifetime (52-59 weeks) (Maltoni et al. 1982, 1985). However, the animals were observed for 136 or 147 weeks in the studies conducted by Maltoni et al. (1982, 1985), thus allowing an adequate latency period for the development of late-appearing tumors.

2.2.3 Dermal Exposure

With the exception of reports describing local irritant effects following dermal contact with DCE in both humans and animals and positive tumor-initiating effects in animals (Van Duuren et al. 1979), no studies were located regarding health effects in humans or animals following dermal exposure to DCE.

2.2.3.1 Death

No studies were located regarding lethal effects in humans or animals following dermal exposure to DCE.

2.2.3.2 Systemic Effects

With the exception of reports describing dermal/ocular irritation following local contact in humans and animals, no studies were located regarding systemic effects in humans or animals following dermal exposure to DCE.

Dermal/Ocular Effects. Liquid DCE is irritating when applied to the skin of humans (Tierney et al. 1979) and animals (Irish 1963), after exposures lasting only a few minutes. Details concerning these studies are lacking, but it has been suggested that these irritant effects may be due to the inhibitor, p-hydroxyanisole (MEHQ), that is present in these formulations. MEHQ is an antioxidant which on contact results in skin depigmentation in concentrations as low as 0.25% (Busch 1985). Similarly, DCE is an ocular irritant in humans (Tierney et al. 1979), and this effect has also been ascribed to MEHQ.

2.2.3.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals following dermal exposure to DCE.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals following dermal exposure to DCE.

2.2.3.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals following dermal exposure to DCE.

2.2.3.6 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals following dermal exposure to DCE.

2.2.3.7 Genetic Effects

No studies were located regarding genetic effects in humans or animals following dermal exposure to DCE.

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects in humans following dermal exposure to DCE.

The carcinogenicity of DCE following dermal exposure has been evaluated by Van Duuren et al. (1979). In this study, DCE at doses of 40 mg or 121 mg (1,143 mg DCE/kg body weight or 3,457 mg DCE/kg body weight, respectively) in

acetone was applied three times weekly for periods up to 595 days to the skin of Swiss mice. No skin tumors were noted in treated animals. Increased incidences of pulmonary papillomas and squamous-cell carcinomas of the forestomach were observed in treated mice; however, the incidences of these tumors were not statistically different from controls. These results suggest DCE is inactive as a complete carcinogen when applied repeatedly to the mouse skin.[1]

Van Duuren et al. (1979) also evaluated the ability of DCE to act as a tumor initiator in the skin of Swiss mice. DCE (121 mg or 3,457 mg DCE/kg body weight) in acetone was applied to the skin once, followed 2 weeks later by dermal application of the tumor promoter, phorbol myristate acetate (TPA) three times a week for periods up to 576 days.[2] Untreated, vehicle-treated, and TPA-only-treated animals served as negative and positive controls. A statistically significant ($p<0.005$) increase in the incidence of skin papillomas was recorded in mice treated with DCE relative to controls. These results indicate that DCE is a tumor-initiating agent.

2.3 RELEVANCE TO PUBLIC HEALTH

Evidence was found in the scientific literature that DCE is toxic to both humans and laboratory animals. Disregarding tobacco smoking, human exposure to DCE occurs primarily in the industrial work environment, in communities surrounding these sites of DCE synthesis and use, and at areas in and around hazardous waste sites. Exposure of the general population distant from these particular emission sources of DCE tends to be low. The available information on adverse health effects associated with DCE exposure in humans comes primarily from reports of accidental exposure to high concentrations for a short period of time. Since these are cases of emergency, the information concerning exposure is limited. It can be ascertained from this limited information that acute inhalation exposure to DCE induces adverse health effects in humans, with central nervous system toxicity and irritation of mucous membranes being the primary manifestations of these toxic effects. There is also some limited evidence to suggest that repeated exposure to DCE is associated with liver damage in humans.

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[1]A complete carcinogen is an agent, which if applied in sufficient concentrations, can induce tumors by itself.

[2]In two-stage tumorigenesis, a tumor initiator is applied in a subthreshold dose. An initiator does not generally produce tumors at this dose but causes "dormant" cell changes so that later repeated applications of a promoter (an agent that by itself will not produce tumors) will induce benign and malignant tumors at the site of application.

2. HEALTH EFFECTS

There is convincing evidence from animal studies to indicate that DCE toxicity is mediated by metabolism to a reactive intermediate that acts at the cellular level to ultimately compromise the viability of the target tissues. While the metabolic pathways for DCE are similar in the rat and mouse, the rate of metabolism is greater in the mouse resulting in a greater concentration of toxic metabolites. Thus, the severity of DCE-induced toxicity in humans may be dependent on the extent to which DCE is metabolized, and which intermediates are formed. Furthermore, it may be possible to identify sensitive subpopulations based on the status of their liver function.

The toxicity of DCE to laboratory animals is fairly well characterized, particularly for acute and intermediate inhalation exposure. As can be seen in Figures 2-1 and 2-2, the major target organs of DCE toxicity in animals appear to be the liver, the kidney, and the lungs with lower level prolonged exposure. In short-term duration, high-concentration exposure, the central nervous system is also affected. Data from animal studies will be discussed here with regard to their implications on human toxicity.

Death. Though no deaths have been reported in humans following DCE exposure, DCE was lethal to animals following acute exposures to high levels via the inhalation or oral routes (see Figures 2-1 and 2-2). DCE-induced lethality appeared to be influenced by the nutritional status of the animal regardless of exposure route, with LD_{50}s for fasted animals generally significantly lower than those reported for fed animals (e.g., Chieco et al. 1981; Jaeger et al. 1973c; Jenkins and Andersen 1978; Moslen et al. 1987; Siegel et al. 1971). Males appeared to be affected to a greater extent by fasting than females. Experimental evidence suggests that this enhanced toxicity in fasted animals resulted from increased levels of the reactive intermediate of DCE available for binding to macromolecules in target tissues after fasting (McKenna et al. 1978a). Carlson and Fuller (1972) reported that fed rats exposed to 20,000 or 32,000 ppm of DCE by inhalation for 1 hour survived for at least 24 hours. However, when animals were pretreated with the microsomal enzyme inducers phenobarbital or methylcholanthrene, these exposure levels were lethal to nearly all of the animals within 2 hours, suggesting that lethality was due to an increase in the formation of toxic metabolites. Similar results (i.e., potentiation of DCE-induced lethality by phenobarbitone) were obtained by Harris and Anders (1980) in rats administered DCE by intraperitoneal injection. However, Carlson and Fuller (1972) found that pretreatment of rats with two different inhibitors of microsomal metabolism which presumably would reduce the formation of reactive intermediates (SKF 525A and Lilly 18947) prior to inhalation exposure to DCE also reduced the survival time following exposure to DCE. Masuda and Nakayama (1983) found that other inhibitors of microsomal metabolism (carbon disulfide and diethyldithiocarbamate) protected mice against all DCE-induced toxic effects at low doses following intraperitoneal injection. These results indicate that biotransformation plays an important role in the expression of DCE-induced effects. Increased susceptibility of fasted animals to the lethal effects of DCE may occur because fasting depleted GSH in the target tissues,

resulting in less GSH available to bind to the active intermediate (Jaeger et al. 1973a).

Mice have been observed to be more sensitive than rats to the lethal effects of inhaled DCE (see Figure 2-1) (Jaeger et al. 1974). This differential sensitivity also has been observed by the oral exposure route (see Figure 2-2) (Jenkins et al. 1972; Jones and Hathway 1978a). Pharmacokinetic studies suggest that, relative to rats, the rate of metabolism is higher in mice resulting in a greater degree of damage from electrophilic species capable of reacting with intracellular macromolecules (McKenna et al. 1977; Reitz et al. 1980).

Though animal studies indicate that nutritional status affects DCE-induced lethality, how nutritional status affects the susceptibility of humans to the toxic effects of DCE is not known. Human subpopulations most likely exist with differing biochemical capacities for DCE metabolism and thereby are more or less able to form reactive intermediates. It is not known if these differing biochemical capacities will affect an individual's susceptibility to DCE-induced lethality.

Respiratory Effects. Irritation of the mucous membranes of the upper respiratory tract and pulmonary congestion, hyperemia, and morphological changes were seen at necropsy in rats and mice acutely exposed to high levels of DCE via inhalation (Henschler 1979; Klimisch and Freisberg 1979a; Rylova 1953; Zeller et al. 1979b). Longer-term inhalation exposure to DCE was associated with similar adverse respiratory effects (Gage 1970; Prendergast et al. 1967; Quast et al. 1986). These effects appeared to be rather nonspecific and most likely resulted from DCE's irritating properties. Therefore, these data suggest that any possible non-genotoxic respiratory effects associated with inhalation exposure to DCE (particularly acute) in humans may be a consequence of local, nonspecific irritation.

However, a local nonspecific irritant effect cannot explain the pulmonary injury observed in mice following the oral administration of a single-dose of DCE. The effects seen included histopathological changes in Clara cells, pulmonary edema, hemorrhage, and focal atelectasis. These effects were reversible since cellular regeneration was evident within 5 days of treatment (Forkert et al. 1985). Clara cell degeneration was also seen in mice following acute intraperitoneal administration of DCE (Forkert et al. 1985; Krijgsheld et al. 1984b). The relevance of these findings to prolonged human exposure is not known since (a) the findings in the one oral study are not substantiated by other studies, and (b) intraperitoneal administration is not a relevant route of administration in humans.

Hepatic Effects. Results from animal studies indicate that the liver is a primary target organ for DCE-induced toxicity. Hepatotoxicity following both inhalation and oral exposure to DCE was manifested by biochemical changes (i.e., increases in serum enzyme markers of liver dysfunction and induction of hepatic enzymes), and mild to marked histological changes (e.g., midzonal

and/or centrilobular vacuolization, swelling, degeneration and necrosis). More severe hepatotoxic effects were seen in fasted animals (particularly males) as compared to fed animals (Andersen et al. 1979; Andersen et al. 1980; Andersen and Jenkins 1977; Chieco et al. 1981; Jaeger et al. 1974; Jaeger et al. 1975b; Jenkins and Andersen 1978; McKenna et al. 1978; Reynolds 1980). The increased susceptibility to DCE-induced hepatotoxicity seen in fasted rats may be related to the depletion of GSH levels.

Indirect evidence of the role of GSH in DCE-induced hepatotoxicity is provided by Jaeger et al. (1974) who demonstrated that diethyl maleate, a substance that depletes liver GSH levels, potentiates liver toxicity in fed rats exposed to DCE via inhalation. In addition, thyroidectomy, a surgical procedure that results in increased liver GSH levels, has been shown to protect against DCE-induced hepatotoxicity and lethality whereas thyroxine replacement restored or even potentiated the susceptibility of thyroidectomized animals to DCE-induced hepatotoxicity (Jaeger et al. 1977b, Szabo et al. 1977).

Results from in vivo studies in animals suggest that DCE-induced hepatic injury may result from the formation of a reactive epoxide or other intermediate in vivo (Andersen et al. 1978, 1980; Jaeger et al. 1977a; Jones and Hathway 1978b), which in turn binds to macromolecules in the target tissues. These intermediates are believed to be generated via the cytochrome P450 mixed function oxidase system (Forkert et al. 1986).

Other subcellular mechanisms of DCE-induced toxicity have been proposed. For example, it has been suggested that DCE-induced inhibition of calcium-dependent ATPase may be the initial biochemical insult that triggers a sequence of events that may culminate in cell death (Luthra et al. 1984). Results of in vitro studies in liver perfusates have suggested that metabolism of DCE reduces viability of liver cells (Reichert et al. 1978). Histochemical and biochemical evidence support the concept that plasma membranes and mitochondrial membranes may be the primary foci of acute hepatocellular injury in fasted rats (Jaeger 1977; Reynolds et al. 1980).

In conclusion, DCE induces hepatotoxicity in animals following both inhalation and oral acute and repeated exposures. The limited information available in humans also suggests that DCE is hepatotoxic. Thus, it may b assumed that humans, particularly those exposed to high levels of DCE in occupational settings or in areas surrounding hazardous waste sites via inhalation and those with compromised hepatic function are at risk for DCE-induced liver toxicity.

Renal Effects. Renal toxicity (e.g., enzyme changes, hemoglobinuria, increases in organ weight, and tubular swelling, degeneration and necrosis) has been observed following both inhalation and oral exposure to DCE in animals (see Figures 2-1 and 2-2) (e.g., Jackson and Conolly 1985; Lee et al. 1977; McKenna et al. 1978; Oesch et al. 1983; Short et al. 1977c). Fasted animals (particularly males) were again more susceptible to these effects than

fed animals (e.g., Chieco et al. 1981; McKenna et al. 1978a), and mice were more susceptible than rats, as was seen for DCE-induced hepatotoxicity (Reitz et al. 1980; Short et al. 1977c; Watanabe et al. 1980). There is some evidence that the kidney damage induced by acutely inhaled or ingested DCE may be reversible (Jenkins and Andersen 1979; Reitz et al. 1980), but this may be concentration or duration dependent.

Though data on kidney toxicity in humans following exposure to DCE do not currently exist, evidence from animal studies in two species suggest that nephrotoxicity may also occur in humans, particularly following acute exposure to DCE. The fact that adverse renal effects were rarely seen following more prolonged exposure to DCE (except in male mice), coupled with the observation that the acute nephrotoxic effects were reversible suggest that repair mechanisms may be operating. The renal effects of long-term exposure to DCE in humans are not known.

Neurological Effects. Central nervous system toxicity has been observed in humans acutely exposed to high concentrations (approximately 4,000 ppm) of inhaled DCE (Tierney et al. 1979). Complete recovery occurred if exposure was n t prolonged. In addition, signs of central nervous system toxicity was the predominant effect observed in animals acutely exposed to high concentrations of DCE via the inhalation route of exposure (see Figure 2-1). Effects on the central nervous system have not been observed following oral or repeated inhalation exposures to DCE in animals (see Figure 2-2). However, these studies were not designed to detect subtle neurological effects.

Developmental Effects. Based on studies by Short et al. (1977a), DCE has weak teratogenic effects in laboratory animals. Developmental toxicity was enhanced following inhalation exposure to DCE as compared to oral exposure. Developmental toxicity was often observed at doses of DCE that also induce maternal toxicity in animals (see Figures 2-1 and 2-2). Studies by Murray et al. (1979) demonstrated that the sensitivity of pregnant rats to DCE was greater by inhalation than by ingestion. After inhalation exposure at 80 and 160 ppm for 7 hours/day on gestation days 6-18, DCE produced maternal toxicity and increased resorption and skeletal alterations. Except for the increased mean fetal crown-rump length in the offspring, no adverse effects were noted in rats receiving 40 mg DCE/kg body weight/day in drinking water. The author hypothesized a possible mechanism to explain the route-dependent differences in DCE-induced toxicity. Since detoxication of DCE was reported to occur via conjugation of its active metabolites with GSH (McKenna et al. 1977) and GSH levels undergo diurnal variations (Jaeger et al. 1973a; Watanabe et al. 1976), Murray et al. (1979) speculated that sufficient GSH levels were available to detoxify 40 mg DCE/kg body weight administered in drinking water over a 24-hour period but not when the animals were exposed via inhalation between 8:30 am and 3:30 pm. When DCE doses are converted into equivalent units, animals exposed by inhalation received approximately 76.6 and 153 mg DCE/kg body weight/day (assuming all DCE was absorbed by the lungs) compared to 40 mg DCE/kg body weight/day in drinking water. Thus, a difference in total dose may also explain the greater toxicity seen following inhalation exposure.

Genotoxicity. The available data suggest that DCE produces genotoxic effects in a number of test systems. The results of in vitro and in vivo studies indicate that DCE exhibited mutagenic properties upon metabolic activation (i.e., requiring the presence of an exogenous mammalian metabolic system) in bacteria and yeast and that it induced gene conversion in yeast. It was also shown to be mutagenic in green plants without activation by mammalian metabolic systems. DCE induced chromosome aberrations and sister chromatid exchanges in cultured mammalian cells in vitro and DNA damage in mice in vivo.

DCE has been shown to be genotoxic in several in vitro test systems. However, a metabolic activation system was required for activity. Results of in vitro genotoxicity studies are shown in Table 2-3. Gene mutations were observed in bacteria, yeast and green plant cells (Bartsch et al. 1975, 1979; Bronzetti 1981; Greim et al. 1975; Jones and Hathway 1978; Oesch et al. 1983; Van't Hof 1982), and it induced gene conversion in yeast (Bronzetti 1981). Both base-pair substitution and frameshift mutations were reported in Salmonella typhimurium after continuous exposure to DCE vapors (Bartsch et al. 1975, 1979; Jones and Hathway 1978; Oesch et al. 1983). Another study reported negative results from tests in Salmonella (Mortelmans et al. 1986). However, the Mortelmans et al. (1986) study incorporated single doses of DCE into the warmed incubation medium instead of exposing the bacteria continuously to vapor. Given that DCE is very volatile and would be expected to escape from the culture, continuous exposure to vapor is considered a more reliable method. DCE was mutagenic in Salmonella after metabolic activation with an exogenous activation system derived from human liver samples (Jones and Hathway 1978b), thus supporting the concept that the human liver is capable of activating DCE into mutagenic metabolites.

In cultured mammalian cells, DCE was reported negative in a point mutation assay in 8-azaguanine and ouabain resistant V79 Chinese hamster lung cells (Drevon and Kuroki 1979), but it produced chromosomal aberrations and sister chromatid exchanges in a Chinese hamster lung fibroblast cell line in the presence of a metabolic activation system (Sawada et al. 1987).

DCE has also been tested in several in vivo studies in animals. Results of in vivo genotoxicity studies are shown in Table 2-4. Negative results were reported in assays for dominant lethal mutations in mice (Anderson et al. 1977) and rats (Short et al. 1977b) and in a micronucleus test in mice using both the bone marrow assay system following gavage administration and the transplacental assay system following intraperitoneal administration to pregnant mothers (Sawada et al. 1987). Inhalation of DCE was associated with low rates of DNA alkylation in the livers and kidneys of mice and rats as compared to dimethylnitrosamine-treated control. Furthermore, DNA repair mechanisms were induced in the kidneys of mice in cells in which normal replicative DNA synthesis had been inhibited. A significant increase in DNA repair rates was not observed in mouse liver nor in the kidneys or liver of rats (Reitz et al. 1980). In a mouse host-mediated assay system, DCE was mutagenic and induced gene conversion in yeast (Bronzetti et al. 1981).

TABLE 2-3. Genotoxicity of DCE *In Vitro*

Endpoint	Species/Test System	Result: With Activation	Result: Without Activation	Reference
PROKARYOTIC ORGANISMS				
Gene mutation	*Salmonella typhimurium*/ desiccator test for exposure to gases	+	NT	Bartsch et al. 1979
	S. typhimurium/gas exposure	+	-	Oesch et al. 1983
	S. typhimurium/gas exposure	+	-	Bartsch et al. 1975
	S. typhimurium/gas exposure	+	NT	Jones and Hathway 1978b
	S. typhimurium/liquid preincubation test	-	-	Mortelmans et al. 1986
	E. coli WP2	+	-	Oesch et al. 1983
	E. coli K12	+	-	Greim et al. 1975
EUKARYOTIC ORGANISMS				
FUNGI				
Gene mutation	*Saccharomyces cerevisiae* D7	+	-	Bronzetti et al. 1981
Gene conversion	*S. cerevisiae* D7	+	-	Bronzetti et al. 1981
PLANT				
Gene mutation	*Tradescantia* clone 4430	NT	(+)	Van't Hof and Schairer 1982
MAMMALIAN CELLS				
Gene mutation	Chinese hamster V79 cells	-	NT	Drevon and Kuroki 1979
Chromosomal	Chinese hamster CHL cells	+	-	Sawada et al. 1987
	Chinese hamster Don-6 cells	NT	-	Sawada et al. 1980
Sister chromatid exchange	Chinese hamster CHL cells	(+)	-	Sawada et al. 1987

NT = Not Tested; - = negative result; + = positive results; (+) = weakly positive or marginal result.

TABLE 2-4

Genotoxicity of DCE In Vivo

Endpoint	Species/Test System	Result	Reference
MAMMALIAN SYSTEMS			
Dominant Lethals	Mouse	Negative	Anderson et al. 1977
	Rat	Negative	Short et al. 1977b
Micronuclei	Mouse bone marrow	Negative	Sawada et al. 1987
	Mouse fetal liver and blood	Negative	Sawada et al. 1987
DNA damage	Mouse kidney/DNA repair	Weak positive	Reitz et al. 1980
HOST-MEDIATED ASSAYS			
Gene mutation	Saccharomyces cerevisiae/ mouse host-mediated assay	Positive	Bronzetti et al. 1981
Gene conversion	Saccharomyces cerevisiae/ mouse host-mediated assay	Positive	Bronzetti et al. 1981

Carcinogenicity. The carcinogenicity of DCE following inhalation, oral, dermal, and subcutaneous exposure has been evaluated in mice (Hong et al. 1981; Lee et al. 1978; Maltoni et al. 1985; Van Duuren et al. 1979), rats (Hong et al. 1981; Maltoni et al. 1982, 1985; Ponomarkov and Tomatis 1980; Quast et al. 1983, 1986; Rampy et al. 1977; Viola and Caputo 1977), and Chinese hamsters (Maltoni et al. 1985). Of the carcinogenicity bioassays conducted to date, only the results of a single inhalation study in mice by Maltoni et al. (1985) provide possible evidence of a positive carcinogenic effect from DCE exposure. In this study, increases in renal adenocarcinomas were noted in male Swiss mice exposed by inhalation to 25 ppm DCE. Mammary gland carcinomas and lung tumors, most of which were benign pulmonary adenomas, were also observed in this study. Results of all other carcinogenicity studies with laboratory animals have been negative. Nonsignificant increases in a variety of malignant and nonmalignant tumors were reported in studies involving inhalation and oral exposure; however, these increases either were not statistically significant or were not considered by the respective authors to be exposure related (Lee et al. 1977, 1978; Maltoni et al. 1985; Ponomarkov and Tomatis 1980; Quast et al. 1983, 1986). Study limitations for several of the investigations included less than lifetime exposure, use of doses below the maximum tolerated dose, small numbers of animals, and limited gross and microscopic examinations. Such limitations reduce the sensitivity of a bioassay system to detect a carcinogenic response.

Van Duuren et al. (1979) evaluated the carcinogenicity of DCE in mice treated by dermal application and by subcutaneous injection. DCE was inactive as a complete carcinogen when applied repeatedly for lifetime to the mouse skin, and did not induce local sarcomas when administered chronically to mice by subcutaneous injection. However, a dermal initiation-promotion study with Swiss mice has shown that DCE was active as a tumor-initiating agent. A statistically significant increase in the incidence of skin papillomas was noted in Swiss mice treated dermally with both DCE and the tumor-promoting agent phorbol myristate acetate (Van Duuren et al. 1979).

On the basis of the suggestive inhalation study by Maltoni et al. (1985), DCE should be regarded as a possible animal carcinogen and therefore as a possible human carcinogen. Results of studies with laboratory animals indicating nonsignificant or non-dose-related increases in various malignant and nonmalignant tumors following oral or inhalation exposure provide limited but suggestive support that DCE may be a weak carcinogen (Lee et al. 1978, 1977; Maltoni et al. 1985; Ponomarkov and Tomatis 1980; Quast et al. 1986, 1983). The positive initiation-promotion study by Van Duuren et al. (1979) also suggests that DCE in concert with tumor-promoting agents can induce cancer. This is particularly relevant to humans in and around hazardous waste sites who are often exposed to more than one potentially carcinogenic and/or tumor promoting substance at a time (e.g., tobacco smoke).

EPA has classified DCE as a Group C agent (Possible Human Carcinogen). This category applies to chemical agents for which there is limited evidence of carcinogenicity in animals. Based on the inhalation study by Maltoni et al. (1985) in which a statistically significant increase in the incidence of renal adenocarcinomas was observed in treated male Swiss mice, EPA (1988) has calculated an inhalation cancer slope factor (or q_1^*) for DCE of 1.2 (mg DCE/kg body weight/day)$^{-1}$.

In experimental studies with mice, it has been observed that doses of DCE that induce renal tumors also induce renal tissue damage (degeneration and necrosis) (Maltoni et al. 1985; Reitz et al. 1980; Watanabe et al. 1980). These tumorigenic doses, however, are associated in mice with only minimal DNA alkylation and DNA repair (Reitz et al. 1980). These findings suggest that kidney toxicity may play a contributing role in the induction of renal tumors (Watanabe et al. 1980), and that tumors observed in mice exposed to DCE may be the result of the chemical's toxic effect upon nongenetic components of the cell (Reitz et al. 1980). However, DCE is mutagenic in lower organisms and has been shown to be a probable initiator in mouse skin (Van Duuren et al. 1979).

It has been suggested that the toxic and carcinogenic effects of DCE may depend on species, strain, and sex of the tested animals (Maltoni 1977; Maltoni et al. 1985). Results of studies suggest that male Swiss mice are more susceptible to the toxic effects of DCE than female Swiss mice, rats, or hamsters (EPA 1985; Oesch et al. 1983). Pharmacokinetic studies also suggest that compared to rats, mice have a greater rate of DCE activation to electrophilic species capable of reacting with intracellular macromolecules (McKenna et al. 1977; Reitz et al. 1980).

2.4 Levels in Human Tissues and Fluids Associated with Effects

Exposure to DCE is primarily determined by the appearance of the compound in expired air. A number of studies were conducted to examine exposure to DCE as measured in expired air (Conkle et al. 1975; Wallace et al. 1984, 1986); small amounts of DCE were found in the breath of study populations in New Jersey and North Carolina, but no health effects were reported. The available data are insufficient to determine the body levels of DCE in human tissues, fluids and expired air associated with health effects.

2.5 Levels in the Environment Associated with Levels in Human Tissue and/or Health Effects

Data from available studies have been insufficient to correlate levels of DCE in the environment with levels in breath. In an investigation on the trace organic compounds in human breath, a 60-minute sampling period yielded 13.0 μg of DCE in the breath (volume unspecified) of one individual (Conkle et al. 1975). This value was corrected for the amount of DCE in the air supplied to the individual during the sampling period. The authors attributed the amount of DCE in the individual's breath to previous exposure; however, no

levels of previous exposure to DCE were reported for the test subject. The breath of 1 out of 12 individuals tested by Wallace et al. (1984) contained DCE (levels not specified). No environmental levels of DCE were reported for this study. Twelve percent of the breath samples from 350 residents of New Jersey contained measurable amounts of DCE, ranging from approximately 0.2 to 2 $\mu g/m^3$ of expired air (Wallace et al. 1986). The levels of DCE in drinking water samples from homes of the test subjects had an arithmetic mean value of 0.2 $\mu g/m^3$ and a maximum value of 2.4 $\mu g/m^3$ which corresponds to values of 2.0×10^{-7} ppm and 2.4×10^{-6} ppm, respectively (Wallace et al. 1987).

Occupational exposure studies have investigated health effects associated with exposure to DCE. Because of the small cohort size and concurrent exposure to other compounds, the information from these studies is not sufficient to correlate levels of DCE in the environment with health effects (Apfeldorf and Infante 1981). A study of 138 workers exposed to DCE (TWA concentrations ranging from less than 5 to 70 ppm) and copolymers other than DCE reported no statistically-related changes attributable to DCE in long-term mortality or health-inventory findings (Ott et al. 1976). Waxweiler (1981) found no association between occupational exposure to DCE (with concurrent exposure to other chemicals) and cases of angiosarcomas of the liver.

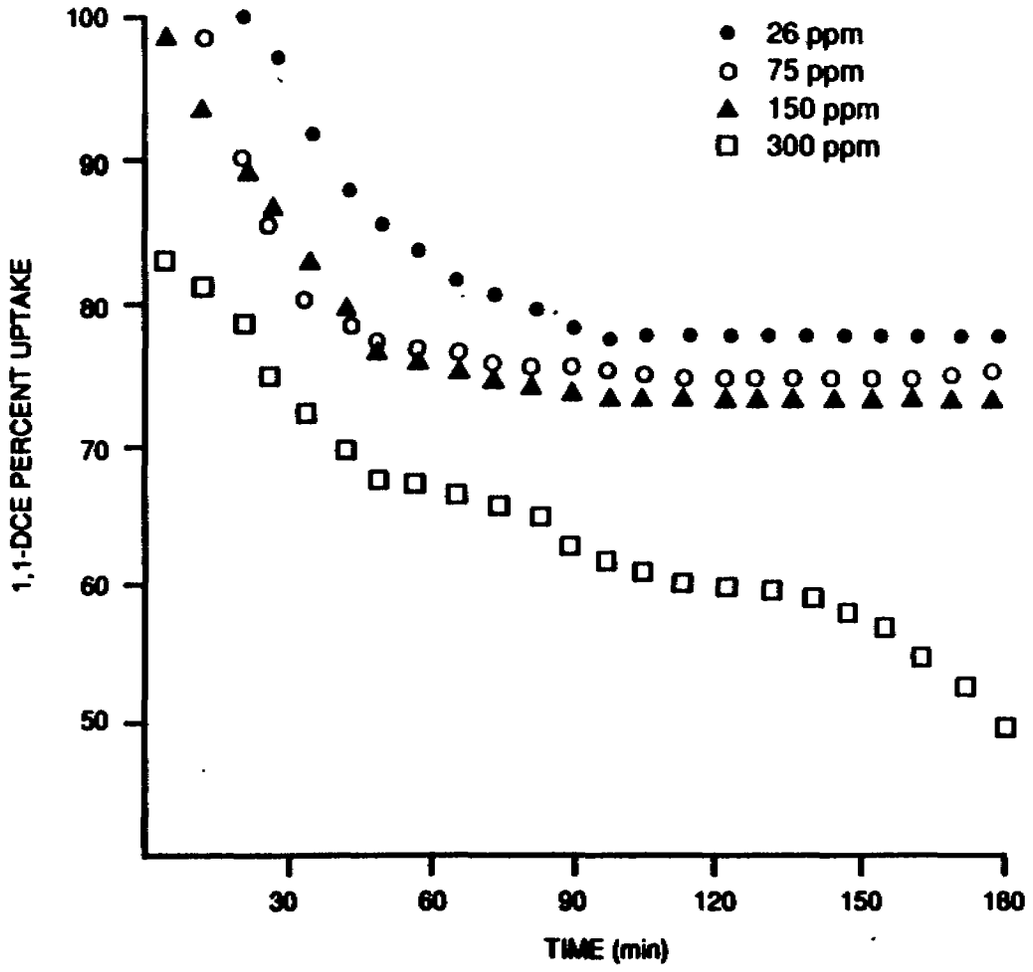
2.6 TOXICOKINETICS

2.6.1 Absorption

2.6.1.1 Inhalation Exposure

No studies were located regarding the absorption of DCE in humans following inhalation exposure. Studies in laboratory animals have demonstrated that DCE was rapidly absorbed following inhalation exposure (Dallas et al. 1983; McKenna et al. 1978a). Substantial levels of the parent compound were found in the venous blood of rats within 2 minutes after inhalation exposure (Dallas et al. 1983). Absorption of DCE was duration- and dose-dependent, as shown in Figure 2-3. The percentage of systemic uptake was found to decrease with time from the onset of exposure until an equilibrium was reached within an hour. Once equilibrium was reached, percentage uptake varied inversely with dose. The cumulative uptake of DCE following inhalation exposure was linear for levels up to 150 ppm. However, at higher levels of DCE exposure, steady-state was never achieved. This finding indicates that DCE absorption following inhalation exposure was saturable at high levels, and the kinetics at these levels are best described by a cubic curve (Dallas et al. 1983). No studies were located that described transport mechanisms for DCE absorption, but since DCE is a small organic molecule with chemical and physical properties similar to lipid soluble anesthetics, it is expected to easily penetrate pulmonary membranes and rapidly enter the blood stream in humans following inhalation exposure.

FIGURE 2-3. Percentage Systemic Uptake of DCE During Inhalation Exposur s



Rats were exposed to 25, 75, 150, or 300 ppm DCE for 3 hours. Percentage uptake was determined at 8-minute intervals. Each point represents the mean percentage uptake in four animals per group. Standard deviation brackets are omitted for the sake of clarity. Reproduced from Dallas et al. 1983.

2.6.1.2 Oral Exposure

No studies were located regarding absorption in humans following oral exposure to DCE. Studies in animals clearly indicated that doses of DCE ranging from 10 to 100 mg DCE/kg body weight were rapidly and almost completely absorbed from the gastrointestinal tract of rats and mice following oral administration in corn oil (Jones and Hathway 1978a; McKenna et al. 1978b; Putcha et al. 1986). Rapid absorption has also been demonstrated to occur following the oral administration of 200 mg DCE/kg body weight in an aqueous emulsion, as evidenced by the observation that the largest percentage of the dose was exhaled during the initial 15-minute period (Chieco et al. 1981). Peak blood levels were achieved in rats within 2-8 minutes after oral administration (Putcha et al. 1986). When 0.5-50 mg radiolabeled DCE/kg body weight was given to female rats by the oral route, approximately 10% of the parent compound was recovered in the expired air by 1 hour post-exposure, indicating that oral absorption was rapid (Reichert et al. 1979). Furthermore, almost complete absorption of orally administered DCE by rats was demonstrated by the fact that 81-99.8% of the administered radioactivity was recovered within 72 hours (i.e., 21% was recovered in the expired air, 53.9% in urine, 14.5% in feces, 2.8% in the carcass and 7.5% in the cage rinse following oral administration of 5 mg [^{14}C]-DCE/kg body weight) (Reichert et al. 1979). Based on these results is likely that DCE is rapidly and c mpletely absorbed in humans following oral exposure (e.g., via ingestion of contaminated groundwater).

2.6.1.3 Dermal Exposure

No studies were located regarding absorption in humans or laboratory animals following dermal exposure to DCE. However, the physical/chemical properties of DCE indicate that absorption of the liquid form of DCE via this route is possible. DCE is a small organic molecule with properties similar to the lipid-soluble anesthetics. Thus, liquid DCE is expected to readily penetrate the skin, which is a lipid-rich tissue.

2.6.2 Distribution

No studies were located regarding distribution in humans following dermal exposure to DCE. Results from animal studies indicated that DCE was rapidly distributed throughout the bodies of both rats and mice following exposure via several routes. DCE appeared to accumulate preferentially in the kidney, liver, and lung. Fasted animals displayed higher levels of DCE and/or its metabolites in these target tissues than fed animals. These findings provide some basis for the observation that the liver, kidney, and lung are target tissues for DCE-induced toxicity, and explain why fasted animals are more susceptible to these toxic effects.

2.6.2.1 Inhalation Exposure

McKenna et al. (1978a) reported that, after inhalation exposure of rats to 10 or 200 ppm of [^{14}C]-labeled DCE, the highest level of radioactivity was found in the liver and kidneys after 72 hours, with only very small amounts present in other tissues. These authors found that tissue burden/gram of tissue (microgram equivalents of [^{14}C]-DCE per gram of tissue/total milligram equivalents recovered per rat) in the liver, kidneys, and lungs of fasted rats were significantly greater than in fed rats at both exposure levels, even though the total accumulation of [^{14}C] in fasted rats was less than in fed rats. The results of this study suggest that fasted rats retain [^{14}C] from administered DCE to a greater extent in specific target tissues.

A preferential accumulation of radioactivity in the kidney and liver of rats, with fasted rats showing higher levels than fed rats in these tissues, was also observed by Jaeger et al. (1977) 30 minutes after a 2-hour inhalation exposure to 2,000 ppm radiolabeled DCE. Examination of [^{14}C]-activity at the subcellular level in these two tissues revealed that significantly more water-soluble [^{14}C]-activity was present in the cytosolic fractions of fasted rats than in fed rats (Jaeger et al. 1977), suggesting that distribution pathways for metabolism differ according to the nutritional status of the animals.

2.6.2.2 Oral Exposure

Jones and Hathway (1978c) demonstrated that DCE is rapidly distributed throughout the body tissues in rats following a single oral administration of the [^{14}C]-labeled compound. They found that the highest amount of radioactivity occurred in the liver and kidneys within 30 minutes of administration. More general redistribution throughout the body followed. Quantitative distribution analyses revealed that the level of radiolabel in tissues decreased rapidly, with less than 3% of the administered dose present in the body 72 hours post-exposure. At that time, the highest levels were found in liver and kidney, with very little remaining in other tissues, including fat (Jones and Hathway 1978c).

2.6.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals following dermal exposure to DCE.

2.6.2.4 Other

In a study by Okine et al. (1985) in which mice were administered a single intraperitoneal injection of 125 mg [^{14}C]-DCE/kg body weight, radioactivity was distributed to all tissues examined, with peak levels seen 6 hours post-administration. The highest levels of radioactivity were found in the kidney, liver, and lung with lesser amounts in the skeletal muscle, heart, spleen, and gut.

2.6.3 Metabolism

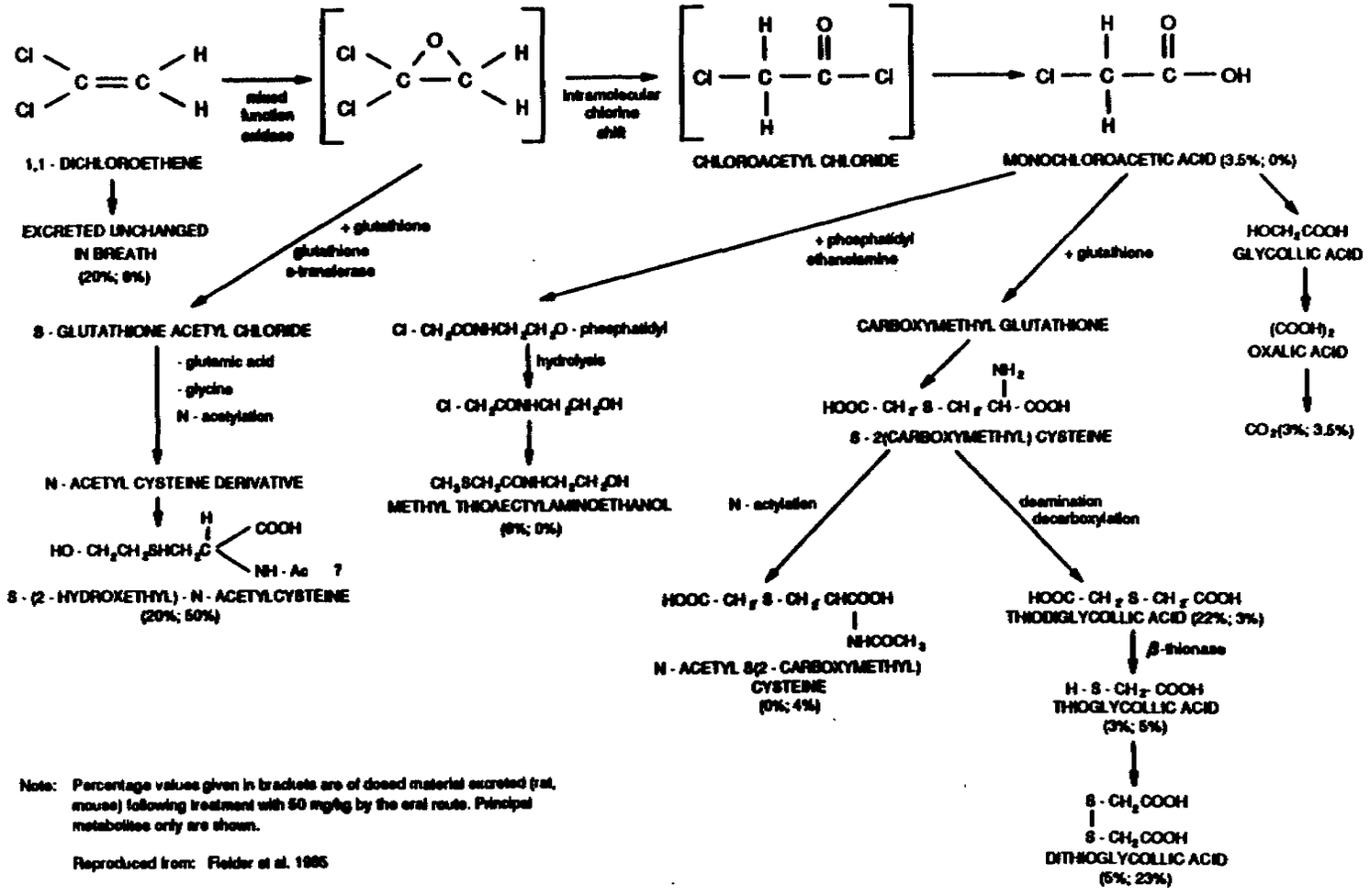
No studies were located regarding metabolism in humans following exposure to DCE. The metabolism of DCE following oral administration in rats has been extensively studied in rats (e.g., Jones and Hathway 1978a; Jones and Hathway 1978c; McKenna et al. 1978b; Reichert et al. 1979). These studies demonstrate that DCE undergoes biotransformation processes and several metabolites have been identified. An overall summary of the metabolic profile of DCE in animals is presented in Figure 2-4.

D'Souza and Anderson (1988) developed a physiologically-based pharmacokinetic model for DCE based on its oxidative metabolism and subsequent conjugation with GSH, a principal pathway (see Figure 2-5). Their model demonstrates that because of DCE's low blood:air partition coefficient and saturable metabolism, the metabolism of DCE is sensitive to the rate of absorption. Furthermore, DCE's metabolic profile (i.e. the percentage of DCE exhaled, metabolized and conjugated with GSH) is different for different routes of exposure and dose levels. This model, which the authors verified experimentally, is useful in predicting the kinetics, and thus the potential toxicity of DCE under various exposure conditions.

An initial step in the metabolism of DCE is possibly the formation of the epoxide (oxirane) intermediate, 1,1-dichloroethylene oxide, but this reactive compound has never been isolated upon administration of DCE to laboratory animals (e.g., Jones and Hathway 1978c; Reichert et al. 1979; McKenna et al. 1977).

An alternate metabolic scheme that does not go through the epoxide intermediate was proposed based on studies in isolated hepatocytes by Liebler et al. (1985, 1988) and is presented in Figure 2-6.

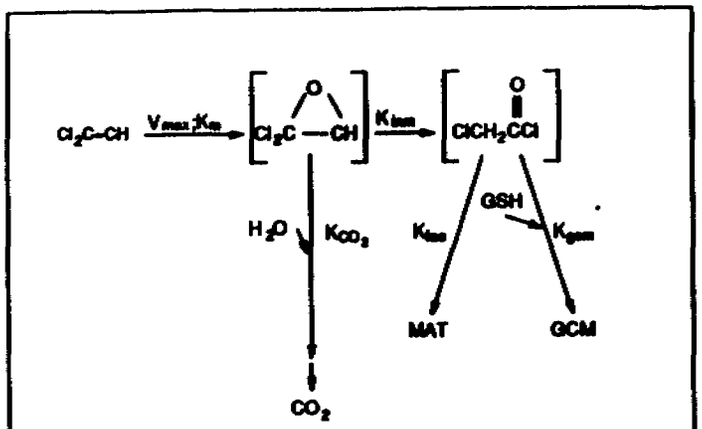
The main biotransformation pathways for DCE in the rat are suggested to involve conjugation with GSH, either with the epoxide or following rearrangement of the epoxide to chloroacetylchloride, with subsequent hydrolysis to monochloroacetic acid. This is consistent with the observation that exposure to DCE causes depletion of GSH levels in the liver (Jaeger et al. 1974; Reichert et al. 1979; Reynolds et al. 1980). For example, Reynolds et al. (1980) reported that there was a linear relationship in rats between intraperitoneally administered DCE and GSH depletion over the range of 20-100 mg DCE/kg body weight; above this level GSH depletion plateaued. The maximum reduction seen (70%) occurred 4 hours post-dose with a subsequent gradual recovery to normal levels within 24 hours. These findings have led several investigators to suggest that DCE-induced hepatotoxicity is related to the depletion of hepatic GSH levels, thereby permitting the reactive intermediate to bind to and alkylate hepatic macromolecules instead of being



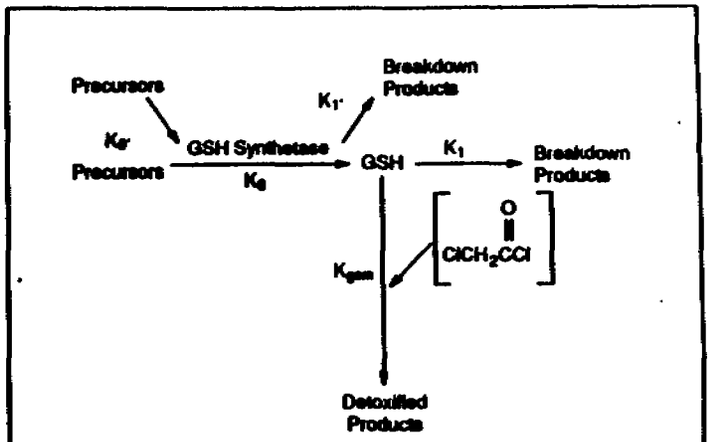
Note: Percentage values given in brackets are of dosed material excreted (rat, mouse) following treatment with 50 mg/kg by the oral route. Principal metabolites only are shown.

Reproduced from: Fielder et al. 1985

FIGURE 2-4. Metabolic Pathway of DCE in Animals



Scheme I. Model for DCE metabolism pathways.



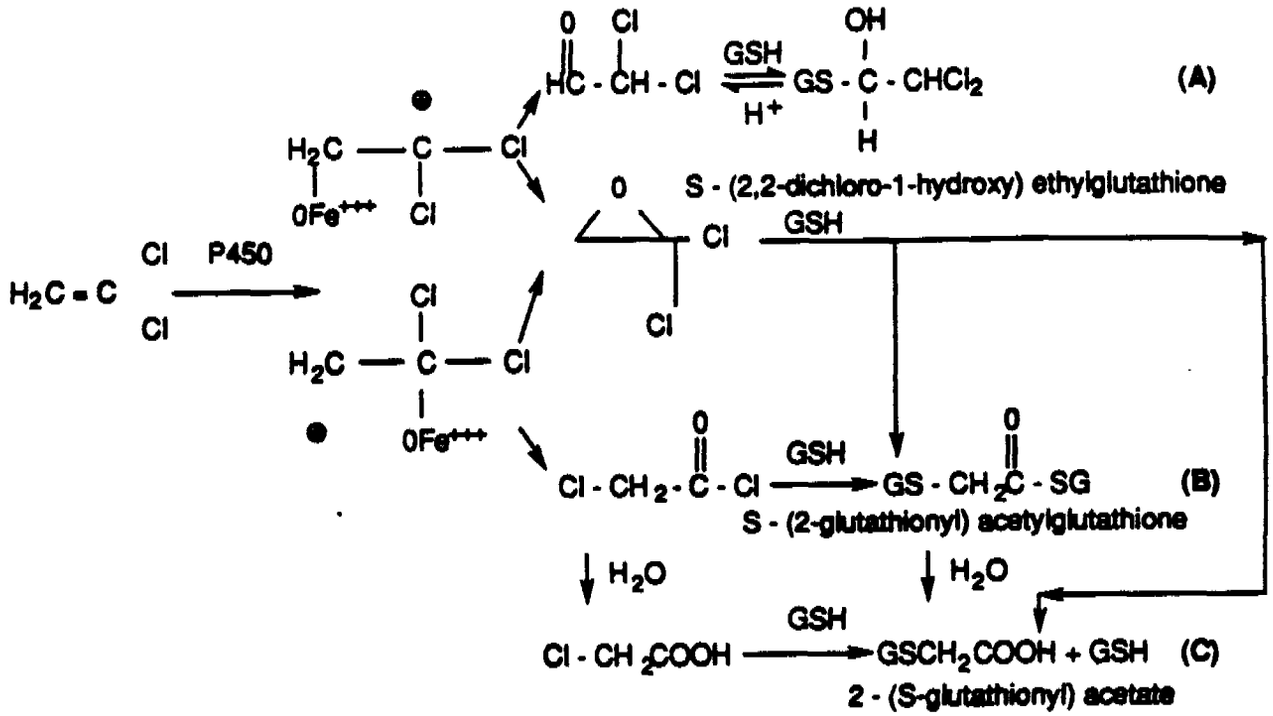
Scheme II. GSH synthesis and depletion by chloroacetyl chloride.

GSH	Glutathione concentration.
K_{bm}	First-order rate constant for formation of MAT.
K_{gsm}	First-order rate constant for formation of GCM.
K_{bm}	First-order rate constant for chloroacetyl chloride formation.
K_m	Michaelis constant for oxidative pathway.
K_d	Zero-order glutathione synthesis, time and GSH dependent.
$K_{d'}$	Glutathione synthetase formation.
K_1	First-order rate constant for glutathione breakdown.
$K_{1'}$	First-order rate constant for glutathione synthetase breakdown.
MAT	Metabolite available for toxicity.
V_{max}	Maximum velocity of oxidative pathway.

Parameters Used in the DCE PB-PK Model	
Partition coefficients	
Liver:blood	1.1
Richly perfused:blood	1.1
Slowly perfused:blood	0.6
Fat:blood	18.4
Blood:air	5.0
Kinetic constants	
V_{max} (mg hr^{-1})	2.6
K_m (mg $liter^{-1}$)	0.25
K_{gsm} (hM^{-1} hr^{-1})	0.33
K_{bm} (hr^{-1})	50
K_{bm} (hr^{-1})	9000
K_{CO_2} (M^{-1} hr^{-1})	1.82×10^{-5}
H_2O (M)	55

Reproduced from D'Souza and Anderson (1988)

FIGURE 2-5. Physiologically-Based Pharmacokinetic Model for DCE



Reproduced from Liebler et al. 1985.

Figure 2-6. General proposed scheme for oxidative and conjugative metabolism of 1,1-dichloroethene not metabolized via the epoxide intermediate.

detoxified, ultimately leading to cell death (Jaeger et al. 1974; McKenna et al. 1977; Reynolds et al. 1980).

Conjugation with monochloroacetic acid following by β-thionase activity appeared to be the major metabolic route on a quantitative basis in rats, since thiodiglycollic acid was the predominant urinary metabolite (Jones and Hathway 1978a). Other metabolites identified in this pathway include monochloroacetic acid itself, thioglycollic acid, and dithioglycollic acid. However, direct GSH detoxication of the epoxide also apparently occurred to a significant degree as demonstrated by the formation of glutathionyl acetyl chloride with subsequent breakdown to an N-acetyl cysteine derivative (Jones and Hathway 1978a).

Evidence exists to suggest that enzymatic hydration of the epoxide by epoxide hydrolase is a minor pathway in the metabolism of DCE in rats. This contention is supported by the observation that exacerbation of DCE-induced toxicity in rats by diethyl maleate and various epoxide inhibitors following inhalation exposure was directly related to their ability to decrease GSH levels and not with their ability to competitively inhibit epoxide hydrolase (Andersen et al. 1980).

Reichert et al. (1979) proposed an alternative metabolic pathway (i.e., one not involving GSH conjugation) to account for the presence of the metabolite, methylthioacetylamino ethanol. They suggested that chloroacetylchloride, instead of being hydrolyzed to monochloroacetic acid, reacts with membrane phosphatidyl ethanolamine which is enzymatically cleaved to yield the ethanolamine derivative of chloroacetic acid. The methylthio group is then probably transferred from methionine as a result of direct nucleophilic attack.

The pathways of DCE metabolism in the mouse were similar to those seen in the rat except that the rate of metabolism was greater in the mouse (i.e., a greater proportion of administered DCE was metabolized per given dose level by the mouse than the rat) (Jones and Hathway 1978a). The predominant urinary metabolite found in mice was the N-acetylcysteine derivative produced by GSH conjugation to detoxify the epoxide intermediate. In mice there were quantitatively greater amounts of water-soluble urinary metabolites present in the urine (and consequently less parent compound in the expired air) attesting to a greater metabolic capacity. Furthermore, β-thionase activity was more pronounced since more dithioglycollic acid was found than thioglycollic acid (Jones and Hathway 1978a). In addition, Oesch et al. (1983) pointed out that DCE may have different effects on cytosolic GSH transferase activity and that this difference may have contributed to the species differences observed.

Radiolabeled material has been shown by several investigators to covalently bind to liver and kidney tissues following the administration of [^{14}C]-DCE, which may provide a basis for the toxic effects seen in these

organs (Jaeger et al. 1977; McKenna et al. 1977). McKenna et al. (1977) reported a linear increase in the amount of covalently bound radioactivity in the liver of rats exposed to 5-200 ppm [^{14}C]-DCE by inhalation for 6 hours. However, GSH depletion (and therefore metabolism) plateaued at about 200 ppm. Therefore, the actual amount of reactive metabolite formed and available for binding was probably determined by a combination of both activation and detoxication pathways.

The increased severity of hepatotoxic and nephrotoxic effects induced by DCE in the mouse as compared to the rat may be partially explained by the observation that greater amounts of covalently bound reactive material were found in these two tissues in the mouse than the rat following exposure to the same dose of DCE (McKenna et al. 1977). The mouse exhibited greater DCE-induced nephrotoxic effects relative to the rat, and McKenna et al. (1977) reported that levels of covalently bound material were six times higher in the mouse kidney as compared to the rat kidney. Short et al. (1977d) reported similar results when a single dose of [^{14}C]-DCE was injected intraperitoneally to rats and mice. The highest level of covalently bound radioactivity was seen in the mouse kidney. The authors found that pretreatment with disulfiram also reduced the amount of covalent binding in both species. The authors speculated that disulfiram may reduce the activation of DCE and increase the extent of its detoxification. Thus, with respect to genotoxicity, conjugation of reactive intermediates of DCE with GSH is a major detoxification mechanism in laboratory animals by reducing the amount of reactive material available to covalently bind to cellular macromolecules.

DCE can also potentially form adducts with hemoglobin, similar to what has been observed with ethylene oxide (Tornqvist et al. 1986). Electrophilic intermediates, such as the epoxide formed in DCE metabolism, can likely bind to proteins in hemoglobin as they have been demonstrated to do in liver and kidney.

2.6.4 Excretion

2.6.4.1 Inhalation Exposure

No studies were located regarding excretion in humans following exposure to DCE. However, elimination of DCE following inhalation exposure in rats is rapid, with the bulk of absorbed material being eliminated as metabolites in the urine, and very little (1% of the administered dose) of the parent compound eliminated unchanged in the expired air at low levels of exposure (McKenna et al. 1978a). Steady-state levels of DCE in the expired air are achieved within 30-45 minutes after exposure to low (25-150 ppm) levels of DCE, indicating that elimination is first-order at these levels of exposure (Dallas et al. 1983). However, metabolic processes are saturated when exposure levels approach 200-300 ppm as evidenced by the fact that steady-state levels of DCE in expired air are never reached. Since DCE is volatile and relatively insoluble in blood, increased amounts can easily be eliminated unchanged via the lung once metabolic processes become saturated. Upon

cessation of exposure, concentrations of DCE in both blood and breath fell rapidly (Dallas et al. 1983). Similar results were obtained by McKenna et al. (1978a).

DCE exhibited a biphasic elimination profile following inhalation exposure in rats (McKenna et al. 1978a). The first phase had a half-life of about 20 minutes for the elimination of unchanged DCE in breath and 3 hours for the elimination of water-soluble metabolites in urine. The second phase had a half-life of about 4 hours in breath and 20 hours in urine. The bulk of the material was eliminated in both the breath and the urine during the rapid phase. Nutritional status did not appear to affect the elimination kinetics of DCE following inhalation exposure in rats (McKenna et al. 1978a).

Limited information is available on elimination following inhalation exposure to DCE in the mouse. However, McKenna et al. (1977) reported that at low levels of exposure (10 ppm for 6 hours), somewhat lower levels of unchanged DCE were eliminated in the expired air and higher levels of water-soluble metabolites were found in the urine as compared to the rat. This finding supports the observation that the mouse metabolizes DCE to a greater extent than the rat.

2.6.4.2 Oral Exposure

No studies were located regarding the excretion in humans following oral exposure to DCE. Elimination of DCE and its metabolites following oral administration in rats has been demonstrated to be very similar to that seen following inhalation exposure. Following oral administration of 1 mg [^{14}C]-DCE/kg body weight in corn oil, less than 1% of the administered dose was excreted unchanged in the expired air, with 5-14% of the administered dose recovered as [^{14}C]-CO_2. The bulk of the administered [^{14}C]-DCE (44-80% of the administered dose) was eliminated in the urine within 3 days, most within th first 24 hours. Smaller amounts of water-soluble metabolites (8-16% of the administered dose) were found in the feces (Jones and Hathway 1978c; McKenna et al. 1978b; Reichert et al. 1979). Following the oral administration of higher doses to rats (50 mg [^{14}C]-DCE/kg body weight), a higher proportion of unchanged parent compound (16-30% of the administered dose) was excreted in the breath with a concomitant reduction in the amount of expired CO_2 (3-6% of the administered dose) and urine metabolites (35-42% of the administered dose) (Jones and Hathway 1978c; McKenna et al. 1978b; Reichert et al. 1979). Similar but more marked trends were observed at even higher doses (Chieco et al. 1981; Jones and Hathway 1978c). Thus, metabolic processes were shown to become saturated at these dose levels.

Putcha et al. (1986) reported that the elimination of orally-administered DCE is triphasic, whereas McKenna et al. (1978a) and Reichert et al. (1979) reported that elimination is biphasic. The first phase identified by Putcha et al. (1986) occurred almost immediately, within the first few minutes after exposure, and the second two phases corresponded to those observed by the other investigators. Half-lives for these 2 phases of elimination in the

breath after inhalation exposure were 20 minutes and 1 hour, and 6 hours and 17 hours in the urine.

Nutritional status of the animal has been found to slightly modify the elimination of DCE by rats following oral administration. McKenna et al. (1978b) demonstrated that 19% of a 50 mg DCE/kg body weight dose was excreted unchanged by the lungs of fed rats, whereas 29% was excreted by fasted rats. This finding provides evidence that fasted rats eliminate unchanged DCE to a greater extent than fed rats. However, elimination of nonvolatile metabolites was slightly greater in fed animals than in fasted animals, indicating a reduced capacity for metabolism in fasted rats.

Mice have been shown to eliminate more DCE as water-soluble metabolites in the urine than do rats at comparable doses (Jones and Hathway 1978a). These results may indicate that mice also metabolize orally administered DCE to a greater extent than rats.

2.6.4.3 Dermal Exposure

No studies were located regarding the excretion of DCE in humans or animals following dermal exposure.

2.6.4.4 Other Routes of Exposure

Using the physiologically-based pharmacokinetic model developed for DCE discussed in Section 2.6.3, D'Souza and Anderson (1988) demonstrated that the half-life of DCE in blood is not representative of metabolism rates, but rather more closely corresponds to reequilibration of DCE from fat. Consequently, rats with higher fat content were verified to have longer DCE blood half-lives following intravenous administration. This could have important implications for obese individuals exposed to high levels of DCE.

2.7 INTERACTIONS WITH OTHER CHEMICALS

As discussed in previous sections, it is apparent that the toxicity of DCE is largely due to the formation of toxic intermediates during metabolism in vivo. The production and biotransformation of toxic metabolic intermediates of DCE can be greatly influenced by various metabolic inhibitors and inducers, and by the availability of precursors of compounds involved in detoxication, such as GSH.

Microsomal mixed-function oxidases (MFOs) are a group of enzymes involved in the biotransformation and detoxication of xenobiotics such as DCE. Inhibitors of some microsomal MFOs include the compound SKF-525-A, disulfiram, and other dithiocarbamates, such as thiram and diethyldithiocarbamate. These compounds reduce the toxic effects of DCE in the liver, probably by inhibiting the enzymes responsible for the formation of reactive, toxic intermediates (Masuda and Nakayama 1983; Short et al. 1977c,d). Inhibitors of metabolic enzymes responsible for the breakdown of these reactive intermediates may also

enhance the toxicity of DCE. For example, 1,1,1-trichloropropane and other inhibitors of epoxide hydrolase can potentiate the toxicity of DCE (Jaeger et al. 1977). Other chemicals that reduce the activity of metabolic enzymes and show some protective effects against the toxicity of DCE include pyrazole, 3-aminotriazol, and carbon tetrachloride (Andersen et al. 1978).

Enzyme inducers (enhancers) may either protect against or exacerbate the toxicity of DCE. Induction of enzymes involved in the formation of toxic intermediates results in potentiation of DCE-induced toxicity following DCE exposure; conversely, induction of enzymes responsible for the biodegradation of the toxic intermediate(s) will decrease toxicity. Examples of compounds that induce MFOs and cause an increased toxic effect upon exposure to DCE include ethanol and acetone (Hewitt and Plaa 1983; Sato et al. 1983).

Many inducers of MFO enzymes do not cause increased hepatotoxicity of DCE, perhaps because they stimulate a pathway not involved in the metabolism of DCE. An example of this type of compound is 3-methylcholanthrene (Carls n and Fuller 1972). The induction of metabolic enzymes by phenobarbital, even though protective against liver damage, has resulted in an increase in the cardiotoxicity of inhaled DCE at very high exposure levels.

Thyroidectomy protected rats from the hepatotoxic effects of DCE (Szabo et al. 1977). Thyroxine replacement in thyroidectomized rats exacerbated the liver damage seen upon subsequent exposure to DCE (Szabo et al. 1977).

Pretreatment of animals with compounds that deplete GSH levels (such as diethyl maleate) increase the amount of liver damage caused by DCE exposure (Reichert et al. 1978). Conversely, pretreatment of animals with supplements containing high concentrations of the amino acids cysteine and/or methionine, both of which are metabolic contributors of the sulfhydryl group required for GSH biosynthesis, has been demonstrated to have a protective effect against the toxicity of DCE (Short et al. 1977d).

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Specific information regarding human subpopulations that are unusually susceptible to the toxic effects of DCE were not located. However, animal studies have suggested that there are factors that may predispose some groups to be at increased risk for the toxic effects of DCE than the general population. These factors are discussed below.

The influence that nutritional status and dietary intake can have upon the metabolism and detoxification of xenobiotics has been well documented. Nutritional status is known to modify the metabolism and toxicity of a variety of halogenated alkenes (Andersen et al. 1978; Nakajima et al. 1982). As discussed in previous sections, fasted animals or animals kept on a low carbohydrate diet exhibited a greater toxic effect when exposed to DCE when compared with similarly exposed control (carbohydrate-fed) animals (Nakajima et al. 1982). Reynolds and Moslen (1977) and Jaeger et al. (1974) note that

starvation prior to DCE exposure resulted in both an earlier appearance of hepatic lesions and a more extensive distribution of lesions compared to control (fed) rats.

Sex differences in the toxic response to DCE have been observed in animals. For example, in a chronic inhalation exposure study in rats, hepatotoxic effects occurred at lower DCE concentrations in female rats than in male rats (24 ppm and 75 ppm, respectively) (Quast et al. 1986). Fasted male animals, particularly, young males, appear to be more susceptible to the toxic effects of DCE than fasted females, as evidenced by their enhanced responses at lower doses of DCE.

Individuals taking certain drugs or who have pre-existing liver, kidney, thyroid, or cardiac disease may be at greater risk for DCE-induced toxicity. Phenobarbital, even though somewhat protective against DCE-generated liver damage (Carlson and Fuller 1972), has been shown to sensitize the heart to DCE-induced arrhythmias (Siletchnik and Carlson 1974). Since phenobarbital is sometimes used as a soporific, and by those with various forms of epilepsy or seizure disorders, people who are taking this medication or those with pre-existing arrhythmic heart conditions should not be exposed to high levels of DCE. Ethanol increases the amount of DCE-induced hepatotoxicity observed in rats, which suggests that alcohol ingestion could exacerbate DCE-induced toxicity in exposed individuals. Therefore, individuals taking alcohol-containing medication or drinking alcoholic beverages may be more susceptible to the toxic effects of DCE. Thyroidectomy, either chemical or surgical, can protect against the hepatotoxicity associated with inhalation of DCE. Conversely, thyroxine treatment to replace or supplement normal thyroid function results in an increased amount of liver damage upon subsequent exposure to DCE in animals (Szabo et al. 1977). Individuals with liver or kidney disease or those with an acute hypersensitivity to DCE should avoid exposure to DCE.

Specific data concerning teratogenicity in humans exposed to DCE were not found in the reviewed literature. DCE has been described as a possible teratogen responsible for soft-tissue anomalies in rats and skeletal defects in mice, rats, and rabbits, often at levels that produced clear evidence of toxicity in the dam. Therefore, pregnant women should also avoid exposure to DCE.

To conclude, groups of people who should be specifically cautioned against exposure to DCE include the very young; the pregnant; those who ingest alcohol; people using phenobarbital (or possibly other hepatic enzyme-inducing drugs); those receiving thyroid replacement therapy or those who are hyperthyroid; people who, for whatever reason, are fasting and those with cardiac, hepatic, renal, and certain central nervous system dysfunctions.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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 DCE is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

2.9.1 Existing Information on Health Effects of DCE

Figure 2-7 graphically depicts the existing health effects information n DCE for a specific route and duration of exposure. There is little information available concerning the long-term health effects of DCE in humans following inhalation exposure. Most of the information concerning health effects in humans is reported in occupational studies that are difficult to interpret due to limitations in study design (e.g., exposure levels and duration cannot be quantified and concurrent exposure to other toxic substances cannot be ruled out). No information concerning oral or dermal exposure to DCE in humans was found in the reviewed literature.

The systemic effects of DCE in animals following inhalation and oral exposure have been studied in a variety of species following acute, intermediate, and chronic exposure durations. Information was not found concerning immunological effects following oral exposure. One oral exposure study reported observations of the "appearance" and "demeanor" of test animals, but this was not considered a good analysis of possible neurological effects. Genetic effect end points were examined following inhalation exposure only. Carcinogenicity studies in animals following exposure by oral, inhalation, and dermal exposure are available.

2.9.2 Data Needs

Single-Dose Exposure. We are reasonably confident that the information available on the systemic toxicity of DCE following single-dose inhalation and oral exposure in animals will allow for extrapolation to effects that might be expected in humans following such exposures. Data on single-dose dermal exposure are lacking. Accidental contact with aqueous solutions of DCE is possible primarily in and around hazardous waste sites, so more information on the adverse systemic health effects in animals of dermal exposure to DCE in animals would be useful.

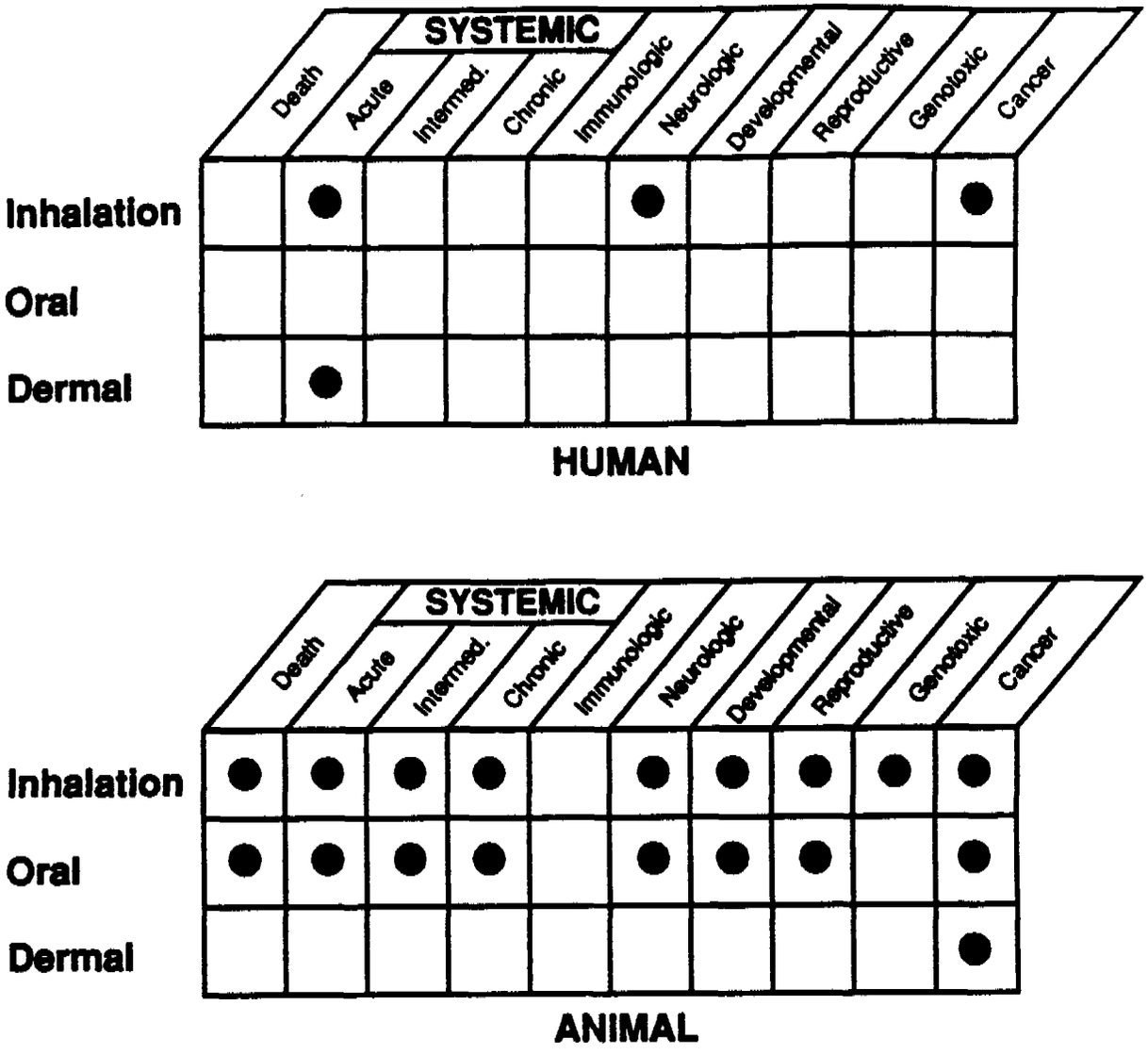


FIGURE 2-7. Existing Information on H Effects of DCE

Repeated-Dose Exposure. Information is available on the systemic toxicity of DCE following repeated-dose inhalation and oral exposure in animals, though these effects are not as well characterized as acute exposures. We are reasonably confident that the existing data will allow for extrapolation to systemic effects that might be expected in humans following such exposures. Data on repeated dose dermal exposure are lacking. However, as discussed above, this is not expected to be a major route of exposure for DCE.

Most information available in the recent literature concerning the toxicity of DCE following both single- and repeated-dose exposure is derived from studies using fasted animals, since they are more susceptible to DCE-induced toxicity. Studies which clearly delineate between fasted and nonfasted experimental conditions would assist in the understanding of DCE toxicity in the human population. These studies need to focus on comparisons of biochemical functioning in laboratory animals and human nutritional status in the general population. For example, how do GSH levels in rodents compare to levels normally seen in human subpopulations, which might determine specific groups at risk? Furthermore, many animal studies have mentioned the occurrence of increased serum enzyme markers of hepatic dysfunction following DCE exposure. Studies that attempt to correlate the presence of these enzymes in blood with functional and histopathological changes in the liver would greatly improve the utility of the data base.

Specific differences with regard to susceptibility to the toxic effects of DCE are evident in animal studies; mice generally respond to lower doses of DCE than rats, and DCE-induced toxicity in male animals is exacerbated by fasting but not in female animals. However, developmental effects in rats are observed at lower doses than in mice in inhalation studies. Though the reasons for the differences are not known, it can be speculated that underlying biochemical differences, such as the ability to form reactive intermediates, may be involved. It is possible that human subpopulations may also differ in their ability to form reactive intermediates of DCE. Thus, further studies investigating the underlying mechanisms of species and sex variation to the toxicity of DCE may help identify sensitive human subpopulations.

Chronic Exposure and Carcinogenicity. Data from animal studies on the chronic toxicity and carcinogenicity of DCE are sparse, and limited in their usefulness because of experimental design flaws. The data presented do not sufficiently characterize the carcinogenic or chronic toxic effects of DCE. However, the available information does suggest that DCE is carcinogenic in animals. Additional information on the chronic toxicity and carcinogenicity of DCE from well-conducted animal bioassays and human epidemiological studies using various routes of exposure would be useful in predicting the likelihood that such effects occur in humans.

Genotoxicity. Information is available from short-term bacterial, yeast, plant and mammalian cell culture and <u>in vivo</u> tests. Though DCE is genotoxic

in in vitro systems, it has generally tested negative in in vivo mammalian systems. More information on the genotoxicity of DCE, particularly in mammals, may clarify these conflicting results.

Reproductive Toxicity. One study has been conducted on the potential reproductive toxicity of DCE in animals (Nitschke et al. 1983). This study was conducted by the oral route in rats, and the results were negative. Studies by Short et al. (1977a) demonstrated that inhalation exposure of pregnant dams to DCE produced a statistically significant increase in the incidence of early embryo resorptions. Inhalation has been shown to be more harmful than oral exposure for several other end points; a standard reproductive toxicity study has not been done by the inhalation route and would be useful.

Developmental Toxicity. Numerous studies on the potential developmental toxicity of DCE have been conducted in animals. We are reasonably confident that the available information is enough to conclude that adverse developmental effects may occur in humans at exposure levels that might cause toxic effects in the mother. However, a NOAEL in mice for continuous in utero inhalation exposure has not been established. A lower dose study to determine a safe level for developmental effects would add further confidence in the database. Monitoring and epidemiological studies in areas surrounding hazardous waste sites would be useful to more fully assess the developmental hazard of DCE in humans.

Immunotoxicity. No information is available on the immunotoxicity of DCE. Studies investigating the potential for this effect would be useful, since compromised immunocompetence can be devastating to human health.

Neurotoxicity. Information is available on the neurotoxic effects of acute inhalation exposures to DCE in both humans and animals. However, no information is available on the potential neurotoxic effects of long-term exposure to DCE. More information would be useful in assessing the neurotoxic effects of prolonged exposure to DCE, such as may occur in the vicinity of hazardous waste sites.

Epidemiological and Human Dosimetry Studies. Most of the available information on the adverse effects of DCE in humans comes from cases of acute poisoning occurring primarily in the workplace. Limitations inherent in these studies include unquantified exposures, concentrations and durations, as well as concomitant exposure to other toxic substances. The few available industrial surveys and epidemiological studies are limited in their usefulness because of small sample size, short follow-up periods and/or brief exposure periods. Despite their inadequacies, studies in humans indicate that DCE can cause central nervous system toxicity and irritation of the mucous membranes. There is also some evidence to suggest that repeated exposure to DCE is associated with liver damage in humans. Well-controlled epidemiological studies of people living in close proximity to areas where DCE has been detected in surface and groundwater, in the vicinity of industries releasing DCE, near hazardous waste sites, and of people occupationally exposed could

add to and clarify the existing database on DCE-induced human health effects. However, occupational studies would probably be difficult to conduct since the majority of exposed workers are carpenters, warehousemen, and machine operators for whom exposure information and health follow-up is difficult to obtain, and the exposed population is either dropping or difficult to define.

Biomarkers of Disease. Adequate methods exist for the analysis of DCE in expired air. However, no good quantitative correlation can be drawn between body levels of DCE and adverse health effects based on the available data. If epidemiological studies are conducted that correlate DCE exposure with specific adverse health effects, it may be possible to correlate these effects quantitatively with changes in tissue and/or body levels of DCE.

Disease Registries. At present, the only known health effects of DCE in humans are central nervous system toxicity, upper respiratory tract irritation, and, possibly, liver damage. If epidemiological studies identify particular diseases produced by DCE, it may be possible to determine the number of people affected and the factors associated with identifying the disease in certain populations, such as exposure to high levels near hazardous waste sites.

Bioavailability from Environmental Media. The monitoring data available indicate that DCE is present in the air, water, soil, and foodstuffs. DCE and metabolites can be measured in the breath, blood, urine, and adipose tissue of humans. Thus, it can be concluded that DCE is bioavailable from the environment. What is lacking is good quantitative data that correlate varying levels in the environment with levels in the body and health effects and the extent to which DCE can be absorbed from various media (i.e., soil). This may be difficult to obtain, since environmental levels can fluctuate widely because of the high volatility and rapid degradation of DCE.

Food Chain Bioaccumulation. More data on levels of DCE in various parts of the food chain and how these levels impact on levels found in humans would be useful.

Absorption. We are reasonably confident that the available animal data sufficiently characterize the absorption of DCE by the inhalation and oral routes of exposure. More data on absorption of DCE following dermal exposur would be useful since humans can be exposed via this route as well.

Distribution. The distribution of DCE following inhalation and oral exposure has been sufficiently characterized in animals. More data on the distribution of DCE following dermal exposure would be useful, since humans can be exposed via this route as well.

Metabolism. The metabolism of DCE to reactive intermediates is thought to be an important factor in the manifestation of DCE's toxic effects. The available data do not unequivocally identify the epoxide as the only reactive intermediate nor establish epoxide formation as the only route of metabolism.

Studies designed to clarify the intermediate metabolism of DCE and relate this metabolism to the manifestation of toxic effects would be useful.

Excretion. We are reasonably confident that the available animal data sufficiently characterize the excretion of DCE following inhalation and oral exposure. More data on the excretion of DCE following dermal exposure would be useful, since humans can be exposed via this route as well.

2.9.3 On-going Studies

A cohort mortality study (1940-1980) among grain millers exposed to several chemicals including DCE is being conducted by Dr. Alavanja at the National Cancer Institute. Data are being supplied by the American Federation of Grain Millers.

Studies are currently being conducted by Dr. Kanz's research group at the University of Texas Medical Branch at Galveston to evaluate the modulation of DCE-induced hepatic injury by hypo- and hyperthyroidism. No other on-going studies on the health effects of DCE were identified.

No on-going studies concerning the association between body tissue and fluid levels of DCE and health effects were located.

No on-going studies concerning the environmental levels of DCE associated with body levels or health effects were identified.

Studies at the University of Texas Medical Branch Department of Pathol gy conducted by Dr. Moslen's research group are trying to establish whether alterations in nutritional state or DCE metabolism cause changes in hepatobiliary clearance functions. Studies by Dr. Poyer's research group at the Oklahoma Medical Research Foundation are observing the extent to which DCE forms free radicals when metabolized by the mixed function oxidase system. Studies being conducted by Dr. Glende's research group at Case Western Reserve University are aimed at determining whether phospholipase A2 activation of DCE plays a role in the hepatotoxic action of this chemical. Dr. Shaikh's research group at the University of Arkansas is investigating the kinetics and mechanisms of the interaction of superoxide with DCE to form active free radicals, which cause toxicity through lipid peroxidation. The overall aim is to determine which biotransformation products are truly responsible for DCE's toxic effects.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

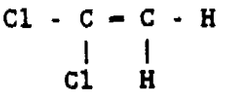
The chemical formula, structure, synonyms, and identification numbers for DCE are listed in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Important physical and chemical properties of DCE are listed in Table 3-2.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of DCE

Property	Value	Reference
Chemical Name	DCE	
Synonyms	1,1-Dichloroethylene; 1,1-DCE; 1,1-Dichloroethene asym-dichloroethylene; chlorure de vinylidene (French); ethene; 1,1,-dichloro; ethylene; 1,1,-dichloro; VDC; vinylidene chloride (inhibited); vinylidene chloride (II); vinylidene dichloride; vinylidine chloride	HSDB
Chemical formula	C2-H2-C12	Merck (1983)
Structure		Merck (1983)
Identification Numbers:		
CAS Registry	75-35-4	HSDB
NIOSH RTECS	KV9275000	HSDB
EPA Hazardous Waste	U078	HSDB
OHM/TADS	7216949	HSDB
DOT/UN/NA/IMCO Shipping	UN 1303;IMCO 3.1	HSDB
HSDB	1995	HSDB
NCI	C54262	HSDB

CAS = Chemical Abstracts Services
NIOSH = National Institute for Occupational Safety and Health
RTECS = Registry of Toxic Effects of Chemical Substances
OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System
DOT/UN/NA/IMCO = Department of Transportation/United Nation/International Maritime Dangerous Goods Code
HSDB = Hazardous Substance Data Bank
NCI = National Cancer Institute

TABLE 3-2.. Physical and Chemical Properties of DCE

Property	Value	Reference
Molecular weight	96.95	Merck (1983)
Color	Colorless	Grayson (1985)
Physical state	Liquid	Merck (1983)
Melting point, °C	-122.5	Merck (1983)
Boiling point, °C	31.7 at 760 mm Hg	Merck (1983)
Density	1.2129 g/cm^3 (20°C)	Merck (1983)
Odor	Mild sweet odor resembling that of chloroform	Merck (1983)
Odor threshold:		
Water		
Air	500 ppm	Clayton and Clayton (1981)
S lubility:		
Water	0.25% by weight in water at 25° C	Clayton and Clayton (1981)
	Practically insoluble in water	Merck (1983)
Organic solvents	Soluble in organic solvents.	Merck (1983)
Partition coefficients		
log octanol/water, kow	2.13	Mabey et al. 1982
log sediment coefficient, koc	1.81	Mabey et al. 1982
Vapor pressure	500 mm Hg at 20° C	
	591 mm Hg at 25° C	
	720 mm Hg at 30° C	Verschueren (1983)
Henry's law constant	0.19 atm m^3/mol	Pankow and Rosen (1988)
Autoignition Temperature °C	517.8-555.0	Weiss (1980)
Flash point	3°F (tag open-cup)	
	-2°F (tag closed-cup)	EPA 1985a
Flammability limits	7.3%-16%	Weiss 1986
Conversion factors	1 ppm x 3.97 = 1 mg/m^3	
	1 mg/m^3 x 0.25 = 1 ppm	

3. CHEMICAL AND PHYSICAL INFORMATION

4. PRODUCTION, IMPORT, USE AND DISPOSAL

4.1 PRODUCTION

DCE does not occur naturally (EPA 1985a). It is produced commercially by the dehydrochlorination of 1,1,2-trichloroethane with excess lime or caustic. Two hundred ppm p-hydroxyanisole is added as an inhibitor of the polymerization reaction, which is later removed by distillation or washing (Grayson 1985). Typically, a commercial grade contains 99.8% DCE (EPA 1985a).

DCE polymerizes after the addition of an initiator by either an ionic or a free radial reaction. DCE can polymerize spontaneously at room temperature by the addition of peroxides (Grayson 1985).

DCE is manufactured in chemical plants located in Texas and Louisiana. Currently, there are two major producers, Dow Chemicals and PPG Industries (Burke 1987, EPA 1977). Production capacity in 1985 was 178 million pounds per year (EPA 1985a). This has been decreased from 1977, when production capacity was estimated at 270 million pounds (EPA 1977). In 1988, plant capacity at PPG (Pittsburgh Paint and Glass) Industries was estimated at 64 million pounds per year (PPG Industries, personal communication, August 1, 1988). Estimated 1989 production is 230 million pounds (CMA 1989).

4.2 IMPORT

In 1984, 40,000 pounds of DCE was imported into the U.S. (SRI 1987). No data are available on the export levels.

4.3 USE

Monomeric DCE is used as an intermediate for captive organic chemical synthesis, and in the production of polyvinylidene chloride copolymers. These polymers which have been commercially important since their introduction in the early 1940s, are used extensively in many types of flexible packing materials (including barrier, multilayer, and monolayer), as flame retardant coatings for fiber and carpet backing, and in piping, coating for steel pipes, and adhesive applications (EPA 1977). The major application of polyvinylidene chloride copolymers is the production of flexible films for food packaging (SARAN™ and VELON™ wraps). DCE is found in many food and other packaging materials. Due to the instability of the pure polymer, DCE is used as a copolymer with acrylonitrile (Grayson 1985). In the late 1960's and early 1970's DCE monomer was used as an intermediate in the production of 1,1,1-trichloroethane; however, the compound is not believed to be currently used in that application (SRI 1987).

4. PRODUCTION, IMPORT, USE AND DISPOSAL

4.4 DISPOSAL

As a hazardous waste, DCE is classified as a flammable liquid (Weiss 1986). As such, the EPA (1987a) requires compliance with the regulations of the Resource Conservation and Recovery Act when producing, treating, transporting, storing, or disposing of this substance. Current disposal regulation of DCE requires dissolving it in combustible solvents and scatter spraying the solvent into a furnace with an afterburner and alkaline scrubber. However, significant revision of the criteria for land treatment and burial is occurring presently (HSDB 1988). The waste mother liquor probably contains higher concentrations (greater than 200 ppm) of the inhibitor, MEHQ.

According to the NPL technical database, DCE has been designated as a chemical of concern at 175 of the 1177 total NPL sites (VIEW 1989). DCE has been detected at 16% of the 2,738 hazardous waste sites that have had samples of all media analyzed by EPA's Contract Laboratory Program statistical database (EPA 1988b).

4.5 ADEQUACY OF THE DATA BASE

Section 104(i)(5) of CERCLA, 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 DCE is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

4.5.1 Data Needs

Production, use, release, disposal. We are reasonably confident that enough information is available on the production, use, and release of DCE. More information on how much DCE has been disposed of at hazardous waste sites and how much has been abandoned would be useful, though it is unlikely to be obtained.

According to the Emergency Planning and Community Right to Know Act of 1986 (EPCRTKA), (§313). (Pub.L. 99-499, Title III, §313), industries are required to submit release information to the EPA. The Toxic Release Inventory (TRI), which contains release information for 1987, became available in May of 1989. This database will be updated yearly and should provide a more reliable estimate of industrial production and emission.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

The primary sources of DCE in the environment are related to the synthesis, fabrication, and transport of DCE and its polymer products. Due to the volatile nature of the chemical, releases to the atmosphere are the greatest source of ambient DCE. Smaller amounts of the chemical are released to surface water and soil, primarily as a result of waste disposal. DCE in waste water should partition to the atmosphere as a result of volatilization during treatment processes. Most of the DCE released to the environment partitions to air or water. DCE is rapidly transformed in the troposphere where oxidation by hydroxyl radicals and photolysis are the dominant transformation processes. Biotransformation is believed to be the dominant transformation process for DCE in water, although this process is probably not important in aerobic surface waters due to the volatility of the compound. Biotransformation in soil has not been studied extensively, but methanogenesis has been shown to occur. Biotransformation will be an important process mainly in subsurface soils, since DCE in surface soils will volatilize to th atmosphere. DCE has been detected in air, surface water, groundwater, and soil, with the frequency of detection and the concentrations greatest near source areas (e.g., industrial areas, hazardous wastes sites).

5.2 RELEASES TO THE ENVIRONMENT

DCE is a man-made chemical and there is no evidence that natural processes produce this compound except by degradation of synthetic chloro-organics. The primary anthropogenic sources of DCE in the environment are related to the synthesis, fabrication, and transport of DCE and 1,1,1-trichloroethane, which upon dehydrochlorination, yields DCE.

5.2.1 Air

Air releases are the largest source of DCE in the environment, and emissions from polymer synthesis and fabrication industries contribute most to overall atmospheric loading. Singh et al. (1981) have estimated that air emissions of DCE from polymer synthesis in the U.S. range between 2-5% of the annual production. EPA (1985a) estimated total annual air emissions of DCE of about 650 tons/year, which was 0.8% of the production volume for that year. Ov r one-half of that total (355 tons) was from the polymer production/fabrication industries. The remaining emissions were from monomer synthesis (223 tons/year; 34%) and monomer storage, handling, and :ransportation (73 tons/year; 11%). Small amounts of DCE (not quantified) were estimated to be released during the incineration (disposal) of polymer products containing the DCE monomer and 1,1,1-trichloroethane used as a metal cleaning solvent. However, more recent data indicate that both the number of emission point sources and the total amount of DCE released to the atmosphere are much less than EPA's earlier estimates. This decrease is the result of shifts away from the use of the compound by processors and improvements in control technology. For example, survey data submitted by the Chemical

Manufacturers Association to EPA indicate that approximately 103.4 tons of DCE per year are released from manufacturing and processing facilities (CMA 1989). Emissions of the compound to the atmosphere in 1987 were estimated to be 836,371 pounds in the SARA Section 313 Toxic Release Inventory (EPA 1989).

Hazardous waste sites where DCE has been improperly disposed are additional potential sources of release of the chemical to the atmosphere due to volatilization (see Section 5.4.1).

5.2.2 Water

Industrial releases of DCE to surface water contribute to the overall environmental loading of the chemical, but to a much lesser extent than atmospheric emissions. Liquid effluent produced during polymerization operations are estimated to contribute approximately 2 tons of waste DCE each year (Neufeld et al. 1977). Other potential industrial sources of waste DCE in surface water are metal finishing and nonferrous metals manufacturing industries, soap and detergent manufacturers, coil coating and battery manufacturers, coal mines, laundries, and industries involving paint and ink formulation. DCE has been measured in raw wastewater from these industries at mean concentrations of 3-760 μg/L (EPA 1981). The total quantity of annual releases from these industries has not been estimated.

Hazardous waste sites where DCE has been improperly disposed are additional potential sources of the chemical. According to EPA's Contract Laboratory Program (CLP) statistical database (EPA 1988b), DCE has been detected in approximately 2% of the surface water and 10% of the groundwater samples of the 2,783 hazardous waste sites that have had samples analyzed by the CLP. Concentration data for the surface water samples were not reported; however, the geometric mean concentration of the compound in the positive groundwater samples was 1.38 mg DCE/L. In addition, surface water or groundwater contaminated with 1,1,1-trichloroethane can be an additional source of DCE through abiotic dehydrochlorination (McCarty et al. 1986). Total releases of DCE from these sources have not been quantified or estimated.

5.2.3 Soil

Limited information is available on the releases of DCE to soil. Neufeld et al. (1977) have estimated that a total of 180 lbs/yr of DCE are disposed of in municipal landfills as residual monomer in some consumer products on a national basis. Hazardous waste sites are additional sources of DCE in soil. DCE has been detected in the soil at an estimated 4.7% of the 2,783 hazardous wastes sites that have had samples analyzed by the CLP; concentration data were not reported (EPA 1988b).

5. POTENTIAL FOR HUMAN EXPOSURE

5.3 ENVIRONMENTAL FATE

The behavior of DCE in the environment is influenced to a large degree by its high volatility. As a result, the majority of DCE released to the environment partitions to the atmosphere. DCE is water soluble (0.25% by weight at 25°C), however, and some DCE released to the environment will dissolve and remain in solution, resulting in surface water or groundwater contamination and transport. DCE has a low propensity for binding to organic or particulate matter, and therefore its movement within and between media is not inhibited by adsorption processes. Once released to the environment, transformations of DCE can occur due to the reaction with radical species in the atmosphere and biodegradation in soil or water environments.

5.3.1 Transport and Partitioning

The tendency of a chemical to partition between soil, water, sediment, air and biota can be inferred from its physical/chemical properties. In a global sense, most of the DCE released into the environment will ultimately partition into the atmospheric environment as shown by the vapor partitioning model of Mackay and Paterson (1981). In localized situations, intervening processes such as biotransformation, may alter this outcome and become more important factors to consider.

As the magnitude of the Henry's Law Constant for DCE presented in Section 3 indicates, DCE is a highly volatile chemical and is likely to partition readily into the atmosphere from water. Because of this, DCE is generally not persistent in surface water in high concentrations. Studies on chemical removal processes indicate that once in the atmosphere, DCE is unlikely to partition to water (e.g., rain) or to adsorb to atmospheric particulates (Cupitt 1980).

DCE spilled onto surface soil will also tend to partition into the atmosphere, while some of the chemical will percolate into the subsurface soil. Once in the subsurface soil, DCE will partition between soil and water. DCE has high water solubility and a small soil organic carbon sorption coefficient (K_{oc}) value (see Section 3.0), indicating that small amounts of DCE will readily dissolve in water and migrate through soil without significant retardation by adsorption to organic carbon. Similarly, DCE will solubilize and migrate relatively freely within groundwater.

DCE in surface water is unlikely to partition significantly into aquatic organisms. Although measured bioconcentration factors were not located in the available literature, partitioning of DCE from water into aquatic organisms can be predicted in part by the magnitude of the octanol/water partition coefficient (K_{ow}) value. Veith et al. (1985) have suggested that chemicals with a log K_{ow} less than 4.0 are unlikely to bioaccumulate to hazardous levels in human food chains. The log K_{ow} presented in Section 3 is 2.13, and based upon this calculation, bioaccumulation in the human food chain is not expected to be significant for this compound.

5.3.2 Transformation and Degradation

Transformations of DCE can occur due to the reaction with radical species in the atmosphere, photolysis, biodegradation in soil or water environments, and abiotic transformations in water.

5.3.2.1 Air

DCE reacts rapidly with hydroxyl radicals. EPA (1983a) investigated the hydroxyl-radical initiated gas-phase oxidation of DCE with oxides of nitrogen. DCE reacted with OH and NO radicals in air to produce chloroacetyl chloride, phosgene, formaldehyde, carbon mon- ide and nitri acid. The atmospheric lifetime of DCE, assuming an OH co: ntration of .0^6 molecules cm^{-3}, is reported as 16.1 hours. This compares favorably with the atmospheric lifetime of 2 days predicted by Cupitt (1980).

Photolysis of DCE in the presence of nitrogen oxides is also rapid. Gay et al. (1976) studied the photoreaction of 4.85 ppm DCE in the presence of 2.26 ppm NO_x and UV radiation. Under the conditions of the study, 83% of the DCE decomposed within 140 minutes. The identified reaction products were formaldehyde, hydrochloric acid, carbon monoxide, formic acid, ozone, phosgene, chloroacetyl chloride, formyl chloride and nitric acid. Dilling et al. (1976) also found rapid photodecomposition of DCE in the presence of NOx, and artificial lighting conditions.

Although this relatively short lifetime indicates that DCE will not accumulate in the troposphere, EPA (1983a) indicated that fairly high concentrations of DCE will be found on urban and regional scales.

5.3.2.2 Water

Biotransformation is believed to be the dominant transformation process for DCE in water. However, the importance of this process under aerobic conditions, such as those normally found in ambient surface water, has not been determined. Conflicting results have been obtained for the aerobic degradation of DCE. Several investigations (McCarty et al. 1986, Bouwer et al. 1981, Pearson and McConnel 1975) have found no evidence for biotransformation of chlorinated ethenes such as DCE under aerobic conditions. In contrast, Tabak et al. (1981) reported transformation of 54% of 5 mg/L and 30% of 10 mg/L test concentrations of DCE under aerobic conditions within one week after incubation with a domestic wastewater seed; these removal figures were adjusted to account for volatilization losses from control flasks of 24% for the 5 mg/L and 15% for the 10 mg/L test concentrations.

Under anaerobic conditions (such as those that occur in groundwater), the importance of biotransformation is more defined. McCarty et al. (1986) found that DCE was nearly quantitatively reduced to vinyl chloride under anaerobic methanogenic conditions after 108 days. In another study, vinyl chloride was produced from the reductive dechlorination of DCE by microorganisms in anoxic

microcosms after 1-2 weeks of incubation (Barrio-Lage et al. 1986). Wilson et al. (1986) studied the behavior of DCE in authentic aquifer material known to support methanogenesis. The disappearance of this compound was observed with an initial long lag time, and vinyl chloride, a daughter product of degradation, was found in trace amounts. Vinyl chloride has been classified as a human carcinogen by the EPA (EPA 1985a). ATSDR has made available a Toxicological Profile on this compound.

Photolysis and hydrolysis of DCE in natural aquatic media are probably not significant processes (Mabey et al. 1982). Similarly, oxidation is not a significant transformation mechanism for DCE in aqueous environments. Degradation rates due to reactions with singlet oxygen and the peroxy radical have been estimated to be environmentally insignificant in aquatic systems (Mill and Mabey 1980).

5.3.2.3 Soil

A methane-utilizing culture isolated from lake sediment was found to degrade DCE to non-chlorinated end products under aerobic conditions (Fogel et al. 1986). These authors found that biodegradation of chlorinated aliphatic compounds carried out by methanotrophs occurred in the order of days, and did not require acclimation as do methanogenic dechlorinations. Information on soil degradation processes under aerobic conditions is lacking.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

The National Ambient Volatile Organic Compound (VOC) Database, updated in 1988 to include ambient and indoor VOC concentrations in urban, rural, remote, source-dominated and indoor environments, reports an ambient daily average concentration for DCE of 4.621 parts per billion (ppb) and an indoor daily average concentration of 19.665 ppb (Shah and Heyerdahl 1988). The ambient average concentration represents contributions from rural, suburban, urban, and source-dominated sites. The median concentration was reported as less than 1 part per trillion (ppt); this concentration was considered by the authors to be more representative of the database than the mean since it does not give undue weight to the higher values found at the source-dominated sites. The indoor average represents input from personal monitoring, and a median value of less than 1 ppt was also reported.

The results of an on-site field data collection program based on short-term studies conducted in seven U.S. cities indicated that DCE was present in air at an average concentration range of 0.005-0.03 ppb in various U.S. cities (Singh et al. 1981, 1982).

DCE has been measured in air in the vicinity of hazardous waste sites as well as a sanitary landfill in New Jersey, with arithmetic mean concentrations ranging from 0.39 to 36.4 ppb measured at waste sites, and an arithmetic mean

concentration of 2.6 ppb measured at the sanitary landfill (LaRegina et al. 1986). Although quantitative information on the air concentrations of DCE at hazardous waste sites on the National Priorities List (NPL) is not available, DCE is probably present in air at those NPL sites where it has been measured in either the soil, surface water or groundwater.

5.4.2 Water

DCE concentrations greater than 5 mg/liter have been measured in raw wastewater from the metal finishing and nonferrous metals manufacturing industries (EPA 1981). Lower concentrations (less than 1 mg/L) have been measured in raw wastewater from industries involving paint and ink formulation, soap and detergent manufacturing, coil coating, battery manufacturing, coal mining and laundries (EPA 1981). Treated wastewaters from all these industries ranged from less than 1 to 4 mg/L (EPA 1981).

DCE has been detected in surface waters sampled near industrial sites at concentrations ranging from less than 1 to 550 μg/L (Going and Spigarelli 1977). However, no DCE was detected in raw surface water during a 105-city survey of U.S. cities (Coniglio and Miller 1980). DCE has been detected infrequently at low concentrations in urban runoff which will contribute to surface water concentrations. The Nationwide Urban Runoff Program (NURP), initiated to evaluate the significance of priority pollutants in urban st rm water runoff, report a detection frequency of only 3%, with a range of concentrations of 1.5-4 μg/L (Cole et al. 1984).

About 3% of the drinking water supplies in the U.S. have been found to contain DCE at 0.2-0.5 μg/L (estimated mean 0.3 μg/L) concentration in a survey conducted by EPA (EPA 1985a). DCE was also detected (quantification limit of 0.2 ppb) in 2.3% of the 945 samples of finished drinking water taken from groundwater sources in a nationwide survey by Westrick et al. (1984). The maximum concentration of DCE detected in the positive samples was 6.3 ppb (subset median values were 0.28-1.2 ppb).

DCE has been detected in groundwater samples taken at 9.5% of the 2,793 hazardous waste sites in the U.S. participating in EPA's Contract Laboratory Program. The compound was detected at a geometric mean concentration of 1.38 mg/L (EPA 1988c).

5.4.3 Soil

No information is available on ambient concentrations of DCE in soil, although this chemical is often found at hazardous waste sites. Because of the tendency of DCE to partition into the atmosphere, with remaining material to percolate into groundwater sources, ambient concentrations in surface soil are expected to be low.

5.4.4 Other Media

DCE copolymers are used in the manufacture of films used in food packaging. Residual DCE monomer has been detected at concentrations of less than 0.02-1.26 ppm in retail food packaging films containing polyvinylidene chloride; residues in a variety of foodstuffs wrapped with the films were in the range of less than or equal to 0.005-0.01 ppm (Gilbert et al. 1980). Concentrations of residual DCE in household films were reported by Birkel et al. (1977) to be 6.5-10.4 ppm (average 8.8 ppm). No information on the levels of DCE in humans was located, although the chemical was tentatively identified as occurring in one of 46 samples of human adipose tissue measured as part of the National Human Adipose Tissue Survey (EPA 1986e).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Information on exposure of various populations to DCE is limited to information on potential exposures in workers. The National Occupational Hazard Survey (NOHS), conducted by the National Institute for Occupational Safety and Health (NIOSH), estimated that 56,857 workers in 3,853 plants were potentially exposed to DCE in the workplace in 1970 (NIOSH 1976). These estimates were derived from observation of the actual use of DCE (1%), the use of tradename products known to contain DCE (19%), and the use of generic products suspected of containing the compound (80%). The largest numbers of exposed workers were special trade contractors or in the fabricated metal products industry or wholesale trade industry. The occupational groups with the largest numbers of exposed workers were carpenters, warehousemen (not otherwise classified) and miscellaneous machine operators.

Preliminary data from a second workplace survey, the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1980 to 1983, indicated that 2,679 workers, including 291 women, in 97 plants were potentially exposed to DCE in the workplace in 1980 (NIOSH 1984). The greatest number of exposed workers were chemical technicians. All estimates were derived from observations of the actual use of the compound.

Neither the NOHS nor the NOES databases contain information on the frequency, concentration, or duration of exposure of workers to any of the chemicals listed therein. Rather, they only provide estimates of workers potentially exposed to the chemicals.

Varying occupational exposure levels can be found in the literature. Ranges of concentrations associated with the monomer and polymer plants have been reported as approximately 23-25 ppb and 6-12 ppb, respectively (Wapora 1982). Exposure concentrations as high as 1,900 ppm have been reported in a copolymer monofilament fiber production plant (Ott et al. 1976). However, in polymer manufacturing plants, worker exposure has been reported as <5 ppm (Ott et al. 1975; Jaeger 1975).

5. POTENTIAL FOR HUMAN EXPOSURE

DCE was found to be produced in significant amounts from the thermal degradation of 1,1,1-trichloroethane (TCA) (Glisson et al. 1986). This implies that inadvertent exposure to DCE may occur in many industrial situations when TCA is used in the vicinity of operations involving heat, such as welding or soldering and metal cleaning. This is of particular concern because TCA has become the solvent of choice in many industries for routine operations such as degreasing. DCE has also been detected as a pyrolysis product of the pesticide endosulfan in tobacco smoke (Chopra et al. 1978).

The Occupational Safety and Health Administration (OSHA) recently reduced the 8-hour time-weighted average permissible exposure level (8-hour TWA PEL) to 1 ppm (OSHA 1989), which should limit future workplace exposures to low levels of this compound.

5.6 POPULATIONS WITH UNUSUALLY HIGH EXPOSURES

Human exposure to DCE is potentially highest in workplace settings and among populations residing in the vicinity of hazardous waste sites where the compound may contaminate environmental media.

The presence of residual monomeric DCE in polymeric food wraps and other consumer products is another potential source of human exposure. Exposure from these sources is difficult to estimate. However, there is no evidence in the literature to implicate consumer products as major sources of DCE exposure (EPA 1985a).

In addition to releases from hazardous waste sites, ambient air and water may be contaminated with DCE by releases from industrial production and polymerization processes (EPA 1977; EPA 1985a; Wang et al. 1985a, 1985b). Levels are significantly higher in areas surrounding production sites (EPA 1977; EPA 1985a).

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in c nsultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of DCE is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

5. POTENTIAL FOR HUMAN EXPOSURE

5.7.1 Data Needs

Physical and Chemical Properties. Available data adequately characterize the physical and chemical properties of DCE.

Environmental Fate. Data which describe the degradation and transformation processes of DCE in surface water and soil are limited. More information is needed to define these processes and to quantify degradation rates. Such information would be helpful in understanding the fate of non-volatilized DCE in these media.

Exposure Levels in Environmental Media. Data on the concentrations of DCE in surface water, soil, food, and human tissues are limited. More data are needed to provide a more complete characterization of human exposure.

Exposure Levels in Humans. Most of the data on exposure levels of DCE are based upon occupational studies conducted under controlled environmental conditions. More current information on the potential exposure resulting from residence in the vicinity of hazardous waste sites would be useful to provide a more accurate characterization of human exposure in the U.S.

Exposure Registries. There is no exposure registry for DCE currently available. Such a registry would have to monitor both duration and intensity of exposure.

5.7.2 On-going Studies

Long-term research studies on the environmental fate of DCE were not identified. However, remedial investigations and feasibility studies on the 112 NPL sites which are known to have DCE contamination (EPA 1988c) should be completed in the near future and may add to the current knowledge regarding the transport and degradation of DCE in the environment.

Environmental monitoring conducted in conjunction with Remedial Investigation/Feasibility Studies at hazardous waste sites on the NPL should add to the current data base on environmental levels of DCE.

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, will be analyzing human blood samples for DCE and other volatile organic compounds. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

5. POTENTIAL FOR HUMAN EXPOSURE

6. ANALYTICAL METHODS

The purpose of this chapter is to briefly describe the analytical methods that are available for detecting and/or measuring and to some extent monitoring DCE in environmental media and in biological samples. Our intent here is not to provide an exhaustive list of a variety of analytical methods that would be applicable to detection and quantification. Rather, we intend to identify well-established methods that are used as the standard methods of analysis by various Federal agencies. Many of the analytical methods listed under the heading of analytical methods for DCE in environmental samples are the methods approved by Federal Agencies such as the Environmental Protection Agency (EPA) and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by a trade association such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). A third category of analytical methods emphasizes research and development activities, where efforts are underway to refine previously used methods, to obtain better resolution, and to increase accuracy and precision.

The analytical methods used to quantify DCE in biological and environmental samples are summarized below. Table 6-1 lists the applicable analytical methods for determining DCE in biological specimens and Table 6-2 lists the methods used for determining DCE in environmental samples.

6.1 BIOLOGICAL MATERIALS

DCE and/or its metabolites are eliminated from the body primarily in the expired air and the urine. Therefore, DCE exposure can be monitored by measuring the levels in expired air and urine. DCE also distributes to liver, kidney, and to a lesser extent, adipose tissue. Methods are available to measure DCE and/or its metabolites in these tissues as well. The GC/MS procedure is the most commonly used method to detect DCE in biological samples. This technique allows the detection of compound at the parts-per-billion (ppb) level. Capillary GC affords the highest resolution of complex mixtures, even when other volatile organic compounds are present that could conceivably mask or interfere with the detection of DCE. Furthermore, specific GC-detectors as well as mass selective detectors enable the quantitation of DCE even when it is not fully separated from other compounds. It is difficult to accurately measure biological concentrations of DCE and correlate these measurements to actual exposure concentrations because of the chemical's short half-life and conversion into metabolites. The concentration of DCE in biological media is continually changing by virtue of its rapid release into the air or biotransformation into other compounds. Also, detection of DCE is more difficult in biological media because it is a low molecular weight volatile compound in a matrix of very large organic molecules.

6. ANALYTICAL METHODS

TABLE 6-1. Analytical Methods for DCE in Biological Samples

Sample Matrix	Sample Preparation	Analytical Method[a]	Sample Detection Limit	Accuracy	References
Human tissue (adipose, kidney, liver, and brain)	Mince tissue, add isooctane/water; extract, purge and trap	GC/ECD	Approximately 50pg	>50% recovery	Lin et al. 1982
Breath	Thermal desorption	GC/MS	1 $\mu g/m^3$	40-60% recovery	Wallace et al. 1984; Pellizari et al. 1985
Fish tissue	Homogenize, add liquid N_2 to prevent evaporation of volatiles, vacuum distillation	GC/MS using a fused-silica capillary column	Not available	Not available	Hiatt 1983
	Purge and trap method to release volatile compounds trapped in the fish tissue	GC/MS	10 $\mu g/kg$	70% recovery	Easley et al. 1981

[a]GC = gas chromatography; MS = mass spectrometry; ECD = electron capture detector.

6. ANALYTICAL METHODS

TABLE 6-2. Analytical Methods for DCE in Environmental Samples

Sample Matrix	Sample Preparation	Analytical[a] Method	Sample Detection Limit	Accuracy[b] (µg/L)	References
Air	Adsorb (charcoal); desorb carbon disulfide	GC/FID	1 mg/m^3	85% recovery	NIOSH 1984 (method 1015); Taylor 1978; Foerst 1979
	Solid sorbent collection	GC/FID	7 µg/sample	>80%	Foerst 1979
	Reversible adsorption	GC/MS	Not available	Not available	Coutant 1984
Water	Purge-and-trap method	GC/HECD	0.13 µg/L	0.98C-0.87	EPA 1984a (method 601)
	Purge-and-trap method	GC/MS	2.8 µg/L	1.12C+0.61	EPA 1984c (method 624)
	Isotope dilution	GC/MS	10 µg/L	Not available	EPA 1984c (method 624)
Groundwater	Purge-and trap method	GC/HECD	0.13 µg/L	0.98C-0.87	EPA 1986a (method 8010)
	Purge-and-trap method	GC/MS	5 µg/L	1.12C+0.61	EPA 1986b (method 8240)
Solids/sludges/ soils/sediments / wastes	Purge-and trap method	GC/MS	Soil, sediment 5 µg/L (ww) wastes 0.5 mg/kg (ww)	1.12C+0.61	EPA 1986b (method 8240)
Soil/chemical waste	Hexane extraction; temperature programmed GC determination	GC/MS	10 ppm	80-90% recovery	DeLeon et al. 1980
Food (potato crisps, cakes, snack products, cheeses, biscuits)	Crush or grind and heat food samples	GC/ECD	<0.005 ppm	Not available	Gilbert et al. 1980
Packaging films	Heat hypovials containing film at 120°C; collect headspace vapor	GC/ECD	0.04 ppm	Not available	Gilbert et al. 1980; Crosby 1982

[a]GC = Gas chromatography; FID = flame ionization detection; MS = mass spectrometry; ECD = electron capture detection.

[b]Expressed a recovery as a function of C=true value for the concentration.

6. ANALYTICAL METHODS

Environmental exposure to DCE at hazardous waste sites may include exposure to other chlorinated hydrocarbons as well. DCE exposure can be monitored by direct measurement of the parent compound or its metabolites. It is difficult to distinguish metabolites of DCE in the body because the same metabolites may be formed as a result of exposure to other chlorinated hydrocarbons.

Determination of DCE in breath samples by GC/MS method is the most commonly used method of monitoring exposure to DCE (Pellizzari et al. 1985). Various other techniques are being studied and developed to monitor DCE in expired air using reversible adsorption (Contant et al. 1984) and impregnated tube methods for continuous monitoring (Denenberg and Miller 1974). The measurement of DCE adducts with DNA in lymphocytes or hemoglobin may also be useful in monitoring exposure to DCE. Such a method has been established in hemoglobin for another volatile organic compound, ethylene oxide (Tornqvist et al. 1986). Because human hemoglobin has a half-life of about 60 days (although half-lives of hemoglobin adducts are somewhat reduced), monitoring of DCE adducts with hemoglobin can be a valuable tool for estimating the daily and weekly exposure.

6.2 ENVIRONMENTAL SAMPLES

The analytical methods required by EPA (1984a,b,c) for the analysis of DCE in water and wastewater are delineated in procedures 601 (GC/ECD), 624 (GC/MS), and 1624 (GC/MS). These are testing procedures required under the Clean Water Act for sites discharging municipal and industrial wastewater. The method required by the EPA Contract Laboratory Program (CLP) for analysis of DCE and other volatile organic compounds is hexadecane extraction, followed by determination of approximate concentration using gas chromatography and flame ionization detection (GC/FID) and final quantitative analysis using GC/MS (EPA 1986a, 1986b).

GC/FID is used to detect DCE in air samples; the GC/MS procedure is used to determine DCE in water, wastewater discharges, and soil samples. Gilbert et al. (1980) detected DCE in food at levels less than 5 ppm using head space GC/ECD. These food products were packaged in PVC films.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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 DCE is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a

separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

6.3.1 Data Needs

Methods for Determining Parent Compounds and Metabolites in Biological Fluids. There are few analytical methods used to determine DCE in biological samples. The current emphasis is on (a) measuring the compound of interest at the parts-per-billion level accurately and consistently, (b) refining sample preparation techniques, and (c) modifying the GC/MS procedure to obtain better resolution. An analytical methodology to distinguish exposure to DCE from compounds with similar metabolic profiles is not available. Accuracy, precision, and recovery data are also lacking since the existing effort concentrates on the extension of detection limits of DCE rather than meeting quality control objectives necessary for analytical method standardization.

Methods for Biomarkers of Exposure. None of the available studies allow a quantitative correlation between monitored levels in tissues or fluids to exposure levels or toxic effects in humans.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. There are media-specific standardized methods available for detecting DCE in environmental samples. Accuracy data and sample detection limit data are available for the EPA-approved methods; however, this information is incomplete for other analytical methods. This may be due to the lack of adequate data to determine method accuracy, precision, or recovery values. There is a growing need for achieving lower detection limits. Kirshen (1984) reported that better resolution and sensitivity are achievable with the application of the proper GC capillary column and selection of the correct detector or detector combination.

6.3.2 On-going Studies

No on-going studies concerning techniques for measuring and determining DCE levels in biological samples were identified. However, the Division of Environmental Health Laboratory Services of the Center for Environmental Health and Injury Control of the Centers for Disease Control in Atlanta, Georgia is developing methods for the analysis of DCE and other volatile organic compounds in blood. These methods use purge and trap methodology and magnetic mass spectrometry which gives detection limits in the low parts per trillion range.

No on-going studies concerning techniques for measuring and determining DCE in environmental samples were identified.

6. ANALYTICAL METHODS

7. REGULATIONS AND ADVISORIES

DCE is on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" (EPA 1987c).

The international, national, and state regulations and guidelines pertaining to DCE in air, water, and food are summarized in Table 7-1.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to DCE

Agency	Description	Value	References
	International		
WHO	Guideline for Drinking Water	0.3 µg/L	WHO 1984
	National		
Regulations			
OSHA	Proposed Medical Records Rule	NA*	OSHA 1982
	Limit for Air Contaminants	1 ppm	OSHA 1989
EPA ODW	Maximum Contaminant Level (MCL) in Drinking Water	0.007 mg/L	EPA 1985 (40 CFR 141)
EPA OWRS	General permits under the National Discharge Elimination System (NPDES)	NA	EPA 1983b (40 CFR 122.28)
	Criteria and Standards for the NPDES	NA	EPA 1979 (40 CFR 125)
	General Pretreatment Regulations for Existing and New Sources of Pollution	NA	EPA 1986d (40 CFR 403)
	Wastewater; Effluent Guidelines for Point Source Categories		EPA 1987b (40 CFR 414)
	Rayon fibers, other fibers, thermoplastic resins, thermosetting resins, commodity organic chemicals, bulk organic chemicals, specialty organic chemicals:		
	maximum for one day	60 µg/L	
	maximum for monthly average	22 µg/L	
	Direct discharge point sources that use end-of-pipe biological treatment (effluent limitations **BAT and NSPS):		
	maximum for one day	25 µg/L	
	maximum for monthly average	16 µg/L	
	Direct discharge point sources that do not use end-of-pipe biological treatment (BAT effluent limitations and NSPS):		
	maximum for one day	60 µg/L	
	maximum for monthly average	22 µg/L	

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Value	References
FDA	Proposed uses of vinyl chloride polymers: deletion of vinyl chloride-DCE copolymers from the list of materials that may be used on fruits	NA	FDA 1986
EPA OERR	Reportable quantity	5000 lb	EPA 1985c (40 CFR 302.4)
	Reportable quantity (proposed)	100 lb	EPA 1987b
EPA OSW	Designation of hazardous substances	NA	EPA 1983b
	Listing as toxic wastes: discarded commercial chemical products, off-specification species, container residues, and spill residues of DCE	NA	EPA 1980a (40 CFR 261.33 (f))
	Listing as a hazardous waste constituent (Appendix VIII)	NA	EPA 1986c (40 CFR 261)
EPA OTS	Toxic Chemical Release Reporting (proposed)	NA	EPA 1987c
Guidelines			
NIOSH	Recommended Exposure Limit		NIOSH 1978
	TWA	4 mg/m^3	
ACGIH	Threshold Limit Value (TLV)		ACGIH 1986
	TWA	5 ppm = 20mg/m^3	
	STEL	20 ppm = 80 mg/m^3	
EPA ODW	Maximum Contaminant Level Goal (MCLG)	0.007 mg/L	EPA 1985c (40 CFR 141)
	Health Advisories		EPA 1987a
	1 day	2.0 mg/L	
	10 day	1.0 mg/L	
	Longer Term		
	Adult	3.5 mg/L	
	Child	1.0 mg/L	
	Lifetime	0.007 mg/L	
NAS	Suggested No-Adverse-Effect Level (SNARL)		NAS 1983
	Chronic	100 µg/L	

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Value	References
EPA OWRS	Ambient Water Quality Criteria to Protect Human Health		EPA 1980
	Ingesting water and Organisms	0.033 µg/L; 0.33 µg/L, 3.3 µg/L for 10^{-6}, 10^{-5}, 10^{-4}, risk levels, respectively	
	Ingesting aquatic organisms only	1.85 µg/L; 18.5 µg/L, 185 µg/L for 10^{-6}, 10^{-5}, 10^{-4} risk levels, respectively	
IARC	Carcinogenic classification	Group 3	IARC 1982
EPA	Reference dose (RfD) (oral)	$9x10^{-3}$ mg/kg/day	EPA 1988a
	$q_{1_o}^*$ (oral)	0.6 $(mg/kg/day)^{-1}$	EPA 1988a
	q_1^* (inhalation)	1.2 $(mg/kg/day)^{-1}$	EPA 1988a
	Carcinogenic classification	Group C	EPA 1988a
	State Regulations and Guidelines		
State environmental agencies	Drinking water quality standards and guidelines for several states		FSTRAC 1988
California		8 µg/L	
Maine		7 µg/L	
Minnesota		7 µg/L	
New Jersey		2 µg/L	
New Mexico		5 µg/L	
Vermont		7 µg/L	
State environmental agencies	Acceptable ambient concentration guidelines or Standards		NATICH 1987
Connecticut		20 $\mu g/m^3$ (8 hour avg.)	
Illinois		0	
Indiana		200 $\mu g/m^3$ (8 hour avg.)	
Kansas		0.238 $\mu g/m^3$ (Annual avg.)	
Massachusetts		0.2000 $\mu g/m^3$ (24 hour avg.)	
North Carolina		8000 $\mu g/m^3$ (15 min. avg.)	
Nevada		0.4760 mg/m^3 (8 hour avg.)	
New York		66.7 $\mu g/m^3$ (1 yr. avg.)	
Pennsylvania		24 $\mu g/m^3$ (1 yr. avg.)	
Virginia		3.5 $\mu g/m^3$ (24 hour avg.)	

*NA = Not applicable.
**BAT = Best available technology.
NSPS = New source performance standards.

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8. REFERENCES

9. GLOSSARY

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

Adsorption Coefficient (Koc) -- 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 (DL) -- 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 (ither parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in th 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.

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

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

In vivo -- Occurring within the living organism.

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

Lethal Concentration$_{(50)}$ (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 chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

9. GLOSSARY

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 (Kow) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

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

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

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

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

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

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are

allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

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

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

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 population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX

PEER REVIEW

A peer review panel was assembled for DCE. The Panel consisted of the following members: Dr. Richard J. Bull, Associate Professor of Pharmacology/Toxicology, University of Washington; Dr. Dietrich Hoffman, Associate Director, American Health Foundation; and Dr. Martha Radike, Research Assoicate Professor, Department of Environmental Health, University of Cincinnati Medical Center. These experts collectively have knowledge of DCE'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 the Superfund Amendments and Reauthorization Act of 1986, Section 110.

A joint panel of scientists from ATSDR and EPA has 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 their approval of the profile's final content. The responsibility of the content of this profile lies with the Agency for Toxic Substances and Disease Registry.

5. POTENTIAL FOR HUMAN EXPOSURE