TOXICOLOGICAL PROFILE FOR VINYL ACETATE

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

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DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) 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 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 lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987; on October 20, 1988; on October 26, 1989; and on October 171 1990. A revised list of 275 substances was published on October 17, 1991.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. 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 ignificant 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, and chronic health effects.
>
> (C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

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

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) 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 beginning 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.

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, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about vinyl acetate and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL). Vinyl acetate has been found at 3 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for vinyl acetate. As EPA evaluates more sites, the number of sites at which vinyl acetate is found may change. The information is important for you because vinyl acetate may cause harmful health effects and because these sites are potential or actual sources of human exposure to vinyl acetate.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

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

1.1 WHAT IS VINYL ACETATE?

Vinyl acetate is a clear, colorless liquid. It has a sweet, pleasant, fruity smell, but the odor may be sharp and irritating to some people. You can easily smell vinyl acetate when it is in the air at levels around 0.5 ppm (half a part of vinyl acetate in 1 million parts of air). It readily evaporates into air and dissolves easily in water. Vinyl acetate is flammable and may be ignited by heat, sparks, or flames. Vinyl acetate is used to make other industrial chemicals (such as polyvinyl acetate polymers and ethylenevinyl acetate copolymers). These other chemicals are used mostly to make glues for the packaging and building industries. They are also used to make paints, textiles, and paper. The Food and Drug Administration (FDA) has determined that vinyl acetate may be safely used as a coating or a part of a coating that is used in plastic films for food packaging, and as a modifier of food starch. You can find more information on the production and uses of vinyl acetate in Chapter 4.

Vinyl acetate does not occur naturally in the environment. It enters the environment from factories and facilities that make, use, store, or dispose of it. When vinyl acetate is disposed of at waste sites or elsewhere

in the environment, it can enter the soil, air, and water. Vinyl acetate will break down in the environment. The half-life (time it takes for l/2 of the chemical to break down) for vinyl acetate is about 6 hours in air and 7 days in water. We have no information on how long vinyl acetate will stay in soil. You can find more information on the chemical and physical properties of vinyl acetate in Chapter 3. You can find more information on the occurrence and fate of vinyl acetate in the environment in Chapter 5.

1.2 HOW MIGHT I BE EXPOSED TO VINYL ACETATE?

Industrial facilities, accidental spills, contact with products that contain vinyl acetate, and hazardous waste disposal sites are possible sources of exposure to vinyl acetate. The most important way that you can be exposed to vinyl acetate if you live around factories that make, use, store, and dispose of vinyl acetate on site or if you live near waste sites in which vinyl acetate or products that contain vinyl acetate have been disposed, is by breathing air or drinking water that contain it. You can also be exposed to vinyl acetate by skin contact with products that were made with vinyl acetate, such as glues and paints. Exposure can also occur through ingestion of food items that were packaged in plastic films containing vinyl acetate or food items that contain vinyl acetate as a starch modifier. However, exposure to vinyl acetate occurs mostly in the workplace. Workers can breathe in the chemical when they are making it or using it to make other chemicals. Workers can also have skin contact with vinyl acetate solutions. It has been estimated thatabout 50,000 workers employed at about 5,000 plants are exposed to vinyl acetate in the United States.

Background levels of vinyl acetate in water, soil, or food have not been reported. However, vinyl acetate has been detected in water and soil from hazardous waste sites on the NPL. It has been measured in the air in industrial areas of Houston, Texas at a level of about 0.5 ppm.

1.3 HOW CAN VINYL ACETATE ENTER AND LEAVE MY BODY?

Vinyl acetate can enter your body through your lungs when you breathe air containing it, through your stomach and intestines when you eat food or drink water containing it, or through your skin. Studies in animals show that most of the vinyl acetate taken in through the nose or mouth enters the body almost immediately. We have no information on how fast it will enter your body tissues once it gets on your skin. Based on information obtained from animal studies, once vinyl acetate is taken into your body through your nose or mouth, vinyl acetate or its breakdown products may quickly be distributed throughout the body and removed. Studies in animals indicate that vinyl acetate is quickly broken down. Most of the vinyl acetate taken into your body leaves in your breath within a few days in the form of carbon dioxide. Small amounts of the vinyl acetate taken into your body also leave in your urine and feces as break down products. Chapter 2 has more information on how vinyl acetate enters and leaves your body.

1.4 HOW CAN VINYL ACETATE AFFECT MY HEALTH?

People who were exposed to vinyl acetate in air for short periods complained of irritation to their eyes, nose, and throat. One in nine volunteers who breathed air containing 4 ppm of vinyl acetate for 2 minutes had throat irritation. Several volunteers exposed to 72 ppm of vinyl acetate in air for 30 minutes reported coughing and hoarseness and eye irritation. No health effects were found in workers who were exposed to levels around 10 ppm of vinyl acetate in work room air for an average of 15 years of employment. However, we do not know if health effects would occur in people exposed to low levels for longer periods.

Exposure to high levels (around 1,000 ppm) of vinyl acetate in air for a couple of weeks caused irritation of the eyes, nose, throat, and lungs of laboratory animals. Vinyl acetate at levels around 200 ppm caused irritation to the respiratory tract and nose when it was breathed by rats and mice for up to 2 years. In this same study, damage to the lungs (congestion and increased lung weight) was seen in rats at 200 and 600 ppm and in mice at 600 ppm vinyl acetate. Studies with animals also suggest that breathing vinyl acetate may affect the immune system and nervous system. The extent and way in which vinyl acetate affects these systems is not well understood.

There is no evidence that vinyl acetate causes cancer in humans. Vinyl acetate caused tumors in the noses of rats that breathed 600 ppm for 2 years. The International Agency for Research on Cancer (IARC) has determined that vinyl acetate is not classifiable as to its ability to cause cancer in humans.

We have no information on health effects in humans exposed to vinyl acetate in contaminated food or water. Information from animals exposed to vinyl acetate in drinking water suggest that the immune system might be affected at very high levels.

There is no information to show that birth defects or low birth weights occur in humans exposed to vinyl acetate. No birth defects were seen in the offspring of animals that were exposed to vinyl acetate during their pregnancy. Pregnant animals exposed to high levels of vinyl acetate in drinking water or air produced offspring which were smaller in size than normal. These effects to the offspring were seen at the same level that caused reduced weight gain in pregnant animals. This suggests that the smaller size of the offspring may be due to the reduced weight gain in the pregnant animals and may not be a direct effect of vinyl acetate on the developing animal.

People who had a mild (2%) solution of vinyl acetate put on their skin for 48-72 hours did not show signs of skin irritation. However, vinyl acetate has caused skin irritation and blisters in workers who accidentally spilled it on their skin. More concentrated solutions of vinyl acetate have caused reddening, blisters, and corrosion to the skin of rabbits. The effects of

continual or repeated skin contact with vinyl acetate or products that contain vinyl acetate over a long time are not known.

Exposure to vinyl acetate in air or direct contact with vinyl acetate solutions has caused irritation to the eyes. Several volunteers exposed to 72 ppm of vinyl acetate in air for 30 minutes reported eye irritation that lasted up to 60 minutes after exposure. Accidental contact of the eye with concentrated solutions of vinyl acetate has caused reddening and irritation to the eyes of workers. Symptoms were relieved after flushing the affected eye with water. We know of no cases in which permanent eye damage resulted after such contact. Rabbits that had very high concentrations of vinyl acetate put in their eyes for a short period also showed irritation and reddening to the eyes.

You can find out more information on the health effects of vinyl acetate in Chapter 2.

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

No test is currently available to measure vinyl acetate in your blood, urine, or body tissues. Because vinyl acetate breaks down very quickly to substances that are normally found in your body, measurements of these breakdown products are not useful for showing whether you have been exposed to vinyl acetate. The symptoms caused by exposure to vinyl acetate can also occur for many other reasons. Therefore, they can not be used as proof of vinyl acetate exposure. You can find more information in Chapters 2 and 6 about tests to find vinyl acetate in the body.

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

The federal government has set standards and guidelines to protect people from the possible health effects of vinyl acetate. EPA requires that any company that spills more than 5,000 pounds of vinyl acetate into the environment report the spill to the National Response Center.

To protect workers, the Occupational Safety and Health Administration (OSHA) has set a limit of 10 ppm vinyl acetate in workroom air during an 8-hour shift and over a 40-hour work week. The American Council of Government Industrial Hygienists (ACGIH) also recommends that workers should not be exposed to more than 10 ppm vinyl acetate in workroom air during an 8-hour shift and over a 40-hour work week. OSHA has also set a short-term exposure limit (STEL) in work room air of 20 ppm for a 15-minute exposure period. The National Institute for Occupational Safety and Health (NIOSH) recommends that exposure to vinyl acetate should not exceed 4 ppm in workroom air for any 15-minute exposure period. For more information on the limits and standards for vinyl acetate exposure, see Chapter 7.

1.7 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, 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

This agency can also provide you with information on the location of thenearest occupational and environmental health clinic. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of vinyl acetate and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for vinyl acetate based on toxicological studies and epidemiological investigations.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing noobserved-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

The level of exposure associated with the carcinogenic effects of vinyl acetate is presented in Table 2-l and plotted in Figure 2-l.

Estimates of exposure levels pos‘ing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer

effect for each exposure duration. MRLs include adjustments to reflect human variability from laboratory animal data to humans.

Although methods have been established to derive these levels (Barnes etal. 1988; EPA 1989), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to vinyl acetate. The following data were available on experimental animals. The 4-hour LC_{50} values for vinyl acetate have been reported to be 4,650 ppm (volume/volume [v/v]) (Weil and Carpenter 1969) and 3,680 ppm (Smyth and Carpenter 1973) in rats, 1,460 ppm in mice, 5,210 ppm in guinea pigs, and 2,760 ppm in rabbits (Smyth and Carpenter 1973). All of these species exhibited labored breathing and clonic convulsions prior to death (Smyth and Carpenter 1973). Lung damage was reported to be the cause of death in all instances.

Vinyl acetate was not lethal to rats following intermediate- or chronic-duration exposure (Hazleton 1979c, 1980c, 198813). Survival was not apparently affected by treatment in either rats or mice following exposure to 1,000 ppm for 4 weeks (Hazleton 1979b, 1979c), in rats following exposure to 1,000 ppm for 3 months (Hazleton 1980c), or in rats or mice exposed to 600 ppm for 104 weeks (Hazleton 1988b). However, 9 out of 20 mice exposed to 1,000 ppm of vinyl acetate for 3 months died, while only 2 out of 20 control mice died (Hazleton 1980b). All deaths occurred during the orbital sinus blood sampling procedure. The author suggested that exposure to 1,000 ppm may have increased animal susceptibility to the anesthesia used (Hazleton 1980b).

The highest NOAEL and lowest LOAEL values in which death was the endpoint and all reliable LCsO values in each study for each species and duration category are presented in Table 2-l and plotted in Figure 2-l.

2.2.1.2 Systemic Effects

The majority of the information available on the systemic effects of inhaled vinyl acetate was obtained from unpublished 4-week, 3-month, and 104-week studies conducted by Hazleton Laboratories, Europe. These studies contain a number of common limitations that are summarized as follows: A

TABLE 2-1. Levels of Significant Exposure to Vinyl Acetate - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat	1 d 4hr/d				3680 (LC50)	Smyth and Carpenter 1973
2	Rabbit	1 d 4hr/d				2760 (LC50)	Smyth and Carpenter 1973
3	Gn pig	1 d 4hr/d				5210 (LC50)	Smyth and Carpenter 1973
4	Mouse	1 d 4hr/d				1460 (LC50)	Smyth and Carpenter 1973
Systemic							
5	Rat	Gd6-15	Resp Other	200 200	1000 (lung congestion) 1000 (decrease in body weight gain)		Hazleton 1980d
Developmental							
6	Rat	Gd6-15			1000 (reduced fetal growth; retardation of skeletal ossification)		Hazleton 1980d
Reproductive							
7	Rat	Gd6-15		1000			Hazleton 1980d
INTERMEDIATE EXPOSURE							
Death							
8	Rat	3 mo 5d/wk 6hr/d		1000			Hazleton 1980c

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
9	Mouse	3 mo 5d/wk 6hr/d		200		1000	Hazleton 1980b
Systemic							
10	Rat	15 d 6hr/d	Resp	630		2000 (nose irritation, excess macrophages in the lungs, respiratory difficulty)	Gage 1970
			Hemato	2000			
			Other	630	2000 (decrease in body weight gain in males)		
				100	250 (decrease in body weight gain in females)		
11	Rat	4 wk 5d/wk 6hr/d	Resp	150	500 (respiratory distress)		Hazleton 1979c
			Cardio	1000			
			Gastro	1000			
			Hemato	1000			
			Hepatic	1000			
			Renal	1000			
			Other	1000			
12	Mouse	4 wk 5d/wk 6hr/d	Resp	150	500 (respiratory distress)		Hazleton 1979b
			Cardio	1000			
			Gastro	1000			
			Hemato	1000			
			Hepatic	1000			
			Renal	1000			
			Other		1000 (decrease in body weight gain)		

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
13	Rat	3 mo 5d/wk 6hr/d	Resp	200	1000 (increased relative lung weight, respiratory distress)		Hazleton 1980c
			Cardio	1000			
			Gastro	1000			
			Hemato	1000			
			Hepatic	1000			
			Renal	1000			
			Other		1000 (decrease in body weight gain)		
14	Mouse	3 mo 5d/wk 6hr/d	Resp	50[b]	200 (inflammation of nasal turbinate epithelium; mild multifocal bronchitis)	1000 (increased lung weight; hyperplasia and metaplasia of the upper respiratory tract)	Hazleton 1980b
			Cardio	1000			
			Gastro	1000			
			Hemato	1000			
			Hepatic	1000			
			Renal	1000			
			Other		1000 (decreased body weight gain)		
Immunological							
15	Rat	4 wk 5d/wk 6hr/d			1000 (decreased relative spleen weight)		Hazleton 1979c
16	Mouse	4 wk 5d/wk 6hr/d			1000 (decreased relative spleen weight)		Hazleton 1979b
17	Rat	3 mo 5d/wk 6hr/d			1000 (decreased absolute spleen and relative thymus weight)		Hazleton 1980c
18	Mouse	3 mo 5d/wk 6hr/d			1000 (decreased relative spleen weight)		Hazleton 1980b

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
Neurological							
19	Rat	4 wk 5 d/wk 6 hr/d			500 (hunched posture; ruffled fur)		Hazleton 1979c
20	Mouse	4 wk 5 d/wk 6 hr/d			500 (hunched posture; ruffled fur)		Hazleton 1979b
21	Rat	3 mo 5 d/wk 6 hr/d			1000 (hunched posture; ruffled fur)		Hazleton 1980c
22	Mouse	3 mo 5 d/wk 6 hr/d			200 (hunched posture; ruffled fur)		Hazleton 1980b
Reproductive							
23	Mouse	3 mo 5d/wk 6hr/d		1000			Hazleton 1980b
CHRONIC EXPOSURE							
Death							
24	Rat	104 wk 5d/wk 6hr/d		600			Hazleton 1988b
25	Mouse	104 wk 5d/wk 6hr/d		600			Hazleton 1988b
Systemic							
26	Human	15.2 yr (mean)	Resp Cardio Hemato Renal	8.6 8.6 8.6 8.6			Deese and Joyner 1969

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)		LOAEL (effect) Serious (ppm)		Reference
27	Rat	104 wk 5d/wk 6hr/d	Resp	50	200	(increased relative lung weight; olfactory atrophy)			Hazleton 1988b
			Gastro	600					
			Cardio	600					
			Hemato	600					
			Hepatic	600					
			Renal	600					
			Other		600	(decreased body weight gain)			
28	Mouse	104 wk 5d/wk 6hr/d	Resp	50	200	(airway irritation, hyperplasia, nasal and tracheal lesions)	600	(increased lung weight; exfoliation of bronchial epithelium; fibroepithelial tags; histiocyte accumulation)	Hazleton 1988b
			Gastric	600					
			Cardio	600					
			Hemato	600					
			Hepatic	600					
			Renal	600					
			Other		600	(decreased body weight gain)			
Immunological									
29	Rat	104 wk 5 d/wk 6 hr/d			50M	(decreased relative spleen weight)			Hazleton 1988b
Neurological									
30	Rat	104 wk 5 d/wk 6 hr/d			50	(hunched posture; ruffled fur; head tilt)			Hazleton 1988b
31	Mouse	104 wk 5 d/wk 6 hr/d			50	(hunched posture; ruffled fur; head tilt)			Hazleton 1988b

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
Cancer							
32	Rat	104 wk 5d/wk 6hr/d				600 (nasal cavity tumors)	Hazleton 1988b

[a]The number corresponds to entries in Figure 2-1.
[b]Used to derive an intermediate Minimal Risk Level (MRL) of 0.01 ppm; concentration corrected for intermittent exposure and human equivalent concentration and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Cardio = cardiovascular; d = day; Gastro = gastrointestinal; Gd = gestation day; Gn pig = guinea pig; Hemato = hematological; hr = hour; LOAEL = lowest-observed-adverse-effect level; LC50 = lethal concentration, 50% kill; M = males; mo = month; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week; yr = year

FIGURE 2-1. Levels of Significant Exposure to Vinyl Acetate - Inhalation

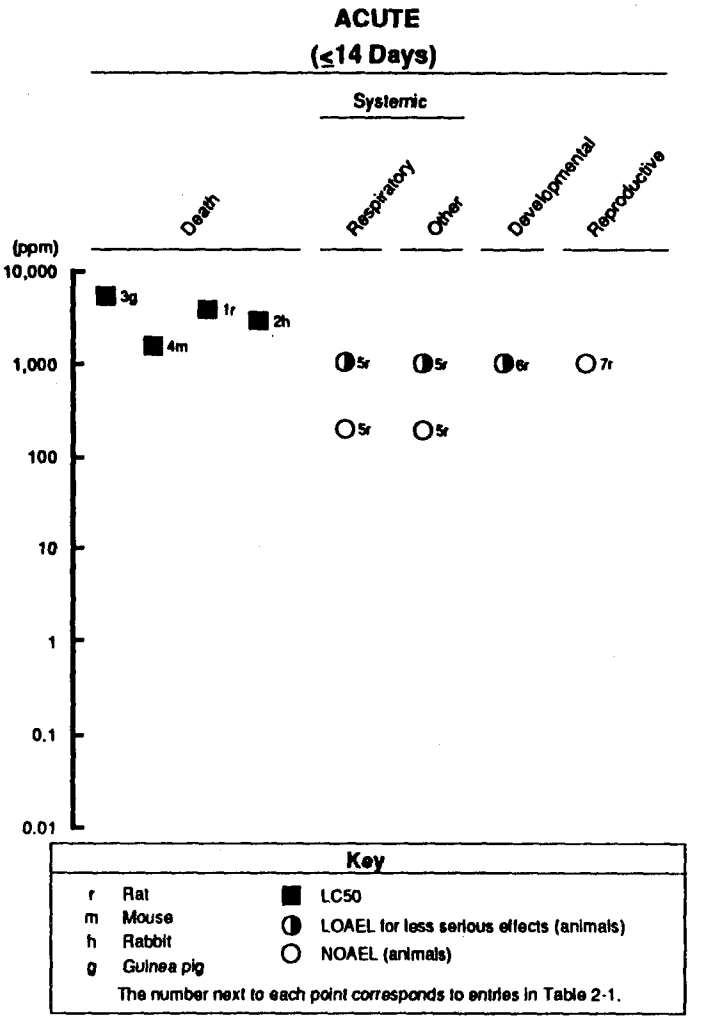


FIGURE 2-1 (Continued)

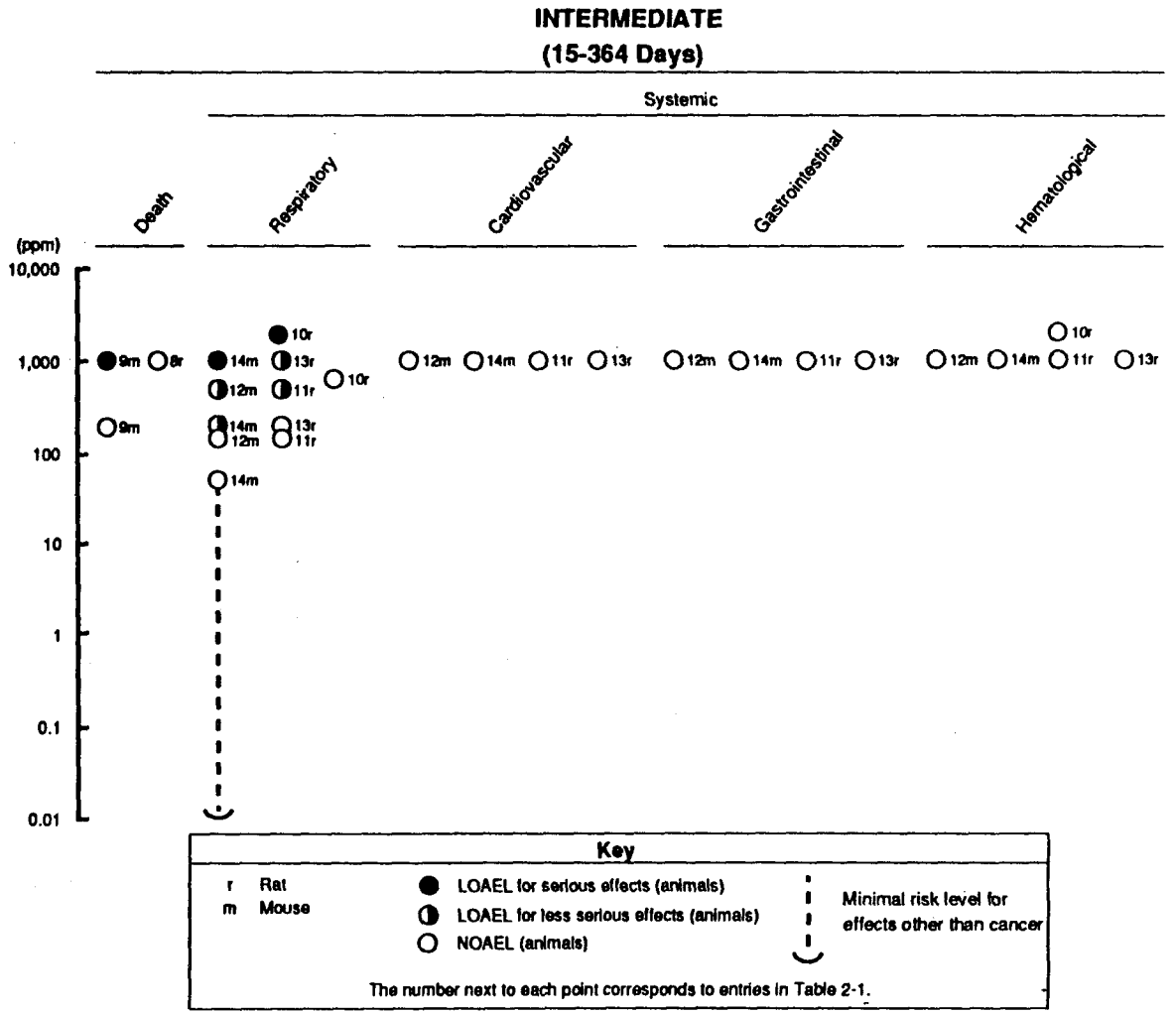


FIGURE 2-1 (Continued)

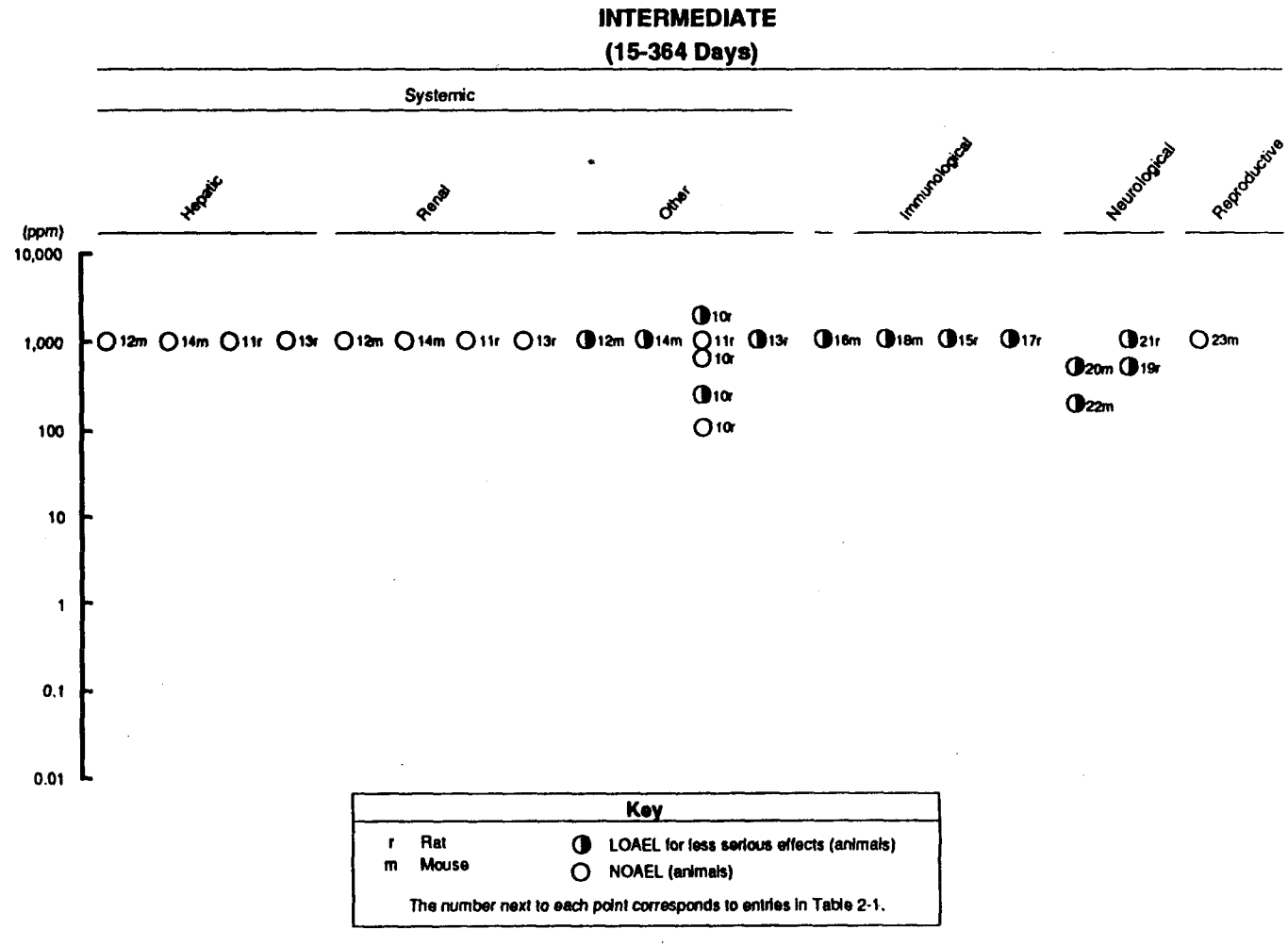
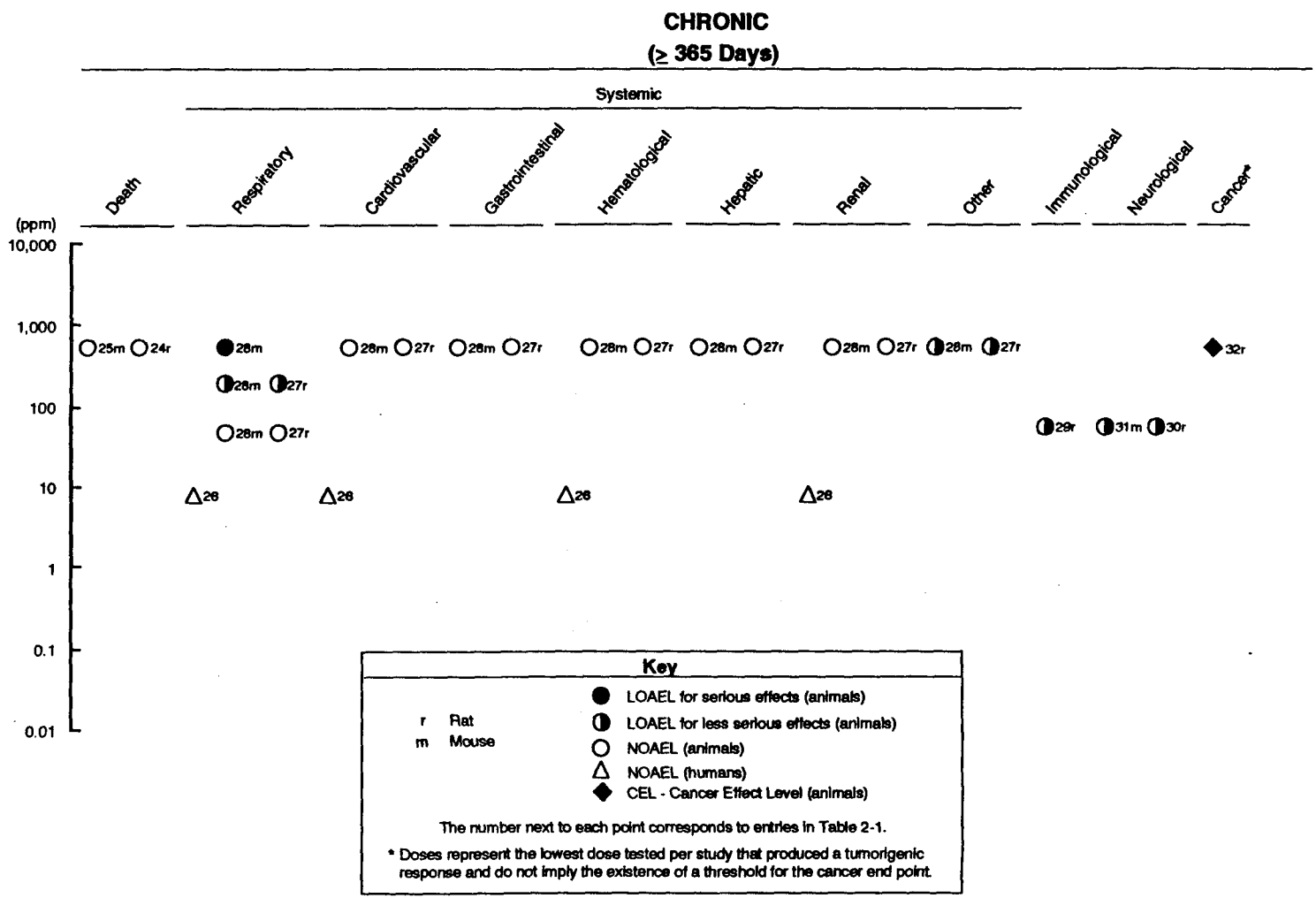


FIGURE 2-1 (Continued)



variety of respiratory lesions, characteristic of those caused by pathogens (e.g., inflammation of the nasal turbinates and bronchial and bronchiolar epithelium), were common to these animals. The authors of the Hazleton studies suggested that pathogens may have acted synergistically with vinyl acetate to produce the lesions. In addition, food and water intake were not monitored which makes interpretation of body weight changes difficult.

In the 4-week studies on rats and mice, the low-dose group animals were initially exposed to 50 ppm vinyl acetate. When no toxic effects were obsenred in the animals exposed to 1,000 ppm vinyl acetate (the highest concentration tested), the concentration to which the low-dose groups were exposed was increased to 1,500 ppm for the remainder of the 4 weeks, resulting in a time-weighted average concentration of 1,034 ppm for rats and 1,138 ppm for mice. In many instances, histopathological examinations were incomplete. In spite of these limitations, the available information from the 4-week study, 3-month, and 104-week studies indicates that the primary systemic target of vinyl acetate toxicity following inhalation exposure in animals is the respiratory system. Other organ systems, such as the immune system andthe nervous system, may be adversely affected by inhalation exposure to vinyl acetate in animals, as indicated by changes in organ weights and clinical observations. No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to vinyl acetate.

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

Respiratory Effects. Acute inhalation exposure of humans to vinyl acetate can cause irritation of the nose and throat (Smyth and Carpenter 1973). The responses of groups of 3 to 9 human volunteers exposed to varying concentrations of vinyl acetate for 2 minutes to 4 hours were monitored. Exposure to 1.3 ppm for 2 minutes was not irritating to the nose, throat, -or eyes of any of the 9 volunteers. Irritation of the mucous membranes of the throat was reported in one out of nine subjects exposed to 4 ppm for 2 minutes, four out of four subjects exposed to 72 ppm for 30 minutes, and one out of three subjects exposed to 20 ppm for 4 hours. Partial to complete olfactory fatigue was also noted in all subjects exposed to 20 ppm vinyl acetate for 4 hours, 34 ppm vinyl acetate for 2 hours, and 72 ppm vinyl acetate for 30 minutes (Smyth and Carpenter 1973). Ten minutes after exposure all subjects were returned to the chamber and noted that the odor was as strong as at the start of exposure, indicating that this effect was transient. Twenty-one male chemical operators exposed to vinyl acetate for a mean duration of 15.2 years were compared to unexposed workers by a thorough multiphasic screening examination that included complete physical examinations, chest X-rays, spirometry, electrocardiograms, and analyses of blood and urine (Deese and Joyner 1969). Air samples obtained at several

locations over a period of 1 month showed that vinyl acetate concentrations ranged from undetectable to 49.3 ppm with a mean of 8.6 ppm. Acute exposures to much higher levels occurred. No major differences were found between the exposed and control groups with respect to any of the respiration parameters studied. However, acute exposure of three volunteers to 21.6 ppm resulted in upper respiratory tract irritation, cough and/or hoarseness (Deese and Joyner 1969).

Respiratory tract damage is characteristic of vinyl acetate exposure in laboratory animals following acute-, intermediate-, or chronic-duration inhalation exposure. As reported in Section 2.2.1.1, respiratory tract damage was reported to be the cause of death in rats, mice, guinea pigs, and rabbits acutely exposed (4 hours) to vinyl acetate (Smyth and Carpenter 1973; Weil and Carpenter 1969). Gasping and labored breathing were usually observed in these animals prior to death, and necropsy revealed lung congestion and hemorrhage, froth in the trachea, and excess pleural fluid.

Effects on the respiratory tract were also seen following intermittent exposure of rats to 2,000 ppm vinyl acetate for 15 days as evidenced by nasal irritation (i.e., sneezing progressing with increasing severity to a nasal discharge and bloody exudate), respiratory difficulty (i.e., as rapid shallow breathing progressing to labored and slow breathing), and the presence of excess macrophages in the lungs (Gage 1970). Respiratory distress was observed in rats and mice during an intermediate-duration inhalation exposure to 500-1,034 ppm (rats) (Hazleton 1979c) and 500-1,138 ppm (mice) (Hazleton 1979b) for 4 weeks. When exposure durations were increased to 3 months, rats and mice exhibited evidence of respiratory distress at vinyl acetate levels of 1,000 ppm (rats) and 200 and 1,000 ppm (mice) (Hazleton 1980b, 1980c). The NOAEL for the 3-month study was 50 ppm for mice and 200 ppm for rats. An intermediate inhalation MRL of 0.01 ppm was calculated based on the NOAEL of 50 ppm for respiratory effects in mice exposed to vinyl acetate for 3 months, as described in the footnote in Table 2-l. Evidence for adverse respiratory effects included respiratory distress; an increase in relative lung weight at 1,000 ppm in both rats and mice, presumably due to lung congestion; and histopathological differences between the exposed and control groups. Rats exposed to 1,000 ppm vinyl acetate exhibited a mild increase in the incidence of focal histiocytic alveolitis. Mice exposed to 200 ppm vinyl acetate exhibited very mild to slight focal areas of inflammation of the nasal turbinate epithelium and mild multifocal bronchitis. Microscopic examination of mice exposed to 1,000 ppm vinyl acetate revealed focal and diffuse rhinitis with associated exudation and transudation into the nasal passages, metaplasia or hyperplasia of the trachea, multifocal bronchitis, bronchiolitis, multifocal bronchiostania, bronchial epithelial metaplasia and hyperplasia, and occasional bronchiolar or bronchial exudation (Hazleton 1980b). These results indicate that the extrathoracic region is more susceptible to the irritant effects of inhaled vinyl acetate in the mouse than the lower respiratory tract since the extrathoracic effects were observed more commonly at lower exposure concentrations.

Chronic inhalation exposure (104 weeks) of rats and mice to vinyl acetate resulted in treatment-related effects on the respiratory tract similar to those seen with shorter-duration exposures (Hazleton 1988b). Significantly increased relative lung weights were seen in all exposed female rats at terminal sacrifice and in both male and female mice exposed to 600 ppm at terminal sacrifice. Histopathological changes were seen in mice and rats exposed to 200 and 600 ppm vinyl acetate. The histopathological changes were considered by the authors to be characteristic of chronic irritation. In rats, olfactory epithelial atrophy was observed at 200 and 600 ppm, whereas lung lesions consisting of exfoliation of bronchial epithelium, presence of fibroepithelial tags, and histiocyte accumulation were observed at 600 ppm. Mice exhibited the same changes, and in addition, were found to have focal epithelial hyperplasia and inflammatory changes in the nasal cavity and hyperplasia of the tracheal epithelium. Slides of the respiratory tract of the rats and mice from the Hazleton (1988b) study were reevaluated by Deems (1988) (mice) and Dreef-van der Meulen (1988b) (rats). In mice the most prominent nasal change was atrophy of the olfactory epithelium at 200 ppm and 600 ppm. Epithelial hyperplasia was also observed in the trachea at 200 and 600 ppm. Changes in the lung were more prominent at higher levels while the larynx was unaffected. In rats, the most prominent lesion was thinning of the nasal olfactory epithelium accompanied by basal cell hyperplasia. Pulmonary changes observed in the higher exposure group were mainly in the bronchi and bronchioli and consisted of fibrous plaques and buds protruding into the lumen of the bronchi and bronchioles, covered by normal bronchial epithelium and without obvious evidence of an associated inflammatory response. Thus, this observation supports the original authors' conclusions that the changes in the respiratory tract of rats and mice were a result of chronic irritation and inflammation, Taken together, the results of the acute-, intermediate-, and chronic-duration exposure experiments, indicate that mice may be more susceptible to the toxic effects of vinyl acetate than rats. This conclusion is supported by the higher susceptibility to the lethal effects of vinyl acetate seen in mice (i.e., a lower LC_{50} value, as discussed in Section 2.2.1.1). Furthermore, the extrathoracic region appears to be the primary site of vinyl acetate-induced lesions at lower levels, with the pulmonary region being affected at higher levels.

Cardiovascular Effects. Twenty-one male chemical operators exposed to vinyl acetate for a mean of 15.2 years were compared to unexposed workers by thorough multiphasic screening examination, that included complete physical examinations and electrocardiograms (Deese and Joyner 1969). Air samples obtained at several locations over a period of 1 month showed that vinyl acetate concentrations ranged from undetectable to 49.3 ppm with a mean of 8.6 ppm. Acute exposures to much higher levels were possible. No major differences were found between the exposed and control groups with respect to any of the parameters studied.

With the exception of a statistically significant decrease in absolute (but not relative) heart weight that was observed in male and female rats exposed to 1,000 ppm vinyl acetate for 3 months (Hazleton 1980c) and 600 ppm for 104 weeks (Hazleton 1988b) no other changes in heart weight or the histological or macroscopic appearance of the heart or blood vessels were found in rats or mice exposed to vinyl acetate at concentrations of up to 1,000 ppm for up to 3 months (Hazleton 1979b, 1979c, 1980b, 1980c) or 600 ppm for 104 weeks (Hazleton 1988b).

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

No histological evidence of treatment-related changes in the gastrointestinal tract was found in rats or mice exposed to vinyl acetate at concentrations of up to 1,000 ppm for up to 3 months (Hazleton 1979b, 1979c, 1980b, 1980c) or 600 ppm for 104 weeks (Hazleton 1988b). However, a doserelated increase in dark material was reported in the intestine of the mice exposed to up to 1,000 ppm of vinyl acetate for 3 months (Hazleton 1980b). This material was observed at an incidence of 0/20 (control), 2/20 (50 ppm), 6/20 (200 ppm), and 6/20 (1,000 ppm). This substance was never identified in the study, and the biological significance of its occurrence 'is not known.

Hematological Effects. Twenty-one male chemical operators exposed to vinyl acetate for a mean of 15.2 years were compared to unexposed workers by thorough multiphasic screening examinations including complete physical examinations, blood pressure, blood chemistry, and urinalysis (Deese and Joyner 1969). Air samples obtained at several locations.over a period of 1 month showed that vinyl acetate concentrations ranged from undetectable to 49.3 ppm with a mean of 8.6 ppm. Acute exposures to much higher levels were possible. No major differences were found between the exposed and control groups with respect to any of the hematological parameters studied.

Rats exposed to 2,000 ppm vinyl acetate for 15 days exhibited no treatment-related hematological changes (Gage et al. 1970). No changes in hematological parameters were found in rats or mice exposed to vinyl acetate at concentrations of up to 1,000 ppm for 3 months (Hazleton 1980b, 198Oc). A decrease in red blood cell count and in packed cell volume, and an increase in prothrombin time were noted in both the rats and mice in the chronic study. However, these changes were not concentration-related, and did not occur consistently across exposure groups, sampling times, or sexes. Therefore, they are most likely not treatment-related.

Hepatic Effects. Twenty-one male chemical operators exposed to vinyl acetate for a mean of 15.2 years were compared to unexposed workers by thorough multiphasic screening examinations including complete physical examinations, blood pressure, blood chemistry, and urinalysis (Deese and Joyner 1969). Air samples obtained at several locations over a period of 1

month showed that vinyl acetate concentrations ranged from undetectable to 49.3 ppm with a mean of 8.6 ppm. Acute exposures to much higher levels were possible. No major differences were found between the exposed and control groups with respect to selected blood parameters of liver function (e.g., alkaline phosphatase, cholesterol, total protein, albumin, or globulin levels).

A significant dose-related decrease in absolute but not relative liver weight was noted in both male and female mice exposed to vinyl acetate at concentrations of 1,000 ppm for 3 months (Hazleton 1980b) and male rats exposed to 1,000 ppm for 3 months (Hazleton 1980c). Similarly, male mice exposed to 600 ppm for 104 weeks exhibited a significant decrease in absolute liver weight, but not liver weight relative to body weight (Hazleton 1988b). Male rats exposed to 200 ppm and 600 ppm vinyl acetate for 104 weeks showed a significant decrease in both absolute and relative liver weights. No histopathological changes or changes in serum enzymes indicative of hepatic dysfunction were noted in these studies. No liver weight changes or alterations in the macroscopic appearance of the liver were found in rats or mice of either sex exposed to 1,034 ppm (rats) or 1,138 ppm (mice) for 4 weeks (Hazleton 1979b, 1979c).

Renal Effects. Twenty-one male chemical operators exposed to vinyl acetate for a mean of 15.2 years were compared to unexposed workers by thorough multiphasic screening examination, including complete physical examinations, blood pressure, blood chemistry, and urinalysis (Deese and Joyner 1969). Air samples obtained at several locations over a period of 1 month showed that vinyl acetate concentrations ranged from undetectable *to* 49.3 ppm with a mean of 8.6 ppm. Acute exposures to much higher levels were possible. No major differences were found between the exposed and control groups with respect to any of the urinary parameters studied.

Urine from rats exposed to 1,000 ppm vinyl acetate for 3 months was decreased in volume and more concentrated when compared to controls (Hazleton 1980c). Reduced urine volume was also observed in rats exposed to 600 ppm of vinyl acetate for 104 weeks (Hazleton 1988b). The authors attributed this effect to reduced food and water intake in these animals. No treatmentrelated macroscopic or histopathologic changes were observed in the kidneys of these animals or of mice similarly exposed (Hazleton 1980b, 1980c, 1988b). Furthermore, no consistent exposure-related changes in blood urea nitrogen were observed in rats or mice exposed to vinyl acetate at concentrations of up to 1,000 ppm for 3 months (Hazleton 1980b, 1980c) or 600 ppm for 104 weeks (Hazleton 1988b). Decreases in blood urea nitrogen were sporadically observed in both rats and mice in these studies, but these changes were generally within the range of historical controls, not dose-related, and not consistently observed across all sampling times.

Demal/Ocular Effects. The responses of human volunteers exposed to varying concentrations of vinyl acetate for an unspecified period (less than 8 hours) were monitored (Deese and Joyner 1969). One of 5 volunteers reported slight eye irritation at 5.7 and 6.8 ppm and all 3 volunteers exposed to 21.6 ppm complained of eye irritation that "would be intolerable over an extended period" (Deese and Joyner 1969). In another study, four volunteers exposed to 72 ppm vinyl acetate in air for 30 minutes reported eye irritation that persisted for up to 60 minutes after exposure (Smyth and Carpenter 1973). These ocular effects are due to direct contact of the eye with vinyl acetate and thus not a true systemic effect. Prolonged occupational exposure to vinyl acetate generally does not cause eye irritation at levels below 10 ppm (Deese and Joyner 1969).

Eye irritation was noted in animals exposed to 2,000 ppm vinyl acetate for 15 days (Gage 1970). However, this effect can be attributed to direct contact of the eye with vinyl acetate vapor. Other dermal/ocular effects resulting from direct contact with vinyl acetate are discussed in Section 2.2.3, Dermal Exposure.

Other Systemic Effects. Decreases in body weight gain have been observed in rats and mice exposed to vinyl acetate for acute, intermediate, and chronic durations (Gage 1970; Hazleton 1979b, 1980b, 1980c, 1980d, 1988b). These effects were statistically significant and occurred at or above the levels that caused adverse respiratory effects, which suggests that reduction in weight gain may be secondary to the poor health of the animals as a result of exposure to vinyl acetate. These effects proved to be transient in animals that were chronically exposed to vinyl acetate, as evidenced by the reversal of the body weight gain reduction during the recovery period (Hazleton 1988b).

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans after inhalation exposure to vinyl acetate.

Reductions in relative thymus and/or spleen weight were consistently noted in rats and mice exposed to vinyl acetate for 4 weeks and 3 months at exposure concentrations of 1,000 ppm, but no gross or histopathological effects were noted in these organs (Hazleton 1979b, 1979c, 1980b, 1980c). In rats chronically exposed to vinyl acetate, only males exposed to 50 or 600 ppm exhibited a decrease in relative spleen weight (Hazleton 1988b). The biological significance of these changes is not known. They may be suggestive of an immunosuppressive action of vinyl acetate, but the appropriate parameters were not investigated to delineate this possibility.

The LOAEL values for spleen and thymus weight changes for each species and duration category are presented in Table 2-l and plotted in Figure 2-l.

2.2.1.4 Neurological Effects

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

All rats and mice exposed to at least the highest concentration of vinyl acetate for 4 weeks, 3 months, and 104 weeks exhibited hunched posture and ruffled fur (Hazleton 1979b, 1979c, 1980b, 1980c, 1988b). These clinical signs occurred intermittently in the 4-week studies (Hazleton 1979b, 1979c). In the 3-month mouse study, hunched posture and ruffled fur were observed from days 1 through 9 in mice exposed to 200 ppm and intermittently through day 34 in mice exposed to 1,000 ppm (Hazleton 1980b). In the 3-month rat study, these clinical signs were consistently observed for the first 13 days of the study and intermittently thereafter in the animals exposed to 1,000 ppm only (Hazleton 1980c). A dose-related increase in the incidence of head tilt was also noted in some rats and mice exposed to vinyl acetate for 104 weeks (Hazleton 198813). These neurological signs were noted only intermittently throughout the chronic studies (Hazleton 1988b). It is possible that these neurological signs were secondary to the poor health of the animals and may not be indicative of a primary effect of vinyl acetate on the nervous system. No other neurological effects have been noted in animals exposed to vinyl acetate. However, no studies have been conducted that investigated the potential neuropharmacologic or neuropathological effects of vinyl acetate; no special histopathological techniques were used to examine the neurological tissues obtained from the animals in the Hazleton studies.

The LOAELs for hunched posture and ruffled fur for each species and duration category are presented in Table 2-l and plotted in Figure 2-l.

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans following inhalation exposure to vinyl acetate.

One inhalation developmental toxicity study in rats was conducted in which pregnant animals were exposed to vinyl acetate during gestation days 6-15, and sacrificed on gestation day 20 (Hazleton 1980d). Dams exposed to 1,000 ppm exhibited a significant reduction in body weight gain of 18% during the exposure period. This effect was transient, as body weight gain returned to normal during the post-exposure period. Several dams in each exposure group were found to have lung congestion at necropsy, with the highest incidence occurring in the animals exposed to 1,000 ppm vinyl acetate. Fetuses of dams exposed to 1,000 ppm exhibited significant growth retardation (e.g., mean litter weight, mean fetal weight, and mean fetal crown/rump length were significantly lower as compared to the controls). This fetal growth retardation may be due to the marked retardation in maternal weight gain observed, and not to a direct developmental effect of vinyl acetate on the fetus. No embryolethality or major teratogenic effects were seen in the

fetuses of the exposed rats. A significant increase in the incidence of minor skeletal fetal defects/variants was observed in the fetuses of dams exposed to 1,000 ppm vinyl acetate. This was mainly variant retarded sternebral ossification, which can be a consequence of the small fetal size and not a direct effect of vinyl acetate. Therefore, under the conditions of this study, the only adverse developmental effect elicited by vinyl acetate was marked growth retardation observed in the fetuses of dams exposed to 1,000 wm . This effect may have been secondary to the maternal toxicity observed.

The LOAEL for reduced fetal growth is presented 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 after inhalation exposure to vinyl acetate.

No gross or histopathological changes in the reproductive organs were observed in the dams or their offspring when rats were exposed to 1,000 ppm vinyl acetate on gestation days 6-15 (Hazleton 1980d). Similarly, no gross or histopathological changes in the reproductive organs were observed in male or female mice exposed to 1,000 ppm vinyl acetate for 3 months (Hazleton 1980b).

The NOAEL for reproductive effects is presented in Table 2-1 and plotted in Figure 2-1.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after inhalation exposure to vinyl acetate. Vinyl acetate failed to produce specific DNA adducts in the liver of rats exposed to 1,200-1,800 ppm for 90 minutes (Simon et al. 1985b). Micronuclei were evaluated in bone marrow smears taken from all rats and mice exposed to up to 1,000 ppm vinyl acetate 6 hours/day, 5 days/week for 4 weeks and 3 months, and no exposure related effects on the incidence of micronuclei were noted (Hazleton 197913, 1979c, 1980b, 1980c).

Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding cancer in humans after inhalation exposure to vinyl acetate.

Rats chronically exposed to 600 ppm vinyl acetate were found to have an increased incidence of nasal cavity tumors as compared to control animals (Hazleton 1988b). Slides of the respiratory tract of the rats from the

Hazleton (1988b) study were reevaluated by Dreef-van der Meulen (1988b). A total of 12 nasal cavity tumors were found in the exposed rats; 5 were benign and 7 were malignant (Dreef-van der Meulen 1988b). These 5 benign papillomas were of various cell types and location in the nose and were seen in 1 200 ppm-exposed male and 4 600 ppm-exposed males. The 7 malignant tumors were found in 3 males and 4 females exposed to 600 ppm vinyl acetate. The malignant tumors were squamous carcinomas with one carcinoma in situ that showed a widespread distribution from anterior to posterior nasal cavity. No nasal cavity tumors were observed in control rats or those exposed to 50 ppm vinyl acetate. The statistical significance of tumor incidence in the nasal cavity was not reported. Effects to the larynx of rats was confined to a single squamous carcinoma in a female rat exposed to 600 ppm. No tumors were seen in the lungs of rats.

Slides of the respiratory tract of mice chronically exposed to vinyl acetate from the Hazleton (1988b) study were reevaluated by Beems (1988b). No tumors were observed in the nasal cavity, larynx, or trachea of the exposed or control mice (Hazleton 1988b). Pathology of the lungs of male mice exposed to 600 ppm vinyl acetate revealed one squamous carcinoma in the major bronchus and one squamous nodule in a terminal airway. No squamous cell carcinomas were seen in animals of either sex from the control group. Bronchiolealveolar adenomas and carcinomas were found in the lungs of both the exposed and control mice at comparable incidences, indicating that their occurrence was not a result of exposure to vinyl acetate.

The cancer effect level for rats is presented in Table 2-l and plotted in Figure 2-l.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to vinyl acetate. Lethality data are available from studies in animals (see Table 2-2 and Figure 2-2). The oral LD_{50} for vinyl acetate has been reported to be 2,920 mg/kg in rats (Smyth and Carpenter 1948) and 1,613 mg/kg in mice (Goeva 1966). The cause of death was not specified for either species.

Vinyl acetate was not lethal to rats or mice administered drinking water that contained up to 5,000 ppm (equivalent to 684-950 mg/kg/day) for up to 3 months (Hazleton 1979d, 1980e, 1980f) or 235 mg/kg/day (rats) following in utero exposure (Hazleton 1988a).

2.2.2.2 Systemic Effects

No studies were located regarding systemic effects in humans following oral exposure to vinyl acetate.

TABLE 2-2. Levels of Significant Exposure to Vinyl Acetate - Oral

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Death								
1	Rat	(NS)	1 d 1x/d				2920 (LD50)	Smyth and Carpenter 1948
2	Mouse	(NS)	NS				1613 (LD50)	Goeva 1966
Developmental								
3	Rat	(W)	Gd6-15		477			Hazleton 1980d
Reproductive								
4	Rat	(W)	Gd6-15		477			Hazleton 1980d
INTERMEDIATE EXPOSURE								
Death								
5	Rat	(W)	3 mo 7d/wk 24hr/d		810F			Hazleton 1980f
6	Mouse	(W)	3 mo 7d/wk 24hr/d		950			Hazleton 1980e
Systemic								
7	Rat	(W)	4 wk 7d/wk 24hr/d	Resp Cardio Gastro Hemato Hepatic Renal Other	700 700 700 700 700 700 700			Hazleton 1979d

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
8	Mouse	(W)	4 wk 7d/wk 24hr/d	Resp Cardio Gastro Hemato Hepatic Renal Other	950 950 950 950 950 950 950			Hazleton 1979d
9	Rat	(W)	3 mo 7d/wk 24hr/d	Resp Cardio Gastro Hemato Hepatic Renal Derm/oc Other	810F 810F 810F 810F 810F 810F 810F 810F			Hazleton 1980f
10	Mouse	(W)	3 mo 7d/wk 24hr/d	Resp Cardio Gastro Hemato Hepatic Renal Other	950 950 950 950 950 950 190	950 (Harderian gland changes)		Hazleton 1980e
Neurological								
11	Rat	(W)	4 wk 7d/wk 24hr/d		700			Hazleton 1979d
12	Mouse	(W)	4 wk 7d/wk 24hr/d		950			Hazleton 1979d

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
13	Rat	(W)	3 mo 7d/wk 24hr/d		810F			Hazleton 1980f
14	Mouse		3 mo 7d/wk 24hr/d		950			Hazleton 1980e
Immunological								
15	Mouse	(W)	4 wk 7d/wk 24hr/d		190	950 (decreased relative thymus weight)		Hazleton 1979d
16	Mouse	(W)	3 mo 7d/wk 24hr/d			38 (decreased relative spleen weight in females)		Hazleton 1980e
Reproductive								
17	Mouse	(W)	3 mo 7d/wk 24hr/d		950			Hazleton 1980e
CHRONIC EXPOSURE								
Systemic								
18	Rat	(W)	104 wk 7d/wk	Resp	235			Hazleton 1988a
				Cardio	235			
				Gastro	235			
				Hemato	235			
				Hepatic	235			
				Renal	235			
				Derm/oc	235			
				Other	235			

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Neurological								
19	Rat	(W)	104 wk 7d/wk		235			Hazleton 1988a
Developmental								
20	Rat	(W)	2 gener-ations		117	431 (decreased F1 pup weight gain)		Hazleton 1987
Reproductive								
21	Rat	(W)	2 gener-ations		431			Hazleton 1987

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

Cardio = cardiovascular; d = day; Derm/oc = dermal/ocular; F = female; F1 = first generation; Gd = gestation day; Gastro = gastrointestinal; Hemato = hematological; hr = hour; LOAEL = lowest-observed-adverse-effect level; LD50 = lethal dose, 50% kill; M = male; mo = month; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; (W) = water; wk = week; 1x = one time

FIGURE 2-2. Levels of Significant Exposure to Vinyl Acetate - Oral

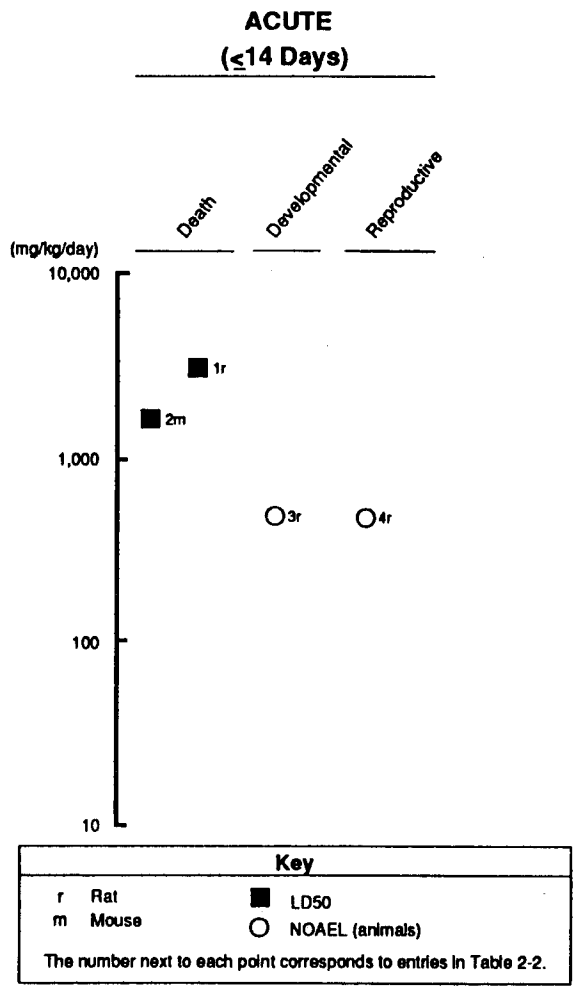


FIGURE 2-2 (Continued)

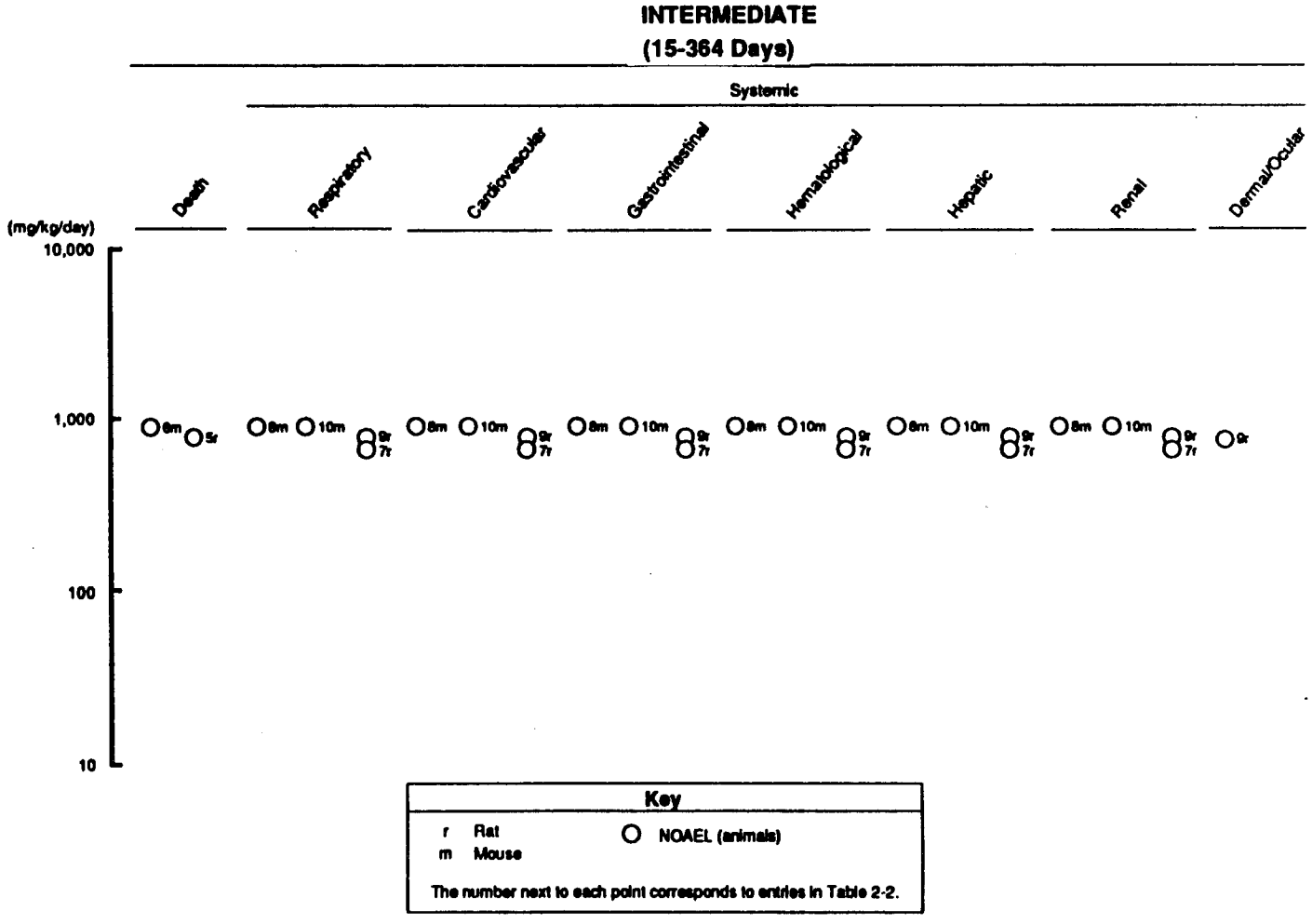


FIGURE 2-2 (Continued)

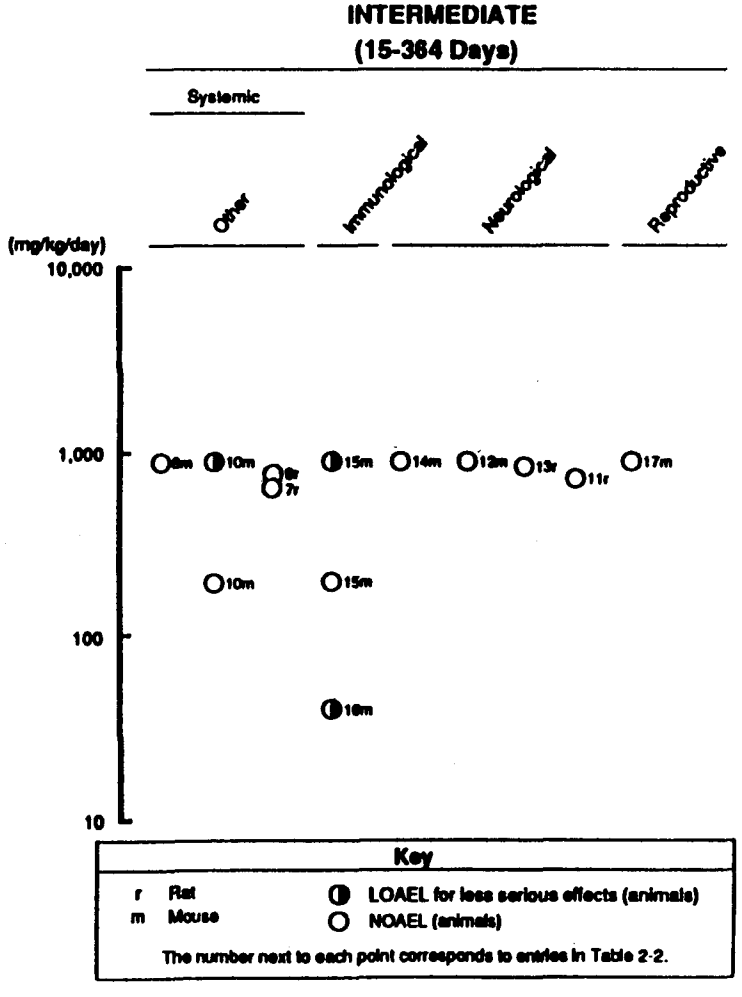
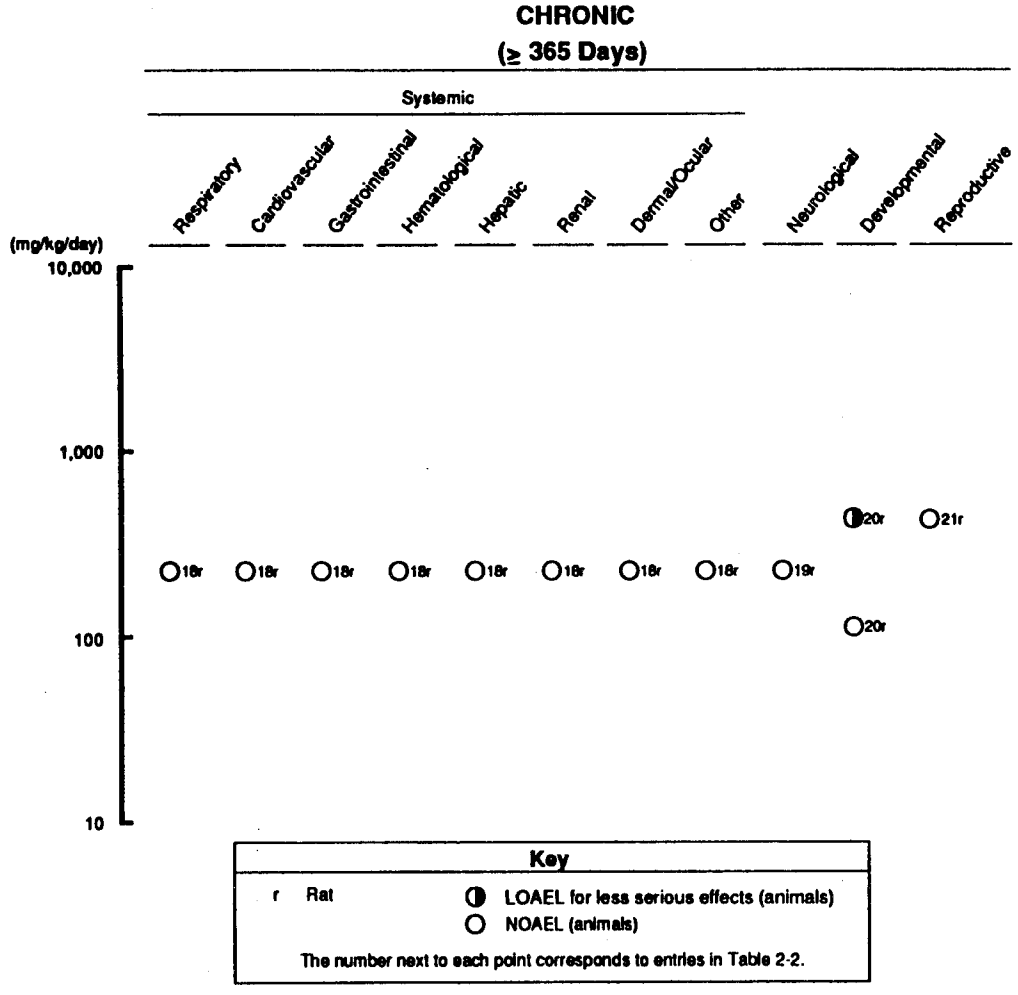


FIGURE 2-2 (Continued)



The majority of the information available on the systemic effects of oral exposure to vinyl acetate was obtained from unpublished 4-week, 3-month, and 104-week studies conducted by Hazleton Laboratories, Europe. In these studies Sprague-Dawley rats and CD-1 mice were exposed to vinyl acetate in drinking water. The vinyl acetate used was 99.9% pure. Because of the volatility and instability of vinyl acetate in water, the drinking water solutions were made fresh daily and overformulated by 5% to allow for decreases in drinking water concentration and to assure that the animals were receiving the target dose. The levels of vinyl acetate in the air of the room housing both control and exposed animals in the 104-week study was measured and found to be less than 1 ppm. These studies contained some common limitations that are summarized as follows: In many cases only a small number of the control and treated animals were examined histologically. In addition, several findings such as an increased incidence of lymphoid hyperplasia of nasal turbinates, and chronic dacryoadenitis of the harderian glands were dismissed as having resulted from the method of histologic sectioning. However, it is likely that these effects, that were seen in both control and treated animals, may indicate that these animals were in poor physical condition. Reduced body weight gain was often observed in intermediate- and chronic-duration drinking water studies in animals. However, these changes are generally attributed to reduced water intake because of unpalatability.

No studies were located regarding musculoskeletal effects in animals after oral exposure to vinyl acetate.

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

Respiratory Effects. No changes in lung weight or histological or macroscopic appearance of the lung were found in rats or mice administered vinyl acetate in the drinking water that provided maximum doses ranging from 684 mg/kg/day to 950 mg/kg/day for up to 3 months (Hazleton 1979d, 1980e, 1980f), or 235 mg/kg/day (rats) for 104 weeks following <u>in utero</u> exposure (Hazleton 1988a). Lymphoid hyperplasia of the submucosa of the paranasal sinuses was reported for mice that received doses of 950 mg/kg/day via the drinking water for 3-months. However, the authors attributed this to variation in histologic sectioning. Since this effect was not observed in the 104 week in utero exposure study, it is not clear if it was treatment-related, and its toxicological significance is not known.

Cardiovascular Effects. No changes in heart weight or histological and macroscopic appearance of the heart or blood vessels were found in rats or mice administered vinyl acetate in the drinking water that provided doses ranging from 684 mg/kg/day to 950 mg/kg/day for up to 3 months (Hazleton

1979d, 1980e, 1980f) or 235 mg/kg/day (rats) for 104 weeks following in utero exposure (Hazleton 1988a).

Gastrointestinal Effects. No changes in histological and macroscopic appearance of the gastrointestinal organs were found in rats or mice administered vinyl acetate in the drinking water that provided doses ranging from 684 mg/kg/day to 950 mg/kg/day for up to 3 months (Hazleton 1979d, 1980e, 1980f) or 235 mg/kg/day (rats) for 104 weeks following in utero exposure (Hazleton 1988a). However, mice administered vinyl acetate for 4 weeks exhibited a dose-related increase in the incidence of dark-colored gastrointestinal contents (Hazleton 1979d). This effect was observed in control and exposed groups at an incidence of 1/10 (control), l/10 (9.5-mg/kg/day), 1/10 (28.5-mg/kg/day), 3/10 (190-mg/kg/day), and 4/10 (950-mg/k/day). A similar effect was observed in mice exposed to 1,000 ppm of vinyl acetate via inhalation for 3 months (Hazleton 1980b) (see Section 2.2.1.2). The identity of the dark-colored material was not determined in either study. This effect was not accompanied by any histopathological evidence of irritation, so the biological significance of this observation is not known.

Hematological Effects. No changes in any of the hematological parameters studied were found in rats administered vinyl acetate in the drinking water that provided doses ranging from 684 mg/kg/day to 950 mg/kg/day for up to 3 months (Hazleton 1979d, 1980e, 1980f) or 235 mg/kg/day (rats) for 104 weeks following in utero exposure (Hazleton 1988a).

Hepatic Effects. Although changes in absolute, and in some instances, relative liver weight occurred in many animals exposed to vinyl acetate in the drinking water, these changes were usually unaccompanied by histopathological changes, (Hazleton 1979d, 1980f). Histopathological evaluation of the rats that received 684-810 mg/kg/day vinyl acetate in the drinking water for 3 months revealed pericholangitis and granulomatous hepatitis, but no weight changes were evident (Hazleton 1980f). The pericholangitis *was* observed *at an* incidence of 3/10 (control male), 10/10 (684-mg/kg/day male), 6/10 (control female), and 7/10 (810-mg/kg/day female). The incidence of hepatitis was 0/10 (control male), 2/10 (684-mg/kg/day male), 2/10 (control female), and 2/10 (810-mg/kg/day female). Although the incidence of pericholangitis and granulomatous hepatitis appears to be somewhat increased in treated rats, none of these lesions were observed in the 104-week study, suggesting that the lesions may not be treatment related. No changes in liver weight or histological and macroscopic appearance of the liver were found in mice administered vinyl acetate in the drinking water at doses of 950 mg/kg/day for 3 months (Hazleton 1980e) or in rats that received 235 mg/kg/day vinyl acetate in the drinking water for 104 weeks following in utero exposure (Hazleton 1988a).

Renal Effects. No changes in the macroscopic appearance of the kidneys or in urinalysis parameters were found in rats administered vinyl acetate in the drinking water at doses of up to 700 mg/kg/day for 4 weeks (Hazleton 1979d). More concentrated and darker colored urine was observed in female rats receiving a dose of 810 mg/kg/day vinyl acetate in the drinking water for 3 months (Hazleton 1980f). This effect was attributed to reduced water intake due to the unpalatability of the drinking water solution. An increase in absolute kidney weight was found in male mice administered vinyl acetate in the drinking water at dosages of 28.5 mg/kg/day for 4 weeks (Hazleton 1979d). A decrease in absolute, but not kidney weight relative to body weight was found in male rats administered vinyl acetate in drinking water at dosages of 684 mg/kg/day for 3 months (Hazleton 1980f). An increase in kidney weight relative to body weight was observed in male rats administered dosages of 235 mg/kg/day vinyl acetate in the drinking water for 104 weeks following in utero exposure (Hazleton 1988a). Male mice that received 190 mg/kg/day of vinyl acetate in drinking water for 3 months showed a statistically significant increase in relative kidney weight, but this effect was not seen in male mice that received higher doses of vinyl acetate or in any of the treated female mice in this study (Hazleton 1980e). Furthermore, no significant gross or histopathological changes were observed in the kidneys in any of these studies. The biological significance of a change in organ weight, especially when the change is not consistent in direction across studies, does not occur consistently in the same species and/or sex, is not always dose-dependent, and that occurs in the absence of histopathological changes is difficult to ascertain.

Other Systemic Effects. Dose-related reductions in body weight gains were observed in rats and mice administered vinyl acetate in drinking water that provided doses up to 950 mg/kg/day (male mice) for 4 weeks (Hazleton 1979d) and 235 mg/kg/day (rats) for 104 weeks following in utero exposure (Hazleton 1988a). These growth retardation effects were generally accompanied by reduced water consumption and may therefore be due to unpalatability of the drinking water.

Changes in the Harderian gland (chronic dacryoadenitis) were observed in mice administered 950 mg/kg/day vinyl acetate in the drinking water for 3 months (Hazleton 1980e). The authors attributed this effect to variation in histologic sectioning, however, the toxicological significance of this finding is not known. In toxicokinetic studies, the Harderian gland was found to have the highest concentration of radiolabel in the body following the administration of radiolabeled vinyl acetate (see Section 2.3.2). This high concentration of radiolabel may be associated with the chronic dacryoadenitis seen in mice. Since Harderian glands are not present in humans, the relevance of this finding to human health is not known.

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans after oral exposure to vinyl acetate.

As was observed following inhalation exposure (see Section 2.2.1.3), changes in thymus and/or spleen weight were consistently noted in rats and mice exposed to vinyl acetate in the drinking water (Hazleton 1979d, 1980e, 1988a). However, these changes were not always dose-related. For example, in the 4-week mouse study, a significant decrease in absolute and relative thymus weight was observed in all mice that received only the highest dose of vinyl acetate (950 mg/kg/day) (Hazleton 1979d). In the 3-month mouse study, absolute and relative spleen weights were significantly reduced in the lowand mid-dose females (38 mg/kg/day and 190 mg/kg/day) and absolute spleen weight was reduced in the mid-dose males, but no changes in spleen weight were observed in animals of either sex administered 950 mg/kg/day vinyl acetate (Hazleton 1980e). However, thymus weights relative to body weights were significantly decreased in male mice that received 950 "g/kg/day vinyl acetate for 3 months. In the 104-week study, only a decrease in absolute spleen weight was noted in the low- and high-dose males (Hazleton 1988a). Extramedullary hematopoiesis was observed in both control mice and mice receiving 950 mg/kg/day vinyl acetate in the 3-month study (Hazleton 1980e), which is suggestive of poor physical condition in the animal colony rather than an immunotoxic effect in the treated animals. In addition, the incidence of grossly-detectable splenomegaly was not increased in the high-dose animals. The decrease in spleen and thymus weight relative to body weight may be suggestive of an immunosuppressive action of vinyl acetate, but the appropriate parameters were not investigated to delineate this possibility. No other studies have provided evidence that vinyl acetate is immunotoxic.

The highest NOAEL values and all reliable LOAEL values for immunological effects in each study for rats and mice in each duration category are presented in Table 2-2 and plotted in Figure 2-2.

2.2.2.4 Neurological Effects

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

No treatment-related clinical signs of neurotoxicity were observed in rats or mice administered vinyl acetate in the drinking water that provided doses ranging from 684 mg/kg/day to 950 mg/kg/day for 3 months (Hazleton 1979d, 1980e, 1980f) and 235 mg/kg/day (rats) for 104 weeks following *in utero* exposure (Hazleton 1988a). However, despite a decrease in relative brain weight observed in males administered 60 mg/kg/day or 235 mg/kg/day vinyl acetate in the drinking water for 104 weeks following *in utero* exposure (Hazleton 1988a), no macroscopic or histopathological evidence of neurotoxicity was found in any of the studies described above.

The highest NOAEL values for neurological effects in each study for rats in each duration category are presented 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 after oral exposure to vinyl acetate.

Administration of up to 5,000 ppm (equivalent to a mean of 477 mg/kg/day, based on authors' calculations of water intake) vinyl acetate in the drinking water of pregnant rats on days 6-15 of gestation failed to elicit any treatment-related effects on reproductive parameters, fetal growth, or development (Hazleton 1980d). Slight reductions in body weight gain were seen in the dams administered 477 mg/kg/day at initiation of treatment, but mean body weight of this group was similar to the control group for the remainder of the study. This initial growth retardation in dams accompanied decreases in food and water consumption. No treatment-related gross or histopathological changes were observed in the dams. No effects of treatment were seen on any of the fetal parameters measured (e.g., weight, crown/rump length, and incidence of visceral or skeletal defects). In this study, vinyl acetate was not a developmental toxicant in rats. However, a statistically significant reduction in F_1 pup weight was observed in a two-generation reproductive toxicity study in which rats received 5,000 ppm vinyl acetate in the drinking water (equivalent to 431-763 mg/kg/day, based on the authors' calculation of test article consumption) prior to mating, throughout gestation and lactation, and into adulthood (Hazleton 1987). This effect may be attributed to the slight growth retardation observed in the F_0 dams administered 431 mg/kg/day vinyl acetate, and thus is most likely not a direct toxic effect of vinyl acetate on the fetus. The F, females exhibited slight (nonsignificant) decreases in body weight gain during the gestation period, but this growth reduction achieved statistical significance during the lactation period. However, a significant reduction in water intake was observed in the F_0 females during the pre-mating period, gestation, and lactation which could have also contributed to the reduced F_1 pup weight. No other developmental effects were observed in any treatment group.

The NOAEL values and one LOAEL value for developmental effects in rats are presented 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 after oral exposure to vinyl acetate.

Although decreased relative testes weight was observed in male mice administered 38 mg/kg/day vinyl acetate in the drinking water for 3 months, this effect was not seen at higher doses and no gross or histopathological

changes were observed in the testes of these animals (Hazleton 1980e). Furthermore, no organ weight, gross, or histopathological changes were observed in male or female reproductive organs of rats or mice administered vinyl acetate in the drinking water at dosages of up to 950 mg/kg/day for 3 months (Hazleton 1980e, 1980f) or in rats receiving 235 mg/kg/day vinyl acetate in the drinking water for 104 weeks following in utero exposure (Hazleton 1988a). A marginal reduction in the number of pregnancies was observed in the F, female rats administered 5,000 ppm vinyl acetate in the drinking water (equivalent to 431-763 mg/kg/day) in a two-generation study (19/24 treated animals became pregnant as opposed to 24/25 of the controls) (Hazleton 1987). However, this difference was not statistically significant and the pregnancy incidence in the treated animals was within the reported range of historical controls. No other effects on reproductive performance were observed in this study.

The NOAEL values for reproductive effects in rats are presented in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were found regarding genotoxic effects in humans after oral exposure to vinyl acetate.

Vinyl acetate administered by gavage to rats (concentration not specified) did not result in DNA-adduct formation in the liver (Simon et al. 1985b). Micronuclei were evaluated in bone marrow smears taken from rats and mice exposed to vinyl acetate in drinking water for 4 weeks (Hazleton 1979d). The group mean incidence of erythrocytes containing micronuclei was increased as compared to the controls in the mice receiving 950 mg/kg/day vinyl acetate. However, all micronuclei counts were within the expected range of spontaneous occurrence. No treatment-related effects on the incidence of micronuclei were seen in the rats exposed to vinyl acetate.

Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

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

Oral administration of 400 mg/kg/day of vinyl acetate to rats for 3 weeks did not result in an increase in preneoplastic enzyme altered foci (gamma-glutamyltranspeptidase-positive or adenosine 5'-triphosphatase-negative foci) in the liver (Laib and Bolt 1986b).

A statistically significant carcinogenic effect of vinyl acetate was observed in a screening study in which this chemical was administered in the drinking water of Fischer-344 rats at doses of 57 mg/kg/day and 143 mg/kg/day

(females) and 36 mg/kg/day and 89 mg/kg/day (males) 5 days/week for 100 weeks (Lijinsky and Reuber 1983; NCI 1982a). Tumor incidences that were significantly increased in the treated animals as compared to the controls included neoplastic nodules of the liver in both sexes, adenocarcinomas of the uterus in the females, and C-cell adenomas or carcinomas of the thyroid in both sexes, but predominantly in the females. The uterine carcinomas were large, malignant invasive neoplasms, that are extremely unusual, which supports the evidence that vinyl acetate is carcinogenic. Limitations associated with this study that may underestimate the carcinogenic risk of vinyl acetate included the possibility that the maximum tolerated dose of vinyl acetate was not achieved, the animals received less than the calculated doses due ,to the instability of vinyl acetate in drinking water, and use of a small sample size (20 animals/sex). Other limitations include the fact that only two dose levels were used and the vinyl acetate used was commercial grade of undetermined purity. Various inhibitors (i.e., p-hydroquinone, benzoquinones, nitrobenzenes, diphenyl, toluenes, anthracene, phenanthrene, naphthalene, see Section 4.1) are added to commercial formulations of vinyl acetate at varying concentrations to prevent polymerization (Daniels 1983; Mannsville 1988). It is not known what effects, if any, these inhibitors may have had in this study. Drinking water solutions for 5 consecutive day exposures were made up once a week. sufficient solutions for 3 days was dispensed in feeding bottles, while the remainder was stored in the refrigerator and dispensed on day 4. The authors calculated that the vinyl acetate in solution decomposed at an average rate of 8.5% per day at room temperature, thus resulting in a substantial loss over the 5 day exposure period. Furthermore, because vinyl acetate hydrolyses to acetaldehyde, the exposure in this experiment was not only to vinyl acetate, but to both vinyl acetate and acetaldehyde. Another factor compromising the validity of this study is that the animals were housed 4 per cage and given 80 mL of vinyl acetate solution per day. The possibility exists that the more aggressive animals received more test solution than their less aggressive cagemates. In addition, the animals received tap water ad libitum on the weekends. The stress imposed on the animals by restricting their water intake during the week and providing water ad libitum on the weekends may be a confounding factor in the study. Lijinsky and Reuber (1983) concluded that the study needed to be repeated with larger numbers of animals per group, higher dose levels, and vinyl acetate solutions that are prepared fresh daily before definitive conclusions regarding the carcinogenicity of vinyl acetate following oral exposure can be made.

In a later study, Sprague-Dawley rats that received up to 235 mg/kg/day vinyl acetate (99.9% pure) in their drinking water for 104 weeks following in utero exposure developed tumors, but they were not considered by the authors to be treatment-related, since they occurred at a similar incidence in the high-dose animals as in the controls, and were commonly occurring tumors in aging Sprague-Dawley rats (Hazleton 1988a). Two squamous cell carcinomas of the oral mucosa were observed in the treated animals, but the incidence was not statistically significant, and the study authors considered them to be a

result of tooth-related problems (Hazleton 1988b). Therefore, this study provides no evidence for the carcinogenicity of vinyl acetate following exposure in the drinking water. The negative data obtained from this study should be given more weight than the positive data obtained from the Lijinsky and Reuber (1983; NCI 1982) screening study because many of the limitations associated with the earlier study were remedied in the Hazleton (1988a) study. For example, in the Hazleton (1988a) study, more animals per group were used (90 vs. 20), and a higher dose was used (5,000 ppm vs. 2,500 ppm, or 235 mg/kg/day vs. 89-143 mg/kg/day). Furthermore, the animals were exposed beginning in utero, resulting in exposure for a greater period of their lives as well as exposure to effectively higher doses (on a mg/kg basis) in the young weanlings as compared to the adults. Finally, the drinking water solutions were prepared daily in the Hazleton (1988b) study, eliminating the problem of stability of the test formulation. Hydroquinone was present in the vinyl acetate at a concentration of $\leq$1 ppm. However, two different strains of rat were used in the Lijinsky and Reuber (1983) and Hazleton (1988b) studies which may have contributed to the difference in results obtained.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to vinyl acetate. The dermal LDsO in rabbits for a 24-hour application of vinyl acetate has been reported to be 8 mL/kg (undiluted vinyl acetate) (Weil and Carpenter 1969) and 2.5 mL/kg (undiluted vinyl acetate) (Smyth and Carpenter 1948). Death was preceded by convulsions, and necropsy revealed congestion of the lungs and liver, mottled spleen and kidney, and prominent liver acini (Weil and Carpenter 1969). The LD_{50} values for rabbits are presented in Table 2-3.

2.2.3.2 Systemic Effects

No studies were located in humans or animals regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to vinyl acetate.

Dermal/Ocular Effects. No irritation was observed when 11 volunteer paperhangers had a 2% vinyl acetate solution applied to their skin for 48 or 72 hours in a patch test (Tanaka and Lucas 1984). However, occupational experience has shown that some workers may react to dermal contact with vinyl acetate with blister formation, particularly on the thin skin of the finger web and the underside of the wrist, and that continued contact, such as that afforded by clothing wet with the chemical might result in severe irritation or blistering of the skin (Union Carbide 1958).

TABLE 2-3. Levels of Significant Exposure to Vinyl Acetate - Dermal

Species	Exposure frequency/ duration	System	NOAEL	LOAEL (effect) Less serious		LOAEL (effect) Serious		Reference
ACUTE EXPOSURE								
Death								
Rabbit	1 d 24hr					8.0 mL/kg	(LD50)	Weil and Carpenter 1969
Rabbit	1 d 24hr					2.5 mL/kg	(LD50)	Smyth and Carpenter 1948
Systemic								
Human	1 d 48-72 hr	Derm/oc	2%					Tanaka and Lucas 1984
Rabbit	4-72 hr	Derm/oc		0.5 mL	(slight edema)			Industrial Bio-Test Laboratories 1972
Rabbit	1 d 24hr	Derm/oc		8.0 mL/kg	(erythema, edema, necrosis)			Weil and Carpenter 1969
Rabbit	1 d 1x/d	Derm/oc		0.5 mL	(minor corneal injury)			Weil and Carpenter 1969
INTERMEDIATE EXPOSURE								
Systemic								
Rat	15 d 6hr/d	Derm/oc	630 ppm	2000 ppm	(eye irritation)			Gage 1970

d = day; Derm/oc = dermal/ocular; hr = hour; LOAEL = lowest-observed-adverse-effect level; LD50 = lethal dose, 50% kill; NOAEL = no-observed-adverse-effect level; 1x = one time

The responses of human volunteers exposed to varying concentrations of vinyl acetate in the air for an unspecified period (less than 8 hours) were monitored (Deese and Joyner 1969). One of 5 volunteers reported slight eye irritation at 5.7 and 6.8 ppm and all 3 volunteers exposed to 21.6 ppm complained of eye irritation that "would be intolerable over an extended period" (Deese and Joyner 1969). In another study, four volunteers exposed to 72 ppm vinyl acetate in air for 30 minutes reported eye irritation that persisted for up to 60 minutes after exposure (Smyth and Carpenter 1973). These ocular effects are due to direct contact of the eye with vinyl acetate. Prolonged occupational exposure to vinyl acetate generally does not cause eye irritation at levels below 10 ppm (Deese and Joyner 1969).

Undiluted vinyl acetate was reported to be nonirritating when 0.1 mL was applied to the clipped intact skin of rabbits (Weil and Carpenter 1969). However, erythema, edema, and necrosis of the skin was observed when near lethal levels of vinyl acetate (8.0 mL/kg of undiluted chemical) were applied to the skin of rabbits (Weil and Carpenter 1969). Slight edema of both intact and abraded skin was observed in rabbits following application of 0.5 mL of undiluted vinyl acetate (Industrial Biotest 1972). Based on these results, the authors classified vinyl acetate as noncorrosive to the skin. Application of vinyl acetate to the conjunctival sac of rabbits caused only a "trace" of eye irritation (Weil and Carpenter 1969). Eye irritation was also noted in animals exposed to 2,000 ppm vinyl acetate in air for 15 days (Gage 1970).

NOAEL and LOAEL values for skin and eye irritation are presented in Table 2-3.

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

2.2.3.3 Immunological Effects
2.2.3.4 Neurological Effects
2.2.3.5 Developmenfal Effects
2.2.3.6 Reproductive Effects
2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding the absorption of vinyl acetate in humans after inhalation exposure.

Studies in rats indicate that vinyl acetate is rapidly and effectively absorbed via this route (Hazleton 1979a). Following administration of radiolabeled vinyl acetate ([vinyl-1,2-^{14}C]-VA, or ^{14}C-VA) in the air at a concentration of 1,000 ppm for 6 hours, almost half of the radioactivity was eliminated via expired air within 6 hours after exposure. The exact dose of vinyl acetate administered by inhalation, however, could not be determined because some of the radioactivity was exhaled during the 6-hour exposure period. A follow-up study using rats exposed to 750 ppm ^{14}C-VA for 6 hours supported these results and showed that the major portion of the radioactivity was eliminated in expired air primarily as CO_2 during the first 24 hours (Hazleton 1980a).

2.3.1.2 Oral Exposure

No studies were located regarding the absorption of vinyl acetate in humans following oral exposure.

Animal studies indicate that vinyl acetate is quickly and effectively absorbed via this route (Hazleton 1979a, 1980a). Following gavage administration of 1 mL of a 5,000 ppm aqueous solution of ^{14}C-VA, high concentrations of the radiolabel were found to be distributed throughout the body, and the majority was eliminated in expired air primarily as CO_2 during the first 6 hours after dosing (Hazleton 1979a). Similarly, 65% of the radioactivity of six 1 mL doses of a 10,000 ppm solution orally administered by gavage to rats in a follow-up study was eliminated during both the 6-hour dosing period and 96-hour collection period (Hazleton 1980a). In mice, 1 mL of a 5,000 ppm ^{14}C-VA aqueous solution was quickly absorbed as shown by the wide distribution of radiolabel in tissues throughout the body 1 hour after oral administration (Hazleton 1980a).

2.3.1.3 Dermal Exposure

No studies were located regarding the absorption of vinyl acetate in humans following dermal exposure.

Dermal penetration of vinyl acetate in rabbits was indirectly demonstrated through the observation of mortality in animals that were dermally treated with 2.5 mL/kg (Smyth and Carpenter 1948) and 8.0 mL/kg (Weil and Carpenter 1969). No further details regarding absorption are available.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding the distribution of vinyl acetate in humans following inhalation exposure.

Studies in male and female rats show that radioactivity is immediately and widely distributed throughout the body after inhalation exposure to 1,000 ppm ^{14}C-VA (Hazleton 1979a). The salivary glands, lacrimal glands, Harderian glands, gastrointestinal mucosa, nasoturbinates, kidneys, and certain portions of the larynges had the highest concentrations of the radiolabel. The brain, spinal cord, liver, fat, and bone marrow also had readily detectable levels of radioactivity. Low levels in the heart, blood, testes, and skeletal muscle were also observed. Whole-body autoradiographs obtained at 1 and 6 hours after exposure show a general decrease in the radioactivity with increased time, Seventy-two hours after exposure, radioactivity was still found in the brain, spinal cord, Harderian glands, maxillary sinuses, adrenal glands, and kidneys. Approximately 19% of the total radioactivity recovered was found in the carcass 96 hours after exposure.

In a follow-up study 16 rats were exposed to air containing 750 ppm ^{14}C-VA for 6 hours (Hazleton 1980a). The tissue distribution of radioactivity is given in Table 2-4. As can be seen in Table 2-4, the highest concentrations were observed in the Harderian gland, followed by the ileum, submaxillary salivary gland, and the contents of the gastrointestinal tract. Radioactivity was also found at significant levels in the liver, kidney, lung, brain, stomach, colon, and ovaries. Differences between the sexes in the distribution of radioactivity was seen in the gonads; females had higher concentrations in the ovaries than did males in the testes. Although the total radioactivity decreased with time, no major differences in the pattern were found at 1, 6, and 72 hours after exposure. Relative tissue concentrations also tended to be higher in animals exposed via inhalation compared with oral exposure. This was particularly true in the lung and brain.

2.3.2.2 Oral Exposure

No studies were located regarding the distribution of vinyl acetate in humans following oral exposure.

In animals, the distribution of radioactivity following oral exposure to ^{14}C-VA has been studied using male and female rats and mice (Hazleton 1979a, 1980a). Similar distribution patterns were observed in rats administered either 6 hourly 1-mL doses of an aqueous solution containing 10,000 ppm vinyl acetate (equivalent to 237 mg/kg) by gavage (Hazleton 1980a) or one dose containing 1 mL of a 5,000 ppm vinyl acetate solution (equivalent to 23.4 mg/kg) (Hazleton 1979a). One hour following administration of either dose, the radioactivity was found to be widely distributed with the highest concentrations found in the Harderian gland and salivary glands. High levels of radioactivity were also found in the liver, kidney, heart, and gastrointestinal tract. As with inhalation exposure, the level of radioactivity decreased with time, and there were no major differences in the distribution pattern at 6 and 72 hours after oral exposure. A mean of 7.1% of

TABLE 2-4. Distribution of Radioactivity in Rats Immediately After Inhalation of 750 ppm [^{14}C]-Vinyl Acetate for 6 Hours[a]

Tissue	Concentration of Radioactivity (µg equivalents/g)
Adrenals	119
Blood	72
Bone	79
Brain	153
Colon	257
Fat	29
Gastrointestinal contents	291
Gonads	117
Harderian gland	2045
Heart	82
Ileum	393
Kidney	204
Liver	204
Lungs	270
Residual carcass	72
Submaxillary salivary gland	341
Skeletal muscle	61
Stomach	210

[a]Adapted from Hazleton 1980a

the administered radioactivity was present in the carcass 96 hours after exposure. As with inhalation exposure, a sex difference in the distribution of radioactivity was seen in the gonads; females had higher concentration in the ovaries than did males in the testes. A similar distribution pattern was seen in mice of both sexes administered a single oral dose of 5,000 ppm of ^{14}C-VA as an aqueous solution (Hazleton 1980a). In this study, the highest concentrations of radioactivity were found in Harderian glands, salivary and lingual glands, gastrointestinal mucosa, liver, and brown fat. The high concentration of ^{14}C found in the Harderian gland may be associated with the chronic dacryoadenitis seen in mice administered vinyl acetate in drinking water for 3 months (Hazleton 1980e, see Section 2.2.2.2). Low levels were found in blood muscle, fat, and testes. As with the rats, the distribution pattern was unchanged 6 and 72 hours after dosing, although the levels were reduced.

2.3.2.3 Dermal Exposure

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

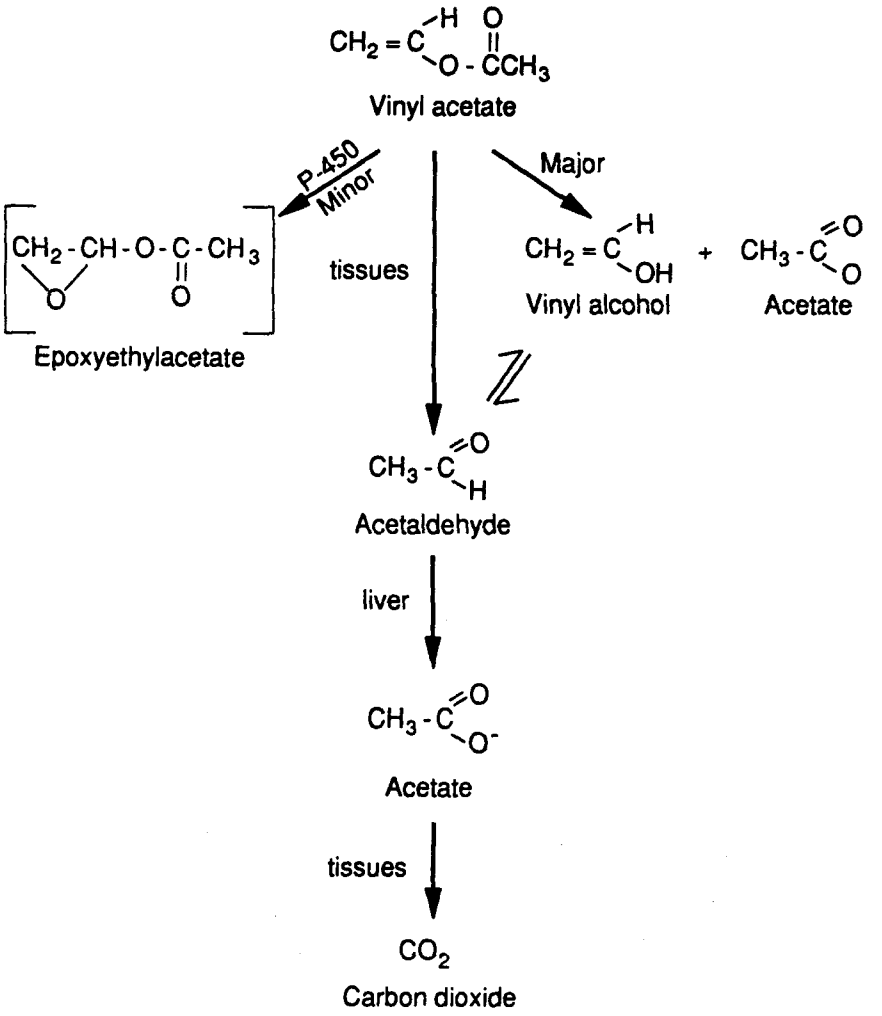
2.3.3 Metabolism

No studies are available on the in vivo metabolism of vinyl acetate in humans via any exposure route.

The metabolism of vinyl acetate has been studied in animals (Boyland and Chasseaud 1967; Hazleton 1979a, 1980a; Holub 1983; Holub and Tarkowski 1982; Simon et al. 1985a; Tiunova and Rumyandsev 1975). A summary of the proposed metabolic pathways for vinyl acetate is presented in Figure 2-3. Vinyl acetate is rapidly hydrolyzed by esterases in the blood to acetate and the unstable intermediate, vinyl alcohol. Vinyl alcohol is rapidly converted to acetaldehyde, which in turn is metabolized to acetate in the liver. This in turn is incorporated into the "2 carbon pool" of normal body metabolism and eventually forms CO_2 as the major breakdo-m product. Therefore, the metabolism of vinyl acetate results in two acetate molecules that enter the 2 carbon pool. This has been confirmed in excretion studies that have documented $^{14}CO_2$ in exhaled air as the major metabolite and source of radioactivity recovered following either inhalation or oral exposure to ^{14}C-VA (Hazleton 1979a, 1980a). A very small amount also appears to be excreted in the urine as urea and several other unidentified metabolites. The metabolic pattern was not influenced by the route of administration.

Similar results were found in rats exposed to concentrations of vinyl acetate (200-2,000 ppm) in the air for 1.4 hours or less (Simon et al. 1985a). The results show that vinyl acetate is rapidly metabolized by blood esterases and that hepatic monooxygenases have a minor role, if any, in the metabolism of vinyl acetate. Zero-order kinetics were observed at higher

FIGURE 2-3. Proposed Metabolic Pathways for Vinyl Acetate



concentrations (800-1,400 ppm) and first-order kinetics at lower concentrations. This indicates that the metabolic pathways of vinyl acetate are saturable at high levels. Following 6 months of exposure to 10-500 mg/m^3 (2.8-142 ppm) of vinyl acetate in the air, a transient decrease in cytochrome P-450 and microsomal protein content was found in the liver of rats (Holub 1983). No further details were given.

The induction of preneoplastic enzyme altered foci is believed to be an indication of DNA alkylation by epoxides and subsequent genotoxicity. If vinyl acetate was metabolized by the microsomal P-450 system to its corresponding epoxide, than it ha's been predicted that this epoxide would produce the same products of DNA alkylation as vinyl chloride and vinyl carbamate (Laib and Bolt 1986). Oral administration of 400 mg/kg/day of vinyl acetate to rats for 3 weeks did not result in an increase in preneoplastic enzyme altered foci (γ-glutamyltranspeptidase-positive or adenosine 5'-triphosphatase-negative foci) in the liver, whereas previous studies have shown that vinyl chloride and vinyl carbamate do induce these foci (Laib and Bolt 1986b). These results suggest that vinyl acetate is not likely epoxidized by the microsomal P-450 system to an ultimate carcinogenic metabolite in the liver. These results also support the observation that the primary route of metabolism for vinyl acetate is hydrolysis by esterases to acetaldehyde and acetate rather than via the P-450 microsomal mixed-function oxygenase system to the corresponding epoxide.

In vitro tests in which vinyl acetate was added to blood, plasma, or liver homogenate from rats and mice provided results that suggested that enzyme-mediated hydrolysis of vinyl acetate occurred at all three sites, resulting in the production of vinyl alcohol (which is unstable) and acetate (Hazleton 1979a). The vinyl alcohol is quickly converted to acetaldehyde. Acetaldehyde added to rat and human whole blood or plasma was not degraded, but when added to rat liver homogenate, it was converted to acetate (Hazleton 1980a). This provides evidence that the metabolism of acetaldehyde to acetate occurs primarily in the liver. Subsequent reactions yield carbon dioxide, and water. It is also known that vinyl acetate hydrolyses in water at 25° C at the rate of 8.5% per day (Lijinsky and Reuber 1983). These in vitro studies show that the half-lives for conversion of vinyl acetate to acetaldehyde in rat plasma to be 57, 58, and 57 seconds at concentrations of 25, 50, or 100 ppm, respectively. Using rat whole blood, the half lives of vinyl acetate were found to be 112, 121, and 141 seconds at the same conditions, respectively. In rat liver homogenates, the half lives were 50, 97, and 167 seconds, again at the same concentrations, respectively. Similar half-lives were seen in mouse plasma, whole blood, and liver homogenates. Furthermore, even with diluted preparations of plasma, whole blood, and liver homogenates the hydrolysis of vinyl acetate is very rapid (Hazleton 1979a). A later in vitro study using human blood and plasma found that the hydrolysis of vinyl acetate proceeded at a similar rate as reported for the rat and mouse (Hazleton 1980a). However, different results were reported by Fedtke and Wiegand (1990) using 200 μM vinyl acetate added to rat and human blood. They

reported that the half-life of vinyl acetate elimination in human whole blood was 4.1 minutes as compared to <1 minute in rat whole blood (Fedtke and Wiegand 1990). The majority of the hydrolysis was found to occur in the red blood cells rather than the plasma of human blood. The half-life in plasma was 62 minutes as compared to 5.5 minutes in red blood cells. However, in rat plasma, the half-life of vinyl acetate elimination was 1.2 minutes as compared to 5.6 minutes in rat red blood cells. While these results differ from those reported above with regard to the location of the hydrolytic enzymes in the blood across species, they do confirm that hydrolysis is the predominant route of metabolism for vinyl acetate in both human and rat blood.

Further in vitro metabolic studies show that vinyl acetate added to preparations of rat liver supernatant did conjuwte (although not to a large degree) with glutathione (Boyland and Chasseaud 1967). The reaction is mediated by glutathione S-transferase and further metabolism produces mercapturic acid derivatives that are eliminated in the urine (Boyland and Chausseaud 1967, 1970). Rats exposed for 5 hours a day for 6 months to vinyl acetate in the air (10, 100, or 500 mg/m^3) showed a significant depletion of free nonprotein thiols in the liver but not in a dose-dependent pattern (Hobub and Tarkowski 1982). According to the authors, the thiol depletion indicates that conjugation with glutathione plays an important role in the detoxification of this chemical. Similar results were seen in rats, guinea pigs, and mice given single intraperitoneal doses of vinyl acetate (Holub and Tarkowski 1982). The highest decrease (50%) in SH content was seen in guinea pigs following a single intraperitoneal injection of 500 mg/kg vinyl acetate. Glutathione conjugation may decrease the toxicity of potentially harmful electrophiles by facilitating excretion into the bile (Chasseaud 1973).

These studies show that vinyl acetate quickly undergoes hydrolysis in the body through several intermediate steps to form the principal end products, carbon dioxide and water. The metabolic pattern was not influenced by the route of vinyl acetate exposure, but did show nonlinear kinetic patterns at high concentrations, indicating that the metabolic processes are saturable. In vivo and in vitro tests indicate that vinyl acetate may bind to various degrees with glutathione in different species, which may help to detoxify vinyl acetate or its metabolites and enhance their elimination.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding the excretion of vinyl acetate in humans following inhalation exposure.

Studies in animals indicate that vinyl acetate is rapidly eliminated following inhalation exposure (Hazleton 1979a, 1980a). In one of these studies, rats were exposed to 750 ppm ^{14}C-VA for 6 hours (Hazleton 1980a). Ninety-six hours following administration, the mean proportions of the

recovered radioactivity found in the urine, feces, and expired air were 4.8%, 3.6%, and 74.6%, respectively. Most of the radioactivity was eliminated in the form of carbon dioxide during the first 24 hours after exposure. Also, a substantial percentage (16.4%) of the total recovered radioactivity was present in the carcasses at 96 hours. Similar results were obtained in an earlier study conducted by Hazleton (1979a). In this study, rats were exposed to 1,000 ppm vinyl-1,2-^{14}C-VA for 6 hours. Ninety-six hours following administration, the mean proportions of the recovered radioactivity in the urine, feces, and expired air were 7.1%, 3.9%, and 70.3%, respectively. As with the above study, much of the radioactivity was eliminated within 24 hours of exposure.

2.3.4.2 Oral Exposure

No studies were located regarding the excretion of vinyl acetate in humans following inhalation exposure.

In animals, the excretion of vinyl acetate following oral exposure has been studied in male and female rats (Hazleton 1979a, 1980a). The excretion of radioactivity in rats following oral administration of 1 mL of a 5,000 ppm [vinyl-1,2-^{14}C]-VA solution (equivalent to 23.4 mg/kg) by gavage was rapid (as in inhalation exposure) (Hazleton 1979a). Ninety-six hours after administration, 3.1%, 1.1%, and 86.3% of the mean radioactivity was excreted in the urine, feces, and expired air, respectively. After 96 hours, an additional 7% was recovered in the carcasses, accounting for a total of 96% of the administered radioactivity. Most of the radioactivity was eliminated during the first 6 hours after exposure. In a later study, rats were given 6 hourly doses of a 10,000 ppm aqueous solution of [vinyl-1,2-^{14}C]-VA by oral gavage (Hazleton 1980a). During the six hours of exposure and the 96-hour collection period, 1.8%, 1.4%, and 61.2% of the mean radioactivity was excreted in the urine, feces, and expired air, respectively. After 96 hours, an additional 5% was recovered from the carcasses, accounting for a total of 70% of the administered radioactivity. The authors attributed the unaccounted 30% to loss in expired air that escaped from the metabolic cages housing the animals. The studies show that following oral exposure, vinyl acetate is eliminated rapidly from the body, primarily through expired air as carbon dioxide.

2.3.4.3 Dermal Exposure

No studies were located regarding the excretion of vinyl acetate in humans or animals after dermal exposure.

2.4 RELEVANCE TO PUBLIC HEALTH

Since few monitoring data are available for vinyl acetate concentrations in environmental media, physical/chemical property data can be used to predict the partitioning of the compound to air, water, and soil and subsequent human

exposure through contact with these media. Based on the high vapor pressure of vinyl acetate, volatilization to the atmosphere will be an important transport process for vinyl acetate released to surface water and soils. The low K_{oc}(soil adsorption coefficient) and high water solubility indicates that vinyl acetate is highly mobile in soils and that when released to subsurface soils it is likely to partition to groundwater. The low K_{ow} (octanol/water partition coefficient) for vinyl acetate, suggests that it is unlikely to bioconcentrate/biomagnify in terrestrial or aquatic organisms/food chains, hence, exposure to vinyl acetate through consumption of meat or fish is not an important exposure pathway for this compound. In the atmosphere, vinyl acetate is rapidly broken down by photochemical oxidation with a half-life on the order of hours. In soils and surface and groundwater, the compound undergoes hydrolysis and biotransformation,.with half-lives on the order of days. The main products of these transformat,ion processes are acetic acid, acetaldehyde, and acetate,

Populations living in areas surrounding hazardous waste sites may be exposed to vinyl acetate through inhalation of contaminated air and ingestion of or dermal contact with contaminated water; the latter route may be particularly important for populations living near certain types of disposal sites (e.g., underground injection sites). The relative importance of these pathways in terms of human exposure potential is difficult to establish given the limited monitoring data available for vinyl acetate. Most people, however, are probably exposed to very small amounts of vinyl acetate through: (1) inhalation of contaminated ambient air and cigarette smoke; (2) dermal contact with products containing the compound (e.g., glues and paints); and (3) ingestion of residual vinyl acetate monomers in food (i.e., that may have migrated from plastic food wraps) or food items containing the compound as a starch modifier. Occupational exposure to vinyl acetate occurs via inhalation of contaminated workplace air and by dermal contact with vinyl acetate vapor or liquids and products containing the compound.

Vinyl acetate is a water soluble volatile organic compound that acts directly on the site of contact. The clinical signs common to both humans and animals after acute exposure to high levels of vinyl acetate in air are respiratory and ocular irritation. Other organ systems apparently affected in animals following inhalation and/or oral exposure include the immune and nervous systems. The mechanism by which vinyl acetate exerts its effects on these systems has not been investigated. Death has been reported in animals following acute inhalation, oral, or dermal exposure to high doses of'vinyl acetate. Reduced body weight gain is often observed in intermediate- and chronic-duration inhalation and drinking water studies in animals. In drinking water studies, these changes have been attributed to reduced water intake due to the unpalatability of the test solution containing vinyl acetate. Similarly, growth retardation has been observed in pups born to rats exposed to vinyl acetate via inhalation or oral administration. This effect is most likely a result of reduced body weight gain in the maternal animals during exposure to vinyl acetate. An increased incidence of some tumor types

has been observed in rats that were chronically exposed to vinyl acetate via inhalation. In most cases, the tumor types observed'following exposure to vinyl acetate (i.e., nasal) were not observed in the control animals. Studies on the carcinogenic potential of vinyl acetate following oral exposure have generally been inconclusive or negative. Very little information is available on the toxicity of vinyl acetate following dermal exposure in humans or animals. However, exposure to vinyl acetate has caused ocular irritation and blistering of the skin of workers and laboratory animals.

An acute-duration inhalation MRL was not derived for vinyl acetate because of the lack of information on target organ(s) of effect for this compound. Clinical studies with human volunteers have shown that irritation of the mucous membranes of the throat can occur at levels as low as 4 ppm for exposure durations of 2 minutes (Smyth and Carpenter 1973). However, this was based on effects reported in one out of nine exposed volunteers. Higher levels and/or longer durations of exposure resulted in an increased incidence of reported irritation.

An intermediate-duration inhalation MRL of 0.01 ppm was derived for vinyl acetate based on the Hazleton 1980b study. This study used the species that shows the greatest sensitivity to the respiratory effects of vinyl acetate (i.e., the mouse). Ten CD-1 mice/sex/group were intermittently exposed to vapor concentrations of 0, 50, 200, or 1,000 ppm for 6 hours/day, 5 days/week, for 3 months. Animals were observed daily for clinical signs of toxicity, body weight was monitored, hematological and blood chemical parameters were assayed, and a full necropsy was performed at terminal sacrifice. There were no exposure-related deaths during the study; however, 11 animals died as a result of the blood sampling procedure (2 out of 20 controls and 9 out of 20 exposed to 1,000 ppm). No treatment-related adverse effects were observed in the control or 50-ppm exposure group. Respiratory distress, hunched posture, and ruffled fur were observed at exposure concentrations of 200 ppm and above. A statistically significant decrease in body weight gain was seen in the animals exposed to 1,000 ppm vinyl acetate. No other clinical or macroscopic signs of exposure-related toxicity were observed in these animals. Inflammation of the nasal turbinate epithelium and mild multifocal bronchitis were observed in animals exposed to 200 ppm vinyl acetate. Focal and diffuse rhinitis associated with exudation and transudation into the nasal passages, metaplasia or hyperplasia of the trachea, multifocal bronchitis, bronchiolitis, multifocal bronchiostania, bronchial epithelial metaplasia and hyperplasia, and occasional bronchiolar and bronchial exudation were observed in the animals exposed to 1,000 ppm vinyl acetate. The 200-ppm vinyl acetate level was considered a LOAEL and the 50-ppm vinyl acetate level was considered a NOAEL for respiratory effects in the extrathoracic region. The NOAEL was used as the basis for calculating the MRL. The administered concentration (50 ppm) was corrected for intermittent exposure and human equivalent concentration as follows:

To convert to mg/m^3:

ppm x (86.09/24.45) = 3.52 mg/m^3 (assuming 25°C and 760 mmHg)
NOAEL (Experimental Concentration, mg/m^3) = $NOAEL_{[EXP]}$
$NOAEL_{[EXP]}$ = 50 ppm x (3.52 mg/m^3)/(1 ppm) = 176 mg/m^3

To correct for noncontinuous exposure ($NOAEL_{[ADJ]}$):

$NOAEL_{[ADJ]}$ = $NOAEL_{[EXP]}$ x (5 days/7 days) x (6 hours/24 hours)
= 176 mg/m^3 x (5 days/7 days) x (6 hours/24 hours)
= 31 mg/m^3

To calculate the human equivalent concentration (HEC) (for a soluble gas that produces a respiratory effect in the extrathoracic region):

$NOAEL_{[HEC]}$ = $NOAEL_{[ADJ]}$ x regional gas dose ratio (RGDR)

RGDR = Regional gas dose for animals (RGD_A)/Regional gas dose for humans (RGD_H)

RGD_A = inhalation rate of animal (m^3/day)/surface area of extrathoracic region (cm^2)

RGD_H = inhalation rate of humans (m^3/day)/surface area of extrathoracic region (cm^2)

Inhalation rate:
CD-1 mouse (subchronic study) = 0.05 m^3/day
Inhalation rate for humans = 20 m^3/day

Surface area for extrathoracic region:
Mouse = 2.9 cm^2
Human = 177 cm^2

$NOAEL_{[HEC]}$ = 31 mg/m^3 x ([0.05 m^3/day/2.9 cm^2]/[20 m^3/day/177 cm^2])
= 31 mg/m^3 x 0.15
= 5 mg/m^3

The MRL value is calculated by dividing the $NOAEL_{[HEC]}$ by an uncertainty factor (UF) of 100 (10 for extrapolation from animals to humans and 10 for human variability).

MRL = $NOAEL_{[HEC]}$/UF
= 5 mg/m^3/100
= 0.05 mg/m^3 or 0.01 ppm

In other studies, respiratory irritation has been observed in both rats and mice following acute-, intermediate-, and chronic-duration exposures. Lung

congestion and histopathological lesions of the respiratory tract have also been observed in 4-week and 2-year studies in rats and mice that support the critical end point chosen for the calculation of the intermediate inhalation MRL (Hazleton 1979b, 1979c, 1980c, 1988b).

A chronic-duration inhalation MRL was not calculated. In the chronic inhalation studies conducted by Hazleton (1988b), neurological and immunological effects were observed at the same exposure levels as the NOAEL for respiratory effects. The neurological effects were reported to be concentration-related, duration-related, and were consistently observed in both intermediate- and chronic-duration studies. Decreases in spleen weight consistently occurred in the intermediate-duration studies at the highest concentration tested. In the chronic duration study, male rats exposed to 50 or 600 ppm exhibited a significant decrease in relative spleen weight and no significant changes in spleen weight were observed in mice. Because studies have not been conducted to further examine these organ systems or to determine the mechanism by which vinyl acetate elicits its effect on these systems, it was decided that neurological and immunological effects needed further clarification before a chronic inhalation MRL could be derived.

No oral MRLs were derived for the following reasons:

(1) Although the LOAELs presented in Table 2-2 represent statistically significant differences, they are either of questionable biological significance (e.g., spleen and thymua weight changes without accompanying gross or histopathological changes) or for changes to the Harderian gland (e.g., chronic dacryoadenitis), which are not relevant to humans. In the absence of further definition, neither of these end points provide an appropriate basis for an MRL.

(2) The developmental LOAELs reported are thought to be due to growth retardation in the maternal animals, which is in turn thought to be due to unpalatability of the drinking water. Therefore, these effects are of questionable biological significance as well.

(3) All of the NOAELs reported are “free-standing”. and are thus not an appropriate basis for the calculation of an MRL.

Death. Although no deaths have been reported in humans following exposure to vinyl acetate, this chemical has caused lethality in animals following inhalation, ingestion, or dermal application of high doses. Death in animals is generally associated with adverse respiratory effects and convulsions following inhalation and dermal exposure, but no cause of death has been specified following ingestion of vinyl acetate. Mice appear to be more sensitive to the toxic effects of vinyl acetate than rats, rabbits, or guinea pigs (Goeva 1966; Smyth and Carpenter 1948, 1973). The doses required

to produce death are relatively high. Furthermore, no treatment-related deaths have been observed in chronic inhalation or oral studies (Hazleton 1988a, 1988b). Therefore, it is likely that the risk of death is very small under conditions of long-term, low-level exposure either from ingestion of contaminated food or water or from inhalation of vinyl acetate.

Systemic Effects

Respiratory Effects. The primary systemic target of vinyl acetate toxicity following inhalation exposure in humans and animals is the respiratory system. Acute inhalation exposure of humans to vinyl acetate can cause irritation of the nose and throat (Smyth and Carpenter 1973). Prolonged occupational exposure to vinyl acetate is generally without adverse respiratory effect at levels below 10 ppm (Deese and Joyner 1969).

Respiratory tract damage is characteristic of vinyl acetate exposure in laboratory animals following acute-, intermediate-, or chronic-duration inhalation exposure. Deaths following acute inhalation exposure to vinyl acetate are generally accompanied by evidence of respiratory irritation. Gasping and labored breathing were generally observed in animals prior to death, and necropsy revealed lung congestion and hemorrhage, froth in the trachea, and excess pleural fluid (Smyth and Carpenter 1973; Weil and Carpenter 1969).

Evidence of respiratory irritation and distress was reported in rats and mice during intermediate-duration inhalation exposure to vinyl acetate (Gage 1970; Hazleton 1979b, 1979c, 1980b, 198oc). These clinical signs were not accompanied by changes in lung weight or macroscopic evidence of respiratory tract damage following 4-week exposures. However, an increase in relative lung weight in both rats and mice, presumably due to treatment-related lung congestion, was observed in the high-exposure groups in the 3-month studies (Hazleton 1980b, 1980c). Histopathological evidence of treatment-related respiratory effects was seen in mice following exposure for 3 months (Hazleton 1980b). Mice exposed to 200 ppm vinyl acetate exhibited very mild to slight focal areas of inflammation of the nasal turbinate epithelium and mild multifocal bronchitis. Microscopic examination of mice exposed to 1,000 ppm vinyl acetate revealed focal and diffuse rhinitis with associated exudation and transudation into the nasal passages, metaplasia or hyperplasia of the trachea, multifocal bronchitis, bronchiolitis, multifocal bronchiostania, bronchial epithelial metaplasia and hyperplasia, and occasional bronchiolar or bronchial exudation (Hazleton 1980b). These results indicate that the extrathoracic region is more susceptible to the irritant effects of inhaled vinyl acetate in the mouse than the lower respiratory tract since the effects to the extrathoracic region were observed more commonly at lower exposure concentrations.

Chronic inhalation exposure (104 weeks) of rats and mice to vinyl acetate resulted in clinical and histopathological treatment-related effects

on the respiratory tract similar to those seen with shorter-duration exposures (Hazleton 1988b). In mice the most prominent nasal change was atrophy of the olfactory epithelium at 200 ppm and 600 ppm. Epithelial hyperplasia was also observed in the trachea at 200 and 600 ppm. Changes in the lung were more prominent at higher levels while the larynx was unaffected. In rats, the most prominent lesion was thinning of the nasal olfactory epithelium accompanied by basal cell hyperplasia. Pulmonary changes observed in the higher dose group were mainly in the bronchi and bronchioli and consisted of fibrous plaques and buds protruding into the lumen of the bronchi and bronchioles, covered by normal bronchial epithelium and without obvious evidence of an associated inflammatory response. Taken together, the results of the acute-, intermediate-, and chronic-duration inhalation exposure experiments, indicate that mice may be more susceptible to the toxic effects of vinyl acetate than rats. This is supported, in part, by the higher susceptibility of mice to the lethal effects of vinyl acetate (i.e., a lower LC_{50} value), as discussed in Section 2.2.1.1.

The effects of vinyl acetate on the respiratory tract differ from those seen after exposure to acetaldehyde. Acetaldehyde is a hydrolysis product of vinyl acetate and is also a respiratory irritant. Acetaldehyde was present in the mid- and high-exposure group inhalation chambers in the chronic rat and mouse study at a concentration of 34 and 49 ppm, respectively (Hazleton 1988b). Dreef-van der Meulen (1988b) compared the non-neoplastic changes observed following chronic inhalation exposure of rats to vinyl acetate with those seen after chronic inhalation exposure to 750-3,000 ppm acetaldehyde. Both compounds cause damage to the olfactory epithelium at lower concentrations. However, exposure to higher concentrations of acetaldehyde (1,500-3,000 ppm) also results in damage to the nasal respiratory epithelium, whereas no damage to the nasal respiratory epithelium was found at levels up to 600 ppm vinyl acetate. In addition, vinyl acetate adversely affects the bronchi and lungs, but not the larynx, whereas acetaldehyde induces damage to the laryngeal epithelium but has no effect on the bronchi and lungs. Based on the differences in responses to the two compounds, and the fact that acetaldehyde was not present in the inhalation chambers in the vinyl acetate study at levels that would be expected to result in adverse respiratory effects, it can be concluded that the effects of vinyl acetate on the respiratory tract were most likely not due to the action of its metabolite, acetaldehyde.

In vitro studies have shown that vinyl acetate is ciliatoxic at a total exposure of 4 μg (Battista 1976). Isolated trachea were exposed to 40 mL puffs of air containing vinyl acetate (0.5 μg/puff) for 12 seconds at 1 minute intervals for 8 puffs. Proper functioning of the respiratory tract cilia is essential for mucociliary clearance, which in turn is essential for the maintenance of a normal pulmonary environment. Impairment of ciliary action can lead to accumulation and retention of noxious chemicals within the respiratory tract.

Hepatic Effects. Prolonged occupational exposure to vinyl acetate did not result in any adverse renal effects in humans at levels below 10 ppm (Deese and Joyner 1969). Elevated serum ornithine carbamyl transferase (OCT) levels, which are indicative of liver damage, were measured in one of four guinea pigs administered 500 mg/kg vinyl acetate by intraperitoneal injection (the remaining three died) (DiVincenzo and Krasavage 1974). Decreases in liver weight have been observed in rats and mice exposed to vinyl acetate by inhalation for 3 months and 104 weeks (Hazleton 1980b, 1980c, 1988a), and in rats and mice administered vinyl acetate in the drinking water for 4 weeks and 3 months (rats) (Hazleton 1979d, 1980f). These weight changes were not accompanied by histopathological changes or biochemical evidence of liver damage. The biological significance of a changes in organ weight in the absence of histopathological or functional changes is difficult to ascertain.

Renal Effects. Prolonged occupational exposure to vinyl acetate did not result in any adverse renal effects in humans at levels below 10 ppm (Deese and Joyner 1969). No adverse renal effects were observed in animals exposed to vinyl acetate by inhalation (Hazleton 1979b, 1979c, 1980b, 1980c, 1988b). A decrease in absolute, but not kidney weight relative to body weight was found in male rats administered vinyl acetate in drinking water for 3 months (Hazleton 1980f). An increase in kidney weight relative to body weight was observed in male rats administered vinyl acetate in the drinking water for 104 weeks following in utero exposure (Hazleton 1988a). Decreased and more concentrated urine was observed in female rats administered vinyl acetate in the drinking water for 3 months and in male and female rats exposed via inhalation to vinyl acetate for 3 months or 104 weeks (Hazleton 1980c, 1980f, 1988b). However, no gross or histopathological changes were observed in the kidneys of these animals. The decreased and more concentrated urine was most likely a result of reduced water intake. Therefore, the toxicological significance of the organ weight and urine changes is questionable. The kidney weight changes observed in the chronically treated male rats may have been due to age-related disease processes that normally occur in male rats and were exacerbated by exposure to vinyl acetate. No other adverse renal effects were observed in rats or mice in any other intermediate-or chronic-duration study (Gage 1970; Hazleton 1979b, 1979c, 1979d, 1980b, 1980c, 1980e, 1980f, 1988a, 1988b).

Dermal/Ocular Effects. Acute exposure of humans or animals to vinyl acetate in air can cause irritation of the eyes (Deese and Joyner 1969; Gage 1970; Smyth and Carpenter 1973). These effects are the result of direct contact with vinyl acetate vapor or liquid. Prolonged occupational exposure to vinyl acetate at levels below 10 ppm generally does not cause eye irritation (Deese and Joyner 1969). Dermal application of diluted solutions of vinyl acetate generally does not cause irritation in either humans or animals (Tanaka and Lucas 1984; Weil and Carpenter 1969). However, occupational experience has indicated that some persons might react to dermal contact with vinyl acetate with blister formation, particularly on the thin skin of the finger web and the underside of the wrist, and that continued

contact, such as that afforded by clothing wet with the chemical might result in severe irritation or blistering of the skin (Union Carbide 1958). High doses of vinyl acetate applied to the skin of rabbits has resulted in erythema, edema, and necrosis of the skin (Weil and Carpenter 1969).

Immunological Effects. No studies were located regarding immunological effects in humans after exposure to vinyl acetate. Decreases in thymus and/or spleen weight were consistently noted in rats and mice exposed to vinyl acetate orally or by inhalation for either 4 weeks or 3 months (Hazleton 1979b, 1979c, 1979d, 1980c, 1980b, 1980e). Extramedullary hematopoiesis was observed at an increased incidence over controls in mice receiving vinyl acetate in the drinking water for 3 months (Hazleton 1980e). However, in this study, the incidence of grossly-detectable splenomegaly was not increased in the high-dose animals, and hematopoietic activity was the same as that seen in the control animals. No other histopathological changes were noted in either the spleen or the thymus in any of these studies. These organ weight changes may be suggestive of an immunosuppressive action of vinyl acetate, but the appropriate parameters were not investigated to delineate this possibility.

Neurological Effects. No studies were located regarding neurological effects in humans or animals after exposure to vinyl acetate. All rats and mice exposed by inhalation to at least the highest concentration of vinyl acetate for 4 weeks, 3 months, and 104 weeks exhibited hunched posture and ruffled fur (Hazleton 1979b, 1979c, 1980b, 1980c, 1988b). A dose-related increase in the incidence of head tilt was also noted in some rats and mice exposed by inhalation to vinyl acetate for 104 weeks (Hazleton 1988b). It is possible that these neurological signs were secondary to the poor health of the animals following inhalation exposure, and may not be indicative of a primary effect of vinyl acetate on the nervous system. These neurological signs were not seen in animals that were orally administered vfnyl acetate, and no other treatment-related clinical or histopathological signs of neurotoxicity have been observed in rats or mice exposed to vinyl acetate (Hazleton 1979b, 1979c, 1979d, 1980b, 198Oc, 1980e, 1980f, 1988a, 1988b). However, neurobehavioral toxicity often occurs in the absence of other clinical or histopathological signs of neurotoxicity, so it is not known if exposure to vinyl acetate is likely to result in any adverse neurological effects in humans.

Developmental Effects. No studies were located regarding developmental effects in humans after exposure to vinyl acetate. Growth retardation and delayed ossification have been observed in pups born to rats exposed to vinyl acetate via inhalation during gestation days 6-15 (Hazleton 1980d). Growth retardation was also observed in pups following oral exposure of rats to vinyl acetate during the pre-mating, gestation, and lactation periods (Hazleton 1987). These effects may be secondary to the reduced body weight gain that occurred in the maternal animals. No other adverse developmental effects have been observed in animals following inhalation or oral exposure to vinyl

acetate. Based on the results obtained in animals, vinyl acetate is unlikely to cause adverse developmental effects in humans at exposure concentrations below those that would cause maternal toxicity.

Reproductive Effects. No studies were located regarding reproductive effects in humans after exposure to vinyl acetate. A marginal reduction in the number of pregnancies was observed in the F_1 female rats administered vinyl acetate in the drinking water in a two-generation study (Hazleton 1987). However, this difference was not statistically significant and the pregnancy incidence in the treated animals was reported to be within the range of historical controls. With the exception of a decrease in relative testes weight which was not dose-related and not accompanied by any histopathological changes in mice administered vinyl acetate in the drinking water for 3 months (Hazleton 1980e), no other gross or histopathological changes in either male or female reproductive organs were observed in rats or mice administered vinyl acetate by inhalation or oral administration (Hazleton 1980b, 1980c, 1980d, 1980e, 1980f, 1987, 1988a, 1988b). Reduced testicular weight and increased sperm abnormalities were reported in male mice given intraperitoneal injections of 125 mg/kg/day and 500 mg/kg/day, respectively (Lahdetie 1988). The authors concluded that in mice, vinyl acetate impaired sperm production in the testis, but did not appear to affect its endocrine function. However, the adverse male reproductive effects may have been a result of the decreased body weight also observed in these animals. Some of the effects (i.e., reduced testicular weight) were not dose-related, and the route of administration is not relevant to human exposure. Given the limitations associated with this study, and the fact that no adverse effect on reproductive performance or histopathology of the reproductive organs has been seen following inhalation or oral exposure of animals to vinyl acetate, the relevance of the effects to human health is not known,

Genotoxicity. Vinyl acetate has been evaluated for genotoxicity in a variety of *in vitro* and *in vivo* assays. As summarized in Tables 2-5 and 2-6, the results of these assays in microorganisms have been negative, but the majority of mutagenicity tests in mammalian cells have been positive.

The mutagenicity of vinyl acetate has been demonstrated in several *in vitro* studies. In cultured human lymphocytes and whole blood, dosedependent increases in the induction of chromosomal aberrations (Jantunen et al. 1986; Norppa et al. 1985), sister chromatid exchanges (He and Lambert 1985; Norppa et al. 1985), micronuclei (Maki-Paakkanen and Norppa 1987; Norppa et al. 1988), and DNA cross-links (Lambert et al. 1985) have been observed. Vinyl acetate also induced a dose-dependent increase in sister chromatid exchanges in Chinese hamster ovary cells with and without metabolic activation (Norppa et al. 1985), and has enhanced adenovirus transformation of Syrian hamster fetal cells (Casto 1980, 1981). Thus, vinyl acetate has demonstrated clastogenicity in mammalian cells, which was more pronounced in isolated human lymphocytes than in lymphocytes in whole blood (Jantunen et al. 1986; Norppa

TABLE 2-5. Genotoxicity of Vinyl Acetate *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	References
Prokaryotic organisms:				
Salmonella typhimurium TA98, TA100, TA1530	Gene mutation	-	-	Bartsch et al. 1976, 1980
S. typhimurium TA98, TA100, TA1535, TA1537, TA 1538	Gene mutation	-	-	Florin et al. 1980; Lijinsky and Andrews 1980; McCann et al. 1975
S. typhimurium TA1530, TA100	Gene mutation	-	-	Bartsch et al. 1979
S. typhimurium TA100	Gene mutation	-	-	Barbin et al. 1978
Mammalian cells:				
Cultured human lymphocytes	Micronuclei	No data	+	Maki-Paakkanen and Norppa 1987; Norppa et al. 1988
Cultured human lymphocytes	Chromosomal aberrations	No data	+	Jantunen et al. 1986; Norppa et al. 1985;
Cultured human lymphocytes	Sister chromatid exchange	No data	+	He and Lambert 1985; Norppa et al. 1985
Cultured human lymphocytes	DNA cross-links	No data	+	Lambert et al. 1985
Cultured hamster fetal cells	Adenovirus transformation	No data	+	Casto 1980, 1981
Chinese hamster ovary cells	Sister chromatid exchange	+	+	Norppa et al. 1985

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

TABLE 2-6. Genotoxicity of Vinyl Acetate In Vivo

Species (test system)	End point	Results	Reference
Mammalian cells:			
Mouse spermatogonial cells	Meiotic micronucleus assay	-	Lahdetie 1988
Rat hepatic cells	DNA-adducts	-	Simon et al. 1985b
Mouse bone marrow polychromatic-erythrocyte assay (micronucleus test)	Micronuclei	+	Maki-Paakkanen and Norppa 1987; Norppa et al. 1988; Hazleton 1979d
		-	Hazleton 1979b, 1980b
Rat bone marrow polychromatic-erythrocyte assay (micronucleus test)	Micronuclei	-	Hazleton 1979c, 1979d, 1980c
Mouse bone marrow	Sister chromatid exchange	+	Takeshita et al. 1986

DNA = deoxyribonucleic acid; - = negative; + = positive

et al. 1985). However, no mutagenic effects have been reported in bacterial assays with the Salmonella typhimurium strains TA98, TA100, TA1530, TA1535, TA1537, or TA1538 with or without metabolic activation (Barbin et al. 1978; Bartsch et al. 1976; 1979, 1980; Florin et al. 1980; Lijinsky and Andrews 1980; McCann et al. 1975). These results indicate that vinyl acetate damage to the genome occurs at the chromosome level, rather than at the gene level.

In vivo, vinyl acetate induced a dose-dependent increase in micronucleated polychromatic erythrocytes in mouse bone marrow cells following a single intraperitoneal injection (Maki-Paakkanen and Norppa 1987; Norppa et al. 1988). However, no treatment-related effect on the incidence of micronuclei was seen in erythrocytes taken from bone marrow smears of animals exposed to vinyl acetate by either inhalation or ingestion (Hazleton 1979b, 1979c, 1979d, 1980b, 1980c). A small dose-related increase in sister chromatid exchanges was observed in the bone marrow cells of hepatectomized and non-hepatectomized mice injected intraperitoneally with vinyl acetate (Takeshita et al. 1986). However, vinyl acetate failed to produce specific DNA-adducts in rat liver following treatment by gavage or by inhalation (Simon et al. 1985b) and did not induce an increase in the.occurrence of micronuclei in the spermatogonial cells of mice following intraperitoneal injection compared to positive controls (Lahdetie 1988). These discrepant results may be due to the tissue distribution of vinyl acetate, route of administration, species differences, the duration of the cell cycles and recovery time of induced damage, and differences in sensitivity of the cell types to
cytotoxicity.

Cancer. No reports of cancer in humans associated with exposure to vinyl acetate have been found. The carcinogenicity of vinyl acetate has been studied in chronic bioassays using Sprague-Dawley and Fischer-344 rats and CD-1 mice (Hazleton 1988a, 1988b; NCI 1982a). Slides of the respiratory tract of the rats and mice from the chronic Hazleton (1988b) inhalation study were reevaluated by Beems (1988) (mice) and Dreef-van der Meulen (1988b) (rats). Tumors were not observed in the lungs or trachea of the exposed rats, but one squamous cell carcinoma of the larynx and twelve nasal tumors were found in this species. Out of twelve, five benign papillomas were found in exposed male rats while seven malignant carcinomas were found in rats of both sexes. Bronchiolar-alveolar adenomas were found in the lungs of both the exposed and control mice at comparable incidences, indicating that their occurrence was not a result of exposure to vinyl acetate. No tumors were seen in the nose, larynx, or trachea of either exposed or control mice. Therefore, either the tumorigenic effect of vinyl acetate is species specific, or the mouse is not as sensitive to the tumorigenic effects of vinyl acetate, and higher exposure levels may be needed to see this effect in mice. It is not known if the increased incidence of nasal cavity tumors seen in rats exposed to vinyl acetate is the result of repeated cell proliferation, or whether a genotoxic mechanism is involved. Respiratory tract tumors in rodents exposed to high levels of irritating vapors that cause cell proliferation are common (Cohen

and Ellwein 1990). If the carcinogenic response to inhalation of vinyl acetate vapor is a result of cell proliferation resulting from irritation and not a genotoxic mechanism, then the risk of cancer to humans exposed to low, nonirritating levels of vinyl acetate vapor should be minimal.

Vinyl acetate is metabolized to acetaldehyde, which is an animal carcinogen following inhalation exposure. Dreef-van der Meulen (1988b) compared the neoplastic changes observed following chronic inhalation exposure of rats to vinyl acetate with those seen after chronic inhalation exposure to acetaldehyde. In the vinyl acetate study, benign and malignant nasal tumors (papillomas and squamous cell carcinomas) were seen with no preferential site of origin (i.e., olfactory or respiratory epithelium). Acetaldehyde induced squamous cell carcinomas of the nasal respiratory epithelium and adenocarcinomas of the olfactory epithelium following inhalation exposure. Both are believed to be the result of acetaldehyde's cytotoxic effects on the epithelium. Therefore, the carcinogenic response to the two compounds differs in, the type and site of origin of nasal tumors as well as the fact that acetaldehyde-induced nasal tumors arose from severely damaged epithelium whereas vinyl acetate-induced tumors arose from epithelium that did not show any signs of damage. Vinyl acetate-damaged olfactory epithelium did not give rise to adenocarcinomas, whereas adenocarcinomas from severely damaged olfactory epithelium were the predominant response to acetaldehyde. Furthermore, these carcinogenic responses to acetaldehyde were not seen at exposure concentrations below 1,500 ppm, whereas the levels of acetaldehyde present in the inhalation chambers in the vinyl acetate study were only 34 and 49 ppm. These observations suggest that neither acetaldehyde or cytotoxicity was involved in the induction of nasal tumors in rats exposed to vinyl acetate in the Hazleton (1988b) study (Dreef-van der Meulen 1988b).

A statistically significant carcinogenic effect of vinyl acetate was observed in a screening study in which this chemical was administered in the drinking water of Fischer-344 rats for 100 weeks (Lijinsky and Reuber 1983; NCI 1982a). Tumor incidences that were significantly increased in the treated animals as compared to the controls included neoplastic nodules of the liver in both sexes, adenocarcinomas of the uterus in the females, and C-cell adenomas or carcinomas of the thyroid in both sexes, but predominantly in the females. There were many limitations associated with this study, as discussed in Section 2.2.2.8. Because of these limitations, Lijinsky and Reuber (1983) concluded that the study needed to be repeated with larger numbers of animals per group, higher dose levels, and vinyl acetate solutions that are prepared fresh daily before definitive conclusions regarding the carcinogenicity of vinyl acetate following oral exposure can be made.

In a later study, Sprague-Dawley rats that received higher doses of vinyl acetate in their drinking water for 104 weeks following <u>in utero</u> exposure than those used by Lijinsky and Reuber (1983) developed tumors, but they were not considered by the authors to be treatment-related, since they occurred at a similar incidence in the high-dose animals as in the controls,

and were commonly occurring tumors in aging Sprague-Dawley rats (Hazleton 1988a). Two squamous cell carcinomas of the oral mucosa were observed in the treated animals, but the incidence was not statistically significant, and the study authors considered them to be a result of tooth-related problems (Hazleton 1988b). Therefore, this study provides no evidence for the carcinogenicity of vinyl acetate following exposure in the drinking water. The negative data obtained from this study should be given more weight than the positive data obtained from the Lijinsky and Reuber (1983; NCI 1982) screening study because many of the limitations associated with the earlier study were remedied in the Hazleton (1988a) study, as discussed in Section 2.2.2.8.

Prior to the Hazleton (1988a) study, IARC (1986) had concluded that there is inadequate evidence for the carcinogenicity of vinyl acetate in humans or animals.

Results of genotoxicity studies are mixed, but generally provide evidence that vinyl acetate is clastogenic and indicate that vinyl acetate damage to the genome occurs at the chromosome level, rather than at the gene level. Therefore, based on the positive results summarized above for inhalation exposure, and the generally positive genotoxicity results, vinyl acetate may pose a carcinogenic risk to humans.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecules or cells that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluids or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances, that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to vinyl acetate are discussed in Section 2.5.1.

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

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

2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to Vinyl Acetate

Metabolic studies demonstrate that vinyl acetate is effectively hydrolyzed by esterases in the blood to vinyl alcohol and acetate. The vinyl alcohol is subsequently converted to acetaldehyde (Hazleton 1979a; Hazleton 1980a; Simon et al. 1985a). Acetaldehyde is subsequently metabolized to acetate in the liver. Acetate enters normal metabolic pathways and is broken down to carbon dioxide which is eliminated in expired air. Because the metabolism of vinyl acetate occurs rapidly (*in vivo* tests indicate that most is eliminated within 24 hours after exposure), it would be difficult to measure the presence of vinyl acetate or acetaldehyde for reasonable periods following exposure to vinyl acetate. Likewise, other metabolites would not be useful because these are incorporated into normal metabolic pathways, making it impossible to determine which metabolites were due to vinyl acetate exposure and which were present as a result of normal metabolic processes.

2.5.2 Biomarkers Used to Characterize Effects Caused by Vinyl Acetate

Numerous positive genotoxic end points in human lymphocytes (e.g., micronuclei,' chromosomal aberrations, sister chromatid exchange, and DNA cross-links) have been associated with exposure to vinyl acetate. However, because these results are from *in vitro* tests and because many other commonly encountered chemicals and factors (e.g., smoking) may also cause these same abnormalities, these changes cannot be considered specific biomarkers of effects caused by vinyl acetate. Another possibility is to use protein or hemoglobin adducts of acetaldehyde as a marker of effect for vinyl acetate. Stable protein-acetaldehyde adducts (Izumi et al. 1988; Lin and Lumeng 1988) and hemoglobin-acetaldehyde adducts (Peterson et al. 1988) have been shown to

be formed following chronic alcohol ingestion. Since vinyl acetate does not form adducts with DNA, this type of marker is also not available to serve as a marker for effect. No other biomarkers (specific or otherwise) have been identified to indicate exposure to vinyl acetate.

2.6 INTERACTIONS WITH OTHER CHEMICALS

There are no chemicals known that influence the toxicity of vinyl acetate in the body.

2.7 POPULATIONS THAT AEE UNUSUALLY SUSCEPTIBLE

Individuals with existing problems in the upper respiratory tract, eyes, and, possibly, skin may be unusually susceptible to effects associated with exposure to vinyl acetate, based on its irritant properties. Preplacement medical examinations to identify such conditions have been recommended for people who may be occupationally exposed to vinyl acetate (NIOSH 1978). Smokers may represent another potentially susceptible subpopulation because vinyl acetate is a respiratory irritant. In addition, vinyl acetate has been shown to have an effect on mucociliary clearance similar to that of nicotine, so the combined effects of vinyl acetate and nicotine in smokers could result in enhanced impairment of respiratory function (Battista 1976).

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to vinyl acetate. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to vinyl acetate. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

Methods for enhancing the elimination of vinyl acetate are not known; however, the relatively short half-life of vinyl acetate in the body may obviate the need to enhance elimination. Furthermore, the mechanism of action by which vinyl acetate produces toxic effects is undetermined. Therefore, the main objective of treating vinyl acetate exposure is to decrease absorption.

Human exposure to vinyl acetate may occur by inhalation, ingestion, or by dermal contact. Vinyl acetate is a respiratory irritant and acute high-dose inhalation exposure may result in respiratory distress requiring the administration of oxygen and ventilation assistance. Treatment for pulmonary

edema may be necessary (Bronstein and Currance 1988; Stutz and Janusz 1988). Administration of water or milk for dilution has been suggested; however, it is not clear whether such treatment would reduce absorption (it may simply reduce irritant effects on the stomach). Gastrointestinal absorption is decreased by administration of activated charcoal (Stutz and Janusz 1988). Cathartics such as magnesium sulfate are also used to accelerate the fecal excretion of ingested vinyl acetate (Stutz and Janusz 1988). Some medical toxicologists advise against the use of emetics to induce vomiting following oral exposure to vinyl acetate (Bronstein and Currance 1988). Dermal exposure to concentrated solutions of vinyl acetate has resulted in blister formation. Procedures that have been employed to reduce the irritating effects and dermal absorption of vinyl acetate following dermal exposure include removal of contaminated clothing and promptly flushing the skin with copious amount of water followed by thorough washing with soap and water (Stutz and Janusz 1988). If the eyes have been exposed, they should be thoroughly irrigated with water (Stutz and Janusz 1988)

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of vinyl acetate is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of vinyl acetate.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of Vinyl Acetate

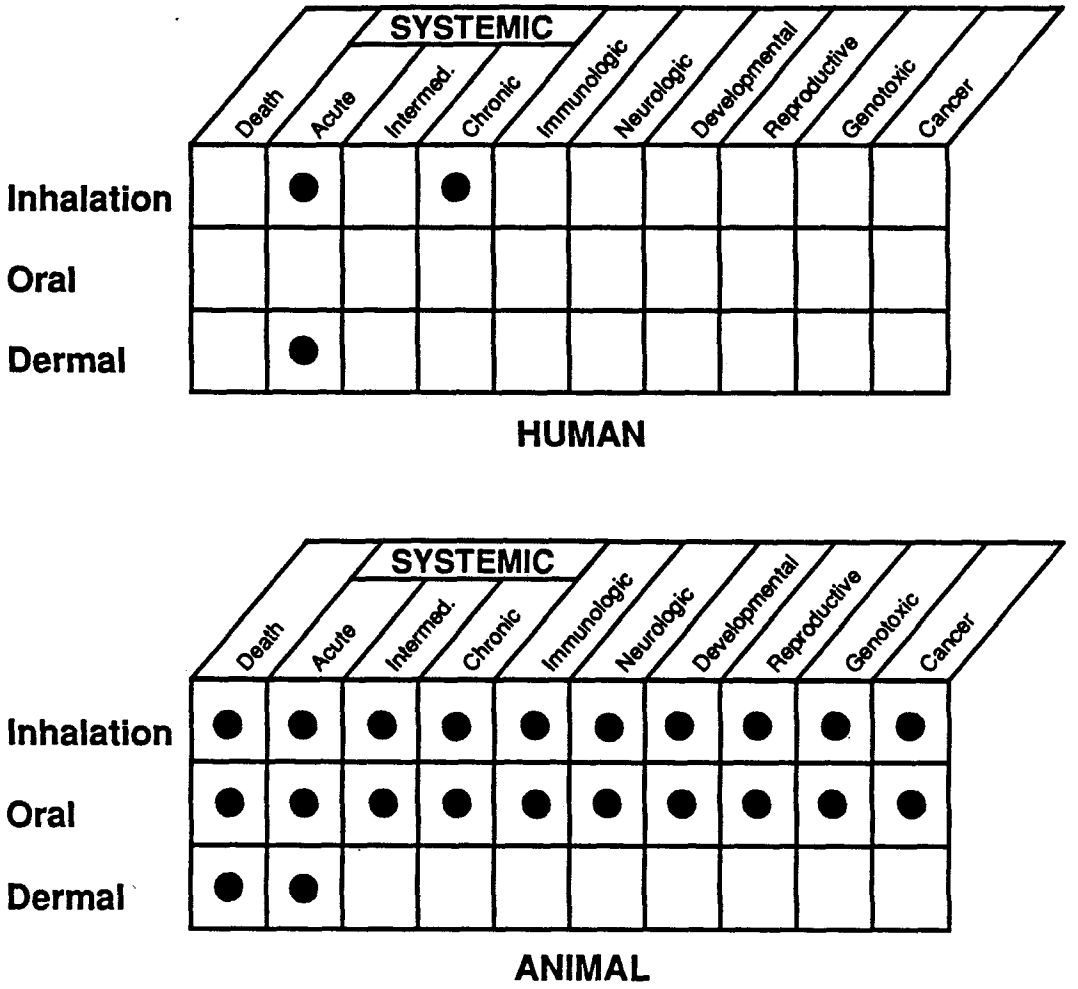
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to vinyl acetate are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of vinyl acetate. Each dot in the figure indicates that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

The only literature available concerning the health effects of vinyl acetate in humans described the results of a controlled study utilizing volunteers and also one occupational study. The route of exposure in these reports was inhalation, but the possibility of some degree of dermal or oral exposure cannot be ruled out. The information on human exposure is limited because of the small sample size employed in these studies.

The database for the health effects of vinyl acetate following inhalation or ingestion in experimental animals consists almost entirely of unpublished reports. Many of the oral studies failed to provide any dose-response information, as the highest dose tested was often without unequivocally treatment-related adverse effect. As can be seen in Figure 2-4, very little information is available on the systemic effects of dermal exposure to vinyl acetate in animals.

Populations living in areas surrounding hazardous waste sites may be exposed to vinyl acetate through inhalation of contaminated air and ingestion of or dermal contact with contaminated water; the latter route may be particularly important for populations living near certain types of disposal sites (e.g., underground injection sites). The relative importance of these pathways in terms of human exposure potential is difficult to establish given the limited monitoring data available for vinyl acetate. Most people, however, are exposed to very small amounts of vinyl acetate through: (1) inhalation of contaminated ambient air and cigarette smoke; (2) dermal contact with products containing the compound (e.g., glues and paints); and (3) ingestion of residual vinyl acetate monomers in food (i.e., that may have migrated from plastic food wraps) or food items containing the compound as a starch modifier. Occupational exposure to vinyl acetate occurs via inhalation of contaminated workplace air and by dermal contact with vinyl acetate vapor or liquids and products containing the compound.

FIGURE 2-4. Existing Information on Health Effects of Vinyl Acetate



2.9.2 Data Needs

Acute-Duration Exposure. Information is available regarding the effects of acute-duration exposure in humans following inhalation and dermal exposure and in animals following exposure by all routes. Vinyl acetate may be lethal to animals by all routes of exposure studied, depending on the dose (Goeva 1966; Smyth and Carpenter 1948; Weil and Carpenter 1969). Only limited information exists on the systemic effects of vinyl acetate following acute exposure. Respiratory effects occur in humans and animals following acute inhalation exposure (Deese and Joyner 1969; Hazleton 1980d; Smyth and Carpenter 1973; Weil and Carpenter 1969). However, since few quantitative human and animal data exist, an acute inhalation MRL was not derived. Although vinyl acetate can be lethal following ingestion (Goeva 1966; Smyth and Carpenter 1948), acute oral exposure studies failed to identify a specific target system in animals. The data in animals are insufficient to derive an acute oral MRL for vinyl acetate. Only dermal and ocular effects have been investigated following dermal exposure (Industrial Biotest 1972; Tanaka and Lucas 1984; Weil and Carpenter 1969). However, necropsy data from rabbits dermally administered lethal levels of vinyl acetate revealed congestion of the lung and liver, mottled spleen and kidney, and prominent liver acini (Weil and Carpenter 1969). The available toxicokinetic data are not adequate to predict whether the behavior of vinyl acetate following dermal exposure would be similar to that seen following inhalation or oral exposure. Since the data suggest that respiratory tract irritation and/or damage is the most likely adverse effect following acute inhalation exposure to vinyl acetate, and since inhalation is the most likely route of exposure to vinyl acetate, additional studies on the acute effects of vinyl acetate following exposure by any route may not be necessary.

Intermediate-Duration Exposure. No information is available on the toxicity of vinyl acetate to humans following intermediate-duration exposure by any route. The main target of toxicity in animals following intermediate-duration inhalation exposure is the respiratory tract (Gage 1970; Hazleton 1979b, 1979c, 1980b, 1980c). With the possible exception of the immune and nervous systems (Hazleton 1979d, 1980f), no other organ system appears to be adversely affected by inhalation exposure to vinyl acetate. An intermediate inhalation MRL of 0.01 ppm was calculated based on a NOAEL of 50 ppm for respiratory effects in mice exposed to vinyl acetate for 3 months (Hazleton 1980b). Intermediate oral exposure studies failed to identify a specific target system in animals. With the exception of organ weight changes that were not accompanied by histopathological changes (Hazleton 1979d, 1980e, 1980f), no adverse health effects were observed in animals at the doses tested. Therefore, the data are insufficient to calculate an intermediate oral MRL. The available toxicokinetic data are not adequate to predict whether the behavior of vinyl acetate following dermal exposure would be similar *to* that seen following inhalation or oral exposure. Since it has been

consistently found that the major adverse effects seen after intermediate-duration inhalation exposure to vinyl acetate in animals is respiratory tract irritation and damage, and since this is the most likely route of exposure to vinyl acetate, additional studies on the intermediate effects of vinyl acetate following exposure by any route may not be necessary.

Chronic-Duration Exposure and Cancer. One occupational study investigated limited parameters following chronic-duration inhalation exposure (15.2 years) to vinyl acetate in humans (Deese and Joyner 1969). No epidemiological studies examining carcinogenicity in humans have been conducted. Information is available regarding the effects of chronic-duration exposure in animals following inhalation and oral exposure. The most noted adverse effect in rats and mice following chronic inhalation exposure was respiratory tract damage (Beems 1988; Dreef-Van der Muelen 1988b; Hazleton 1988b). In the chronic inhalation studies conducted by Hazleton (1988b), neurological and immunological effects were observed at the same exposure levels as the NOAEL for respiratory effects. Because studies have not been conducted to further examine these organ systems or to determine the mechanism by which vinyl acetate elicits its effect on these systems, it was decided that neurological and immunological effects needed further clarification before a chronic inhalation MRL could be derived. No organ system appears to be adversely affected by chronic-duration oral exposure to vinyl acetate in animals. Reduced weight gains (in both adults and fetuses) (Hazleton 1987) and kidney weight changes (Hazleton 1988a) have been observed following chronic oral exposure, but the organ weight changes were not accompanied by any functional or morphological changes, and the body weight changes were most likely due to unpalatability of the drinking water solution containing vinyl acetate. The marginal reduction in pregnancies observed in the two-generation drinking water study was only apparent in one generation, was within the range of historical control data, and was therefore of questionable toxicological significance (Hazleton 1987). The data are insufficient to calculate a chronic oral MRL because no specific target organ could be identified at the doses of vinyl acetate tested. No studies were located on health effects resulting from chronic dermal exposure. The available toxicokinetic data are not adequate to predict whether the behavior of vinyl acetate following dermal exposure would be similar to that seen following inhalation or oral exposure. Since inhalation is the most likely route of exposure to vinyl acetate, additional studies on the chronic effects of vinyl acetate following oral and dermal exposure may not be necessary.

No reports of cancer in humans associated with exposure to vinyl acetate by any route have been found. The carcinogenicity of vinyl acetate has been studied in chronic bioassays using rats (inhalation and oral) and mice (inhalation only) (Hazleton 1988a, 1988b; Lijinsky and Reuber 1983; NCI 1982a). The available data in experimental animals were positive for inhalation exposure (in rats only) and negative or inconclusive for oral exposure (Hazleton 1988a, 1988b; NCI 1982a). Although the NCI

(1982a)/Lijinsky and Reuber (1983) oral bioassay provided suggestive evidence for carcinogenic effects of vinyl acetate, there were many limitations (refer to Section 2.2.2.8) with the study that rendered it inadequate for drawing definitive conclusions regarding the carcinogenicity of vinyl acetate following oral exposure. No significant increase in tumor incidence was seen in an oral study in which the animals were exposed to higher doses of vinyl acetate (both in utero and for 104 weeks after birth in the drinking water) than those in the NCI (1982a)/Lijinsky and Reuber (1983) bioassay (Hazleton 1988b). Therefore, this study provides no evidence for the carcinogenicity of vinyl acetate following exposure in the drinking water (Hazleton 1988a). The nasal cavity tumors seen in rats in the chronic inhalation bioassay (Hazleton 1988b) were-treatment related. It is impossible at this time to speculate on the carcinogenic potential of vinyl acetate in humans by any route of exposure. Since inhalation is the most likely route of exposure to vinyl acetate, an additional well-conducted 2-year inhalation bioassay would provide valuable information on whether vinyl acetate has the potential to be carcinogenic in humans.

Genotoxicity. Vinyl acetate has been evaluated for genotoxicity in a variety of in vitro and in vivo assays (Bartsch et al. 1976, 1979, 1980; Lahdetie 1988; Maki-Paakkanen and Norppa 1987; Norppa et al. 1985, 1988; Simon et al. 1985b; Takeshita et al. 1986). The results are mixed, but generally provide evidence that this compound is clastogenic (Jantunen et al. 1986; Norppa et al. 1985) and indicate that vinyl acetate damage to the genome occurs at the chromosome level, rather than at the gene level (Barbin et al. 1978; Bartsch et al. 1976, 1979, 1980; Florin et al. 1980; Lijinsky and Andrews 1980; McCann et al. 1975). Since conflicting results were obtained in in vivo studies (Hazleton 1979b, 1979c, 1979d, 1980b, 198Oc; Lahdetie et al. 1988; Maki-Paakkanen and Norppa 1987; Norppa et al. 1988; Simon et al. 1985b; Takeshita et al. 1986), further animal testing may help resolve whether vinyl acetate has the potential to be genotoxic in humans, and the mechanism by which it may induce these effects.

Reproductive Toxicity. No information is available in humans to indicate that vinyl acetate affects reproductive function. A marginal reduction in the number of pregnancies was observed in F_1 female rats administered vinyl acetate in a two-generation study (Hazleton 1987). However, this difference was not statistically significant, occurred in only one generation, and the pregnancy incidence was reported to be within the range of historical controls. No other effects on reproductive performance were observed in this study. Decreased relative testes weight was observed in male mice administered vinyl acetate in the drinking water for 3 months, this effect was not seen at higher doses and no gross or histopathological changes were observed in the testes of these animals (Hazleton 1980e). No histopathological changes in either male or female reproductive organs were observed in rats or mice following inhalation or oral exposure to vinyl acetate (Hazleton 1987). However, a two-generation inhalation study has not

been conducted. No information is available on the reproductive effects of dermally administered vinyl acetate. Therefore, although the available reproductive studies indicate that vinyl acetate probably has no adverse effects on reproductive performance in animals following oral exposure, further investigation is warranted to clarify whether this chemical has the potential to affect reproduction 'in humans. Any additional reproductive toxicity testing should be by the inhalation route of exposure since limited information exists on reproductive performance following exposure to vinyl acetate by this route and because it is most relevant for humans living in the vicinity of hazardous waste sites.

Developmental Toxicity. No information is available in humans to indicate that vinyl acetate affects fetal development. Growth retardation and delayed ossification have been observed in pups born to rats exposed to vinyl acetate via inhalation for an acute duration, and growth retardation was also observed in pups following oral exposure of rats to vinyl acetate in a two generation study(Hazleton 1980d, 1987). These effects were observed at levels causing decreased body weight gain in dams. No other adverse developmental effects have been observed in animals following oral exposure to vinyl acetate. Any additional developmental toxicity testing should be by the inhalation route of exposure since limited information exists on developmental toxicity following exposure to vinyl acetate by this route and it is the most relevant route for humans living in the vicinity of hazardous waste sites.

Immunotoxicity. No information is available on the immunological effects of vinyl acetate in humans or animals by any route of exposure. Reductions in thymus and/or spleen weight were consistently noted in rats and mice exposed to vinyl acetate for either 4 weeks or 3 months (Hazleton 1979b, 1979c, 1979d, 1980b, 1980c, 1980e). Furthermore, an increased incidence of extramedullary hematopoiesis was observed in mice receiving vinyl acetate in the drinking water for 3 months (Hazleton 1980e). These changes may be indicative of an immunosuppressive action of vinyl acetate, but the appropriate parameters need to be investigated to delineate this possibility. Therefore, additional studies that examine sensitive parameters of immunological function following inhalation exposure, since this is the most likely route of human exposure, would be useful to more fully assess the immunotoxic potential of vinyl acetate.

Neurotoxicity. No studies were located regarding neurological effects in humans or animals after exposure to vinyl acetate. Hunched posture, ruffled fur, and head tilt were observed in animals exposed by inhalation to vinyl acetate. No other treatment-related clinical or histopathological evidence of neurotoxicity has been observed in rats or mice exposed to vinyl acetate (Hazleton 1979b, 1979c, 1979d, 1980b, 1980c, 1980e, 1980f, 1988a, 1988b). Therefore, although it appears that the nervous system may be a target of vinyl acetate toxicity following inhalation exposure, further testing by the inhalation route employing more sensitive measurements of

functional neurotoxicity and neuropathology would be useful, given the clinical signs noted in the inhalation studies.

Epidemiological and Human Dosimetry Studies. Only two studies were found concerning the health effects of vinyl acetate in humans. Both assessed the occurrence of respiratory and ocular irritation following either acute (Smyth and Carpenter 1973) or long-term occupational exposure (Deese and Joyner 1969), and are limited by the small sample size studied. The most likely identifiable subpopulation exposed to vinyl acetate is chemical workers involved in its production and use. Results of animal inhalation studies indicate that the respiratory and nervous systems and possibly the immune system are adversely affected by vinyl acetate (Beems 1988; Dreef-Van der Meulen 1988b; Gage 1970; Hazleton 1979b, 1979c, 1980b, 1980c, 1988b), well designed epidemiological studies of exposed workers that specifically examine the effects of vinyl acetate on these systems would be especially useful to further characterize the extent of possible injury to these systems in humans. More definitive characterization of the adverse effects of vinyl acetate in humans may be useful as a tool to monitor vinyl acetate exposure in individuals living near hazardous waste sites.

Biomarkers of Exposure and Effect. Metabolic studies have shown that vinyl acetate is quickly hydrolyzed to acetaldehyde and acetate, which then enters normal metabolic cycles to produce primarily carbon dioxide and water (Hazleton 1979a; Simon et al. 1985a). A small amount also has been shown to be excreted in the urine as urea and other unidentified metabolites (Hazleton 1980a). Because of the relatively rapid hydrolysis and the fact that metabolites are incorporated into normal metabolic pathways, it would be difficult to use vinyl acetate metabolites as biomarkers of exposure to this chemical (Hazleton 1979a; Simon et al. 1985a).

Exposure to vinyl acetate in vitro has been shown to result in various positive genotoxic end points in human lymphocytes (e.g., micronuclei, chromosomal aberrations, sister chromatid exchange, and DNA cross-links) (He and Lambert 1985; Jantunen et al. 1986; Lambert et al. 1985; Maki-Paakkanen and Norppa 1987; Norppa et al. 1985, 1988). Because these results are from in vitro tests and because many other chemicals may induce such abnormalities, these should not be considered specific biomarkers of the effects of vinyl acetate. Another possibility is to use protein or hemoglobin adducts of acetaldehyde as a marker of effect for vinyl acetate. Stable proteinacetaldehyde adducts (Izumi et al. 1988; Lin and Lumeng 1988) and hemoglobinacetaldehyde adducts (Peterson et al. 1988) have been shown to be formed following chronic alcohol ingestion. Since vinyl acetate does not form adducts with DNA, this type of marker is also not usable as a marker for effect. No other biomarkers (specific or otherwise) have been identified following exposure to vinyl acetate. Additional animal or epidemiological studies that measure changes in body fluids or enzyme levels following vinyl

acetate exposure would be useful to determine if such biomarkers exist and to devise sensitive and specific early biomarkers of effect.

Absorption, Distribution, Metabolism, and Excretion. No information is available to assess the relative rates and extent of vinyl acetate absorption following exposure by any route in humans. Quantitative and qualitative evidence indicates that vinyl acetate is rapidly and efficiently absorbed by laboratory animals following inhalation and oral exposures (Hazleton 1979a, 1980a). Qualitative evidence also indicates that vinyl acetate penetrates the skin of rabbits (Smyth and Carpenter 1948; Weil and Carpenter 1969). Given the clear evidence across different animal species, it may be assumed that similar absorption would occur in humans. Studies designed to investigate the extent of absorption following dermal exposure would be helpful.

No studies were available in humans describing the distribution of vinyl acetate following exposure by any route. Animal studies indicate that vinyl acetate is rapidly and widely distributed throughout the body following inhalation and oral exposure (Hazleton 1979a, 1980a). In these studies, vinyl acetate was primarily distributed to the Harderian glands, lacrimal glands, salivary glands, gastrointestinal mucosa, kidney, and larynges. No data on the distribution of vinyl acetate following dermal exposure were located. Such information would be useful because absorption via this route has been shown to occur and because dermal exposure is a probable route of exposure for humans.

No in vivo studies were available in humans describing the metabolism of vinyl acetate following exposure by any route. The metabolism of vinyl acetate has been characterized in animals. Studies in animals have shown nonlinear kinetic patterns at high concentrations, indicating that the metabolic process is saturable (Simon et al. 1985a). The metabolic pattern was not different following oral or inhalation exposure (Hazleton 1980a). Information on the metabolism of vinyl acetate following dermal exposure would be useful.

No studies were available in humans describing the excretion of vinyl acetate following exposure by any route. Vinyl acetate has been shown to be rapidly eliminated from the body following oral and inhalation exposure in animals (Hazleton 1979a, 1980a). Most of the vinyl acetate is eliminated in expired air as carbon dioxide but small amounts have also been excreted in the urine and feces (Hazleton 1979a, 1980a). Differences in the amount of radioactivity eliminated in exhaled air following oral and inhalation exposure to radiolabeled vinyl acetate have been minor (Hazleton 1979a, 1980a). No data on the elimination of vinyl acetate following dermal exposure were located.

Comparative Toxicokinetics. No data are available on the toxicokinetics of vinyl acetate in humans. However, quantitative and qualitative information

on the absorption and metabolism of vinyl acetate in rats and mice following oral and inhalation exposure indicates that little variation exists between these two species (Hazleton 1979a, 1980a). However, there does appear to be some variation across routes of exposure in the distribution and excretion patterns of vinyl acetate (Hazleton 1979a, 1980a). There were some minor differences in the distribution pattern between the sexes (Hazleton 1979a, 1980a). No studies are available that investigate the kinetics of vinyl acetate following dermal exposure. Therefore, studies that investigate the toxicokinetics of vinyl acetate in animals following dermal exposure would be useful to better understand the disposition of this chemical.

Mitigation of Effects. All of the treatment methods currently available for use in vinyl acetate exposure are supportive in nature (Bronstein and Currance 1988; Stutz and Janusz 1988). Since the mechanism(s) of vinyl acetate toxicity are not known, there are currently no methods geared towards mitigating the effects of vinyl acetate by interfering with the mode of action. Additional information on the ultimate mechanism of vinyl acetate toxicity is needed before insights can be gained on how to treat exposure victims.

2.9.3 On-going Studies

E.I. DuPont de Nemours and Company's Haskell Laboratory has initiated a basic research program investigating the mechanisms of chronic toxicity and carcinogenicity of vinyl acetate. The objective of the program is to develop a biologically based model for assessing human health risk from exposure to vinyl acetate vapor. Major phases of the program are to investigate the biochemical mechanism of action of vinyl acetate in isolated rodent nasal turbinates; to measure *in vitro* enzyme kinetics describing vinyl acetate hydrolysis to acetaldehyde and acetic acid in rodent and human nasal tissue; to measure *in vivo* cell proliferation responses following short-term (2-week) inhalation exposure; and to develop a physiologically-based pharmacokinetic risk assessment model for extrapolating human health risk from exposure to vinyl acetate. Results of this work are not yet available.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

The chemical identity of vinyl acetate is shown in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of vinyl acetate are shown in Table 3-2.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of Vinyl Acetate

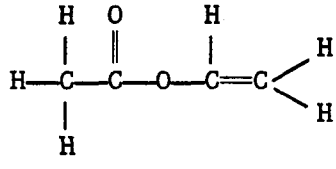
Characteristic	Information	Reference
Chemical name	Vinyl acetate	Windholz 1983
Synonyms	Acetic acid, ethenyl ester; acetic acid, ethylene ester; acetic acid, vinyl ester; 1-acetoxyethylene; ethanoic acid; ethenyl ester; ethenyl acetate; ethenyl ethanoate; vinyl A monomer; vinyl ethanoate	RTECS 1989
Trade names	VAC; vinyl acetate HQ; VYAC; ZESET T	RTECS 1989
Chemical formula	$C_4H_6O_2$	Windholz 1983
Chemical structure		IARC 1979
Identification numbers:		
CAS registry	108-05-4	HSDB 1987
NIOSH RTECS	AK0875000	HSDB 1987
EPA hazardous waste	No data	
OHM/TADS	7216946	HSDB 1987
DOT/UN/NA/IMCO shipping	Vinyl acetate (DOT); Vinyl acetate, inhibited (DOT)	RTECS 1989
	UN 1301, vinyl acetate; IMCO 3.2, vinyl acetate	HSDB 1987

Table 3-1 (Continued)

Characteristic	Information	Reference
HSDB	190	HSDB 1987
NCI	No data	

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

TABLE 3-2. Physical and Chemical Properties of Vinyl Acetate

Property	Information	Reference
Molecular weight	86.09	Windholz 1983
Color	Colorless	U.S. Coast Guard 1978
Physical state	Liquid (polymerizes in light to a colorless, transparent mass)	Windholz 1983
Melting point	-93.2°C	Weast 1986
Boiling point	72°-73°C	Windholz 1983
Density/specific gravity	0.932 (20/4°C)	Windholz 1983
Odor	Sweet smell in small quantities, pleasant fruity characteristic	U.S. Coast Guard 1978
Odor threshold:		
Water	0.088 ppm (w/v)[a]	Amoore and Hautala 1983
	0.25 ppm	Goeva 1966
Air	0.5 ppm (v/v)[b]	Amoore and Hautala 1983
	0.12 ppm	US Coast Guard 1978
Solubility:		
Water at 20°C	2 g/100 mL	Windholz 1983
Organic solvents	Soluble in alcohol, ether, acetone, benzene, and chloroform	Weast 1986
Partition coefficients:		
Log K_{ow}	0.21-0.73	Fujisawa and Masuhara 1981; Howard 1989
Log K_{oc}	No data	
Vapor pressure at 20°C	83 mmHg	Verschueren 1983
at 25°C	115 mmHg	Verschueren 1983
at 30°C	140 mmHg	Verschueren 1983
Henry's law constant;	4.81×10^{-4} atm-m^3 mol^{-1}	Howard 1989
Autoignition temperature	402°C	NFPA 1978
	426.6°C	Hawley 1981
Flashpoint	-8°C (closed cup)	Windholz 1983
	-1.1°C (Tag open cup)	Hawley 1981

Table 3-2 (Continued)

Property	Information	Reference
Flammability limits	2.6%-13.4%	NFPA 1978
Conversion factors	1 mg/m^3 = 0.28 ppm; 1 ppm = 3.52 mg/m^3	
Explosive limits	2.6%-13.4%	HSDB 1987

[a]w/v = Percent "weight in volume" (Windholz 1983)
[b]v/v = Percent "volume in volume" (Windholz 1983)

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

It is not known whether vinyl acetate occurs naturally (IARC 1986). Vinyl acetate is a man-made compound that was first produced in 1912 as a by product in the synthesis of ethylidene diacetate (Matthews 1974). This reaction involved bubbling acetylene through a mixture of mercurous sulfate and anhydrous acetic acid (Leonard 1970). During the 1920s, the Germans converted this liquid-phase process to a vapor phase process that allowed Germany to achieve a production volume of 12 million kg per year by the 1940s and which accounted for most of the world's production of vinyl acetate until about 1970 (Leonard 1970; Rhum 1970). The vapor phase process involved passing a 4:l acetylene-to-acetic acid mixture over a catalyst bed made of zinc acetate-saturated activated carbon at 180°-200°C. (Daniels 1983; Llewellyn and Williams 1972). Mercury salts can also be used as a catalyst in this reaction when it is conducted at 40°-50°C (International Labour Office 1985). Originally, acetylene was generated from calcium carbide (Leonard 1970). More recently, acetylene has been produced by cracking petroleum (Llewellyn and Williams 1972).

Currently, the manufacturing process most widely used to produce vinyl acetate is the vapor phase ethylene process, an oxidative reaction in which ethylene is bubbled through acetic acid at 120°C in the presence of palladium chloride catalyst (Daniels 1983; IAKC 1986). Impurities found in the reaction have been reported at less than 1% (for one manufacturer) and have included the following: acetaldehyde, ethyl acetate, and methyl acetate. The vapor phase ethylene process was developed in 1967 to take advantage of ethylene as a cheaper feedstock than acetylene, and came into widespread use in the 1970s (Daniels 1983; IARC 1986; Llewellyn and Williams 1972). By 1981, the vapor phase ethylene process accounted for 92% of U.S. production and the vapor phase acetylene process accounted for the remainder (Dylewski 1981). Various firms in the United States, Japan, West Germany, and the United Kingdom have independently and/or jointly modified the vapor phase ethylene process by using different types of catalysts in the reaction. The catalyst is usually palladium or its salt, although salts of rhodium, gold, platinum, ruthenium, vanadium, and iridium have also been used (Daniels 1983; Leonard 1970; Llewellyn and Willizms 1972). The advantage of these processes is that the catalyst lasts longer and undergoes less corrosion (Mannsville 1982).

A less important commercial manufacturing process for vinyl acetate involves the reaction between acetaldehyde and acetic anhydride. The intermediate species, ethylidene diacetate, undergoes pyrolytic cleavage to vinyl acetate and acetic acid (Daniels 1983; Leonard 1970; Mannsville 1988). This process was used in the United States until the 1960s, and may still be in use at small plants in China, India, and Mexico (Daniels 1983; Mannsville 1982, 1988). Vinyl. acetate can also be synthesized in high yields by reacting vinyl chloride with sodium acetate in solution at 50°-75°C, using palladium chloride as a catalyst (Daniels 1983). New methods for vinyl acetate

manufacture were being developed in 1982 that were to utilize synthetic gas as a feedstock. The gas would undergo a series of carbonylation reactions to yield ethylidene diacetate, which can be pyrolytically converted to vinyl acetate and acetic acid (Mannsville 1982). No information has been found that would indicate whether or not such new methods have been perfected or adopted for industrial production in the United States.

Vinyl acetate is normally produced in three grades that differ only in their content of inhibitor, which is added to prevent spontaneous polymerization (Daniels 1983; Mannsville 1988). To obtain these grades, either 3-7 ppm, 12-17 ppm, or 200-300 ppm p-hydroquinone is added to freshly produced vinyl acetate, depending upon how long the product is to be stored prior to use. Longer storage times require higher concentrations of inhibitor (Daniels .1983). Vinyl acetate is often stored and/or shipped with a variety of other inhibitors including benzoquinones, nitrobenzenes, diphenyls, toluenes, anthracene, phenanthrene, naphthalene, and others (Operations Research Inc. 1974).

Commercial production of vinyl acetate in the United States was first reported in 1928 (U.S. Tariff Commission 1930). From 1960 to 1979, U.S. production rose from 250 million pounds to 2.0 billion pounds. Production levels were approximately 1.9 billion pounds between 1980 and 1982, and then rose from 1.96 billion pounds in 1983 to 2.1 billion pounds in 1985. Levels dropped to 1.7 billion pounds in 1986 and then climbed to 1.8 billion pounds in 1987 (Daniels 1983; USITC 1979, 1980, 1981, 1982, 1983, 1984, 1985, 1986, 1987, 1988).

In 1984, with an increasing demand for vinyl acetate derived copolymer emulsions, due primarily to strong automobile and housing industries, production (over 2 billion pounds) was rapidly approaching the "practical effective capacity" of 2.2 billion pounds and supply was limited (Greek 1984). It was forecasted in 1984 that an increased demand for vinyl acetate for making adhesives and coatings would result in a greater capacity in production (Greek 1984). By 1989, the demand for vinyl acetate reached 2.6 billion pounds and is expected to reach 2.9 billion pounds by 1993 (Van et al. 1989). In 1989, five U.S. production facilities had a combined annual production capacity of 2.8 billion pounds (Van et al. 1989).

The following chemical companies currently produce vinyl acetate in the United States: E.I. DuPont de Nemours and Company, Polymer Products Division located in La Porte, Texas; Hoechst Celanese Corporation, Commodity Chemicals located in both Bay City, Texas and Clear Lake, Texas; Quantum Chemical Corporation, U.S.I. Division located in both La Porte, Texas and Clinton, Iowa; Union Carbide Corporation, Solvents and Coatings Materials Division located in Texas City, Texas; Monsanto Company located in Trenton, Michigan (SRI 1989; TR187 1989). For further information on facilities in the United States that manufacture or process vinyl acetate, refer to Table 4-1. Vinyl acetate is also produced in Australia, Brazil, Canada, China, France, West

TABLE 4-1. Facilities That Manufacture or Process Vinyl Acetate[a]

State[b]	No. of facilities	Range of maximum amounts on site in thousands of pounds[c]	Activities and uses[d]
AL	4	1-499,999	7, 13
CA	16	0.1-9,999	2, 7, 8, 10, 12, 13
CT	1	10-99	7
DE	2	100-999	3, 7
GA	8	10-999	2, 7, 8, 9
IA	1	100-999	1, 3, 4
IL	16 (1)[e]	10-9,999	7, 8, 10
IN	2	1-999	7, 8, 9
KS	2	1-999	7, 13
KY	5 (1)[e]	10-9,999	7, 8
LA	4	10-9,999	3, 7, 12, 13
MA	2	10-9,999	7
MD	1	1,000-9,999	7
MI	3	1-999	1, 5, 7, 13
MO	2	10-999	13
NC	5	1-999	2, 7
NH	1	10-99	7
NJ	11	10-499,999	7, 9, 10
NY	3	1-999	7, 12
OH	7	1-999	7, 8, 13
OR	2	100-999	7
PA	5	1-999	7, 12
SC	10	10-9,999	4, 7
SD	1	10-99	8, 9
TN	2	1-999	7
TX	27	0-49,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 13
PR	2	100-999	7

TABLE 4-1 (Continued)

State[b]	No. of facilities	Range of maximum amounts on site in thousands of pounds[c]	Activities and uses[d]
VA	2	0.1-9	7, 8
WI	1	0-0.09	8
WV	1	1,000-9,999	4, 7, 10
WY	1	1-9	7

[a]TRI87 1989
[b]Post office state abbreviations
[c]Data in TRI are maximum amounts on site at each facility.
[d]Activities/Uses:

1. produce
2. import
3. for on-site use/processing
4. for sale/distribution
5. as a byproduct
6. as an impurity
7. as a reactant
8. as a formulation component
9. as an article component
10. for repackaging only
11. as a chemical processing aid
12. as a manufacturing aid
13. ancillary or other use

[e]Number of facilities reporting "no data" regarding maximum amount of the substance on site.

Germany, Great Britain, India, Italy, Japan, Mexico, South Africa, and Spain (CIS 1988; IARC 1986; Mannsville 1988). In Japan alone there are eight manufacturers of vinyl acetate (CIS 1988). Five Japanese companies reported a combined production capacity of 1.3 billion pounds in 1981 (IARC 1986).

4.2 IMPORT / EXPORT

U.S. imports of vinyl acetate declined, with large fluctuations from 31 million pounds in 1970 to 1 million pounds in 1984 (Mannsville 1988). Imports remained at 1 million pounds until 1986, when a sharp rise to 12 million pounds was observed. Imports then decreased to 1 million pounds in 1987 (Mannsville 1988). Only a small fraction of the vinyl acetate consumed in the U.S. is imported.

Exports of vinyl acetate increased rapidly from 15 million pounds in 1965 to 645 million pounds in 1980 (Mannsville 1988). In 1984, as the demand for vinyl acetate increased and supply was limited, it was predicted that any surplus demand that existed after anticipated increases in production capacity would be satisfied by diversion of the chemical from exports (Greek 1984). Exports were down in 1984 at 515 million pounds, compared with 589.9 million pounds in 1983 (Anonymous 1984; Mannsville 1988). Exports increased steadily after 1984 to a level of 736 million pounds in 1987 (Mannsville 1988). In 1987, U.S. exports of vinyl acetate accounted for approximately 40% of the total production volume (1.8 billion pounds in 1987).

4.3 USE

The primary use for vinyl acetate is as a monomer in the production of polyvinyl acetate and polyvinyl alcohol (IARC 1986). These products, synthesized via polymerization of vinyl acetate, accounted for 75%-80% of total U.S. consumption in 1982 (Mannsville 1982, 1988). Vinyl acetate is also polymerized with vinyl chloride to produce copolymers. Polyvinyl butyral, polyvinyl acetals, ethylene-vinyl acetate copolymers, and acrylonitrile copolymers (for acrylic fibers) are also produced. It is also used in polymeric lubrication oil additives (Daniels 1983; IARC 1986).

Polyvinyl acetate emulsions (homopolymer and copolymer), the major derivatives of vinyl acetate, are widely used in adhesives for packaging and construction (wood gluing) and in water-based paints (IARC 1986; Mannsville 1988). Other important uses include nonwoven textile fibers, textile sizings and finishes, paper coatings, and inks. Polyvinyl alcohol is widely used in textile finishing, adhesives, and as a raw material for polyvinyl butyral, which is used as the adhesive interlayer in architectural and automobile laminated safety glass (Cincera 1983; Mannsville 1,988). Uses of other polymers made from vinyl acetate include barriers in packaging, paint and coatings applications, plastic floor coverings, phonograph records, flexible film and sheeting (including plastic films used for wrapping food), food starch modifier, and moulding and extrusion compounds.

In 1987, the estimated end-use distribution pattern for vinyl acetate was as follows: 55% was used to produce polyvinyl acetate emulsions (homopolymer and copolymer), for use in adhesives (23%), paint emulsions (20%) and textile and paper emulsions (12%); 20% was used to produce polyvinyl alcohol; 10% to produce ethylene/vinyl acetate; 5% to produce polyvinyl butyral; 5% to produce polyvinyl chloride copolymers; and 5% to produce miscellaneous products (Mannsville 1988).

4.4 DISPOSAL

The disposal method for vinyl acetate recommended in Japan, as reported in 1982 by its International Technical Information Institute, was to incinerate the compound by mixing it with a more flammable solvent and spraying it into a furnace (ITII 1982). Information on disposal methods for vinyl acetate that have been accepted or commonly used in the United States is limited. Since underground injection accounts for 2.1 million pounds of vinyl acetate releases, it is a probable method of disposal (TRI87 1989); however, additional information on this method of disposal for vinyl acetate is not available.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Vinyl acetate is released to the environment, principally to the atmosphere, as a result of emissions from manufacturing, processing, and storage facilities. Vinyl acetate partitions to the atmosphere and to surface water and groundwater. The compound is transformed by photochemical oxidation in the atmosphere, and by hydrolysis and biodegradation in surface waters, groundwater, and soils. As a result of its high vapor pressure and water solubility/hydrolysis, vinyl acetate should not bioconcentrate in terrestrial or aquatic organisms or biomagnify in food chains.

Workplace exposure via inhalation or dermal contact appears to be the most important source of human exposure to vinyl acetate. Populations living in areas surrounding hazardous waste sites may be exposed to vinyl acetate through inhalation of contaminated air and ingestion of or dermal contact with contaminated water; the latter route may be particularly important for populations living near certain types of disposal sites (e.g., underground injection sites). The relative importance of these pathways in terms of human exposure potential is difficult to establish given the limited monitoring data available for vinyl acetate. Most people, however, are probably exposed to very small, amounts of vinyl acetate through: (1) inhalation of contaminated ambient air and cigarette smoke; (2) dermal contact with products containing the compound (e.g., glues and paints); and (3) ingestion of residual vinyl acetate monomers in food (i.e., that may have migrated from plastic food wraps) or food items containing the compound as a starch modifier.

EPA had identified 1,177 NPL sites in 1989. We do not know how many of the 1,177 NPL sites have been evaluated for vinyl acetate. Vinyl acetate has been found at 3 of the total number of sites evaluated for that compound. As more sites are evaluated by EPA, this number may change (View 1989). The frequency of these sites within the United States can be seen in Figure 5-l.

5.2 RELEASES TO THE ENVIRONMENT

Vinyl acetate is released to the environment as a result of its commercial production, use, storage, and disposal. According to the SARA Section 313 Toxics Release Inventory (TRI), an estimated total of at least 8.8 million pounds of vinyl acetate was released to the environment from manufacturing and processing facilities in the United States in 1987 (see Table 5-l) (TR187 1989). The quality of the TRI data must be viewed with caution since the 1987 data represent first-time reporting of estimated releases by these facilities. Only certain types of facilities were required to report. This is not an exhaustive list.

5.2.1 Air

Releases to the atmosphere accounted for about 75%, or 6.6 million pounds, of the estimated total environmental releases from domestic

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

* Derived from View 1989

TABLE 5-1. Releases to the Environment from Facilities That Manufacture or Process Vinyl Acetate[a]

State[c]	No. of facilities	Range of reported amounts released in thousands of pounds[b]						
		Air	Underground injection	Water	Land	Total Environment[d]	POTW[e] transfer	Off-site waste transfer
AL	4	0.1-35	0-0	0-1.7	0-0.3	0.1-37	0-0.3	0-0
CA	16	0.1-53	0-0	0-0	0-0	0.1-53	0-3.4	0-79.4
CT	1	0.5-0.5	0-0	0-0	0-0	0.5-0.5	0.8-0.8	0-0
DE	2	8.3-29	0-0	0-0.4	0-0.3	8.3-29.7	0-0.3	0-0.3
GA	8	0-5.8	0-0	0-0.3	0-30	0.1-30.3	0-5.2	0-5.8
IA	1	36-36	0-0	0-0	0-0	36-36	0-0	0-0
IL	16	0.3-96.1	0-0	0-1.3	0-1.3	0.3-96.1	0-0.3	0-19.6
IN	2	0-0.9	0-0	0-0	0-0	0-0.9	0-0	0-0
KS	2	0.1-14.4	0-0	0-0	0-0	0.1-14.4	0-0.6	0-0
KY	5	1.3-504	0-0	0-0.1	0-0.1	1.3-504	0-0.3	0-33
LA	4	0-212	0-0	0-3.5	0-0	0-215.5	0-11.1	0-0
MA	2	0.5-72.6	0-0	0-0.3	0-0	0.5-72.9	0-48	0-0.5
MD	1	14.2-14.2	No data	0-0	0-0	14.2-14.2	1.7-1.7	2-2
MI	3	0.1-40.3	0-0	0-0	0-0	0.1-40.3	0-0.3	0-10.9
MO	2	0.1-0.1	0-0	0-0	0-0	0.1-0.1	0-0	0-0.1
NC	5	0.3-20.2	0-0	0-0	0-0	0.3-20.2	0-3.9	0-0.2
NH	1	0.3-0.3	0-0	0-0	0-0	0.3-0.3	0-0	0.3-0.3
NJ	11	0.1-63.6	0-0	0-0.1	0-0.3	0.1-63.6	0-24	0-17
NY	3	0-2.5	0-0	0-0	0-0	0-2.5	0-0.5	0-0.5
OH	7	0.2-90.7	0-0	0-1.1	0-0	0.2-90.7	0-5.5	0-2
OR	2	1-1	0-0	0-0	0-0	1-1	0-0	0-0
PA	5	1-100	0-0	0-0.3	0-0.9	1-100.9	0-0.1	0-2.1
PR	2	0.7-0.7	0-0	0-0	0-0	0.7-0.7	0.1-0.1	0.1-0.1

TABLE 5-1 (Continued)

State[c]	No. of facilities	Range of reported amounts released in thousands of pounds[b]						
		Air	Underground injection	Water	Land	Total Environment[d]	POTW[e] transfer	Off-site waste transfer
SC	10	0.1-7.5	0-0	0-0.3	0-0	0.1-7.7	0-2.6	0-0.3
SD	1	0.3-0.3	0-0	0-0	0-0	0.3-0.3	0-0	0-0
TN	2	0.3-0.6	0-0	0-0	0-0	0.3-0.6	0-0.1	0-0
TX	27	0-1,873	0-1,540	0-0.3	0-0	0-1,873	0-0.3	0-128.6
VA	2	0.8-5.4	0-0	0-0	0-0	0.8-5.4	0-0.3	0-0
WI	1	0.3-0.3	No data	0-0	0-0	0.3-0.3	0-0	No Data
WV	1	64-64	No data	0-0	0-0	64-64	19-19	14-14
WY	1	0.5-0.5	No data	0-0	0-0	0.5-0.5	0-0	0-0

[a]TRI87 1989
[b]Data in TRI are maximum amounts released by each facility. Quantities reported here have been rounded to the nearest hundred pounds, except those quantities more than 1 million pounds, which have been rounded to the nearest thousand pounds.
[c]Post office state abbreviation
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility.
[e]Publicly owned treatment works

manufacturing and processing facilities in 1987, according to TRI (TR187 1989).

The industrial organic chemicals, plastic materials and resins, paints and allied products, and commercial printing industries have been identified as potential sources of atmospheric releases of vinyl acetate (EPA 1987d). Emission factors for volatile organic compounds (VOCs) and nonmethane hydrocarbons (NMHCs) have been developed for vinyl acetate production via the ethylene vapor-phase process. Emissions of VOCs from uncontrolled sources (excluding fugitive emission sources) in a typical vinyl acetate production plant have been estimated to total about 176 kg/hour; this estimate includes about 36 kg/hour from vinyl acetate storage facilities (Dylewski 1980). Fugitive emissions from valves and pump seals contribute an estimated additional 0.0021 kg NMHC/hour and 0.0020 kg NMHC/hour, respectively (Langley et al. 1981).

5.2.2 Water

Vinyl acetate has been detected in groundwater samples taken at an estimated 0.71% of the NPL hazardous waste sites that have had samples analyzed in the Contract Laboratory Program (CLP) at a geometric mean concentration of 10 ppb for the positive samples (CLPSD 1989). The compound was not detected in surface water samples at NPL sites participating in the CLP. Note that these data from the CLP Statistical Database represent frequency of occurrence and concentration information for NPL sites only.

According to TRI (TR187 1989), an estimated total of at least 10,000 pounds of vinyl acetate were released to surface waters in 1987 from domestic manufacturing and processing facilities; an additional 147,219 pounds were released in effluents to publicly owned treatment works (POTWs).

Vinyl acetate has been detected in waste water from a polyvinyl acetate production facility at a concentration of 50 mg/L (Stepanyan et al. 1970)

5.2.3 Soil

Vinyl acetate has been detected in soil samples taken at an estimated 2.13% of the NPL hazardous waste sites included in the CLP at a geometric mean concentration of 19.5 ppb for the positive samples (CLPSD 1989). Note that these data from the CLP Statistical Database represent frequency of occurrence and concentration information for NPL sites only.

According to the TRI, an estimated total of at least 33 thousand pounds of vinyl acetate were released to soils in 1987 from domestic manufacturing and processing facilities; an additional 2.1 million pounds were released by underground injection (TR187 1989).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

No information was found in the available literature regarding the transport and partitioning of vinyl acetate in environmental media. However, estimates of the movement of the compound between the air, water, and soil compartments following release to the environment can be made on the basis of available physical and chemical property data.

Vinyl acetate is a volatile compound that is released mainly to the atmosphere. Vinyl acetate is also highly soluble in water. Therefore, dissolution of vinyl acetate released to the atmosphere in rainwater and transport of the compound back to surface waters and soils in wet deposition can be expected.

Using the vapor pressure and water solubility data presented in Table 3-2, a Henry's law constant value of 4.8×10^{-4} atm-m^3 mol^{-1} can be calculated. The magnitude of this value indicates that volatilization to the atmosphere will be an important transport process for vinyl acetate released to surface waters. Using this value and the methods reviewed by Thomas (1982), a volatilization half-life of about 4 hours at 20°C can be estimated for a river 1 meter deep flowing at a current of 1 m/second, with a wind velocity of 3 m/second.

Vinyl acetate released to surface soils is also expected to volatilize to the atmosphere. Releases of vinyl acetate to subsurface soils may leach to and be transported in groundwater, depending upon site-specific hydrogeological conditions, if the compound is not transformed or degraded (Section 5.3.2.2). Sorption of the compound to soils and sediments is not expected, given its high water solubility and low K_{oc} value.

The log octanol/water partition coefficient for vinyl acetate has been reported to be 0.21 (Fujisawa and Masuhara 1981) and 0.73 (Howard 1989). The magnitude of these values indicates that bioconcentration and food chain biomagnification will not be important processes for vinyl acetate.

5.3.2 Transfozmation and Degradation

5.3.2.1 Air

Vinyl acetate does not absorb ultraviolet light at wavelengths longer than 250 nm (Daniels 1983), therefore, direct photolytic degradation of the compound in the troposphere is not expected to occur. However, vinyl acetate has been found to undergo rapid photochemical oxidation and polymerization in laboratory studies in the absence of inhibitor (HSDB 1989). The average second order rate constant for reaction with singlet molecular oxygen has been reported to be 0.82 L $mole^{-1}$ sec^{-l} (Datta and Rao 1979). In smog chamber

studies with NO_x concentrations representative of rural and urban atmospheres, the photooxidation half-life of vinyl acetate was determined to be 4.1-6.5 hours (Joshi et al. 1982).

5.3.2.2 Water

Vinyl acetate undergoes hydrolysis in surface water and groundwater. The hydrolytic half-life of the compound at 25°C and pH 7.0 has been estimated to be 7.3 days (Mabey and Mill 1978). Decreasing pH decreases the hydrolysis rate; for example, the rate is minimal at pH 4.4 (Daniels 1983). Acetic acid and acetaldehyde are the main products of vinyl acetate hydrolysis (Daniels 1983; Stuckey et al. 1980).

Vinyl acetate also undergoes biologically-mediated transformation. The results of several older laboratory studies with aqueous solutions of the compound suggest the occurrence of biodegradation by domestic sewage effluent microorganisms both under aerobic (Pahren and Bloodgood 1961; Price et 'al. 1974) and anaerobic (Chou et al. 1979; Stuckey et al. 1980) conditions. In a more recent laboratory study, 17 isolates of bacteria and yeasts, capable of utilizing vinyl acetate as a sole carbon source under aerobic conditions, were obtained from samples of domestic sewage and loamy soil. Microorganisms contained in a sludge inoculum were also found to be capable of biotransforming vinyl acetate under anaerobic conditions. Under both aerobic and anaerobic conditions, enzymatic hydrolysis of vinyl acetate yielded acetaldehyde as a metabolic intermediate and acetate as an end product, although the reaction was more rapid under aerobic conditions. A half-life of 12 hours was obtained for the enzymatic hydrolysis utilizing one of the bacterial isolates under aerobic conditions, whereas, the half-life for the nonenzymatic hydrolysis of the compound in a sterile medium was found to be 60 hours (Nieder et al. 1990).

5.3.2.3 Soil

In soils, vinyl acetate is also expected to be transformed by hydrolysis and biotransformation. The rate of hydrolysis should increase as soil moisture content and pH increase. As described in Section 5.3.2.2, microbial isolates obtained from a loamy soil were found to be capable of utilizing vinyl acetate as a sole carbon source under aerobic conditions (Nieder et al. 1990). Metabolism studies utilizing one of the bacterial isolates indicated that vinyl acetate was transformed via enzymatic hydrolysis to acetaldehyde and acetate. The half-life for this biologically-mediated hydrolysis was found to be about one-fifth that of the nonenzymatic hydrolysis of the compound (12 versus 60 hours).

Aqueous solutions containing 4.5 g/L of polyvinyl acetate have been reported to undergo biotransformation by the soil fungi Aspergillis niger and Penicillium following incubation for 15 days at 22°-25° C (Garcia 1988). Polyvinyl acetate was the sole carbon source in the test media. Evidence of

biotransformation included increased biomass of the fungi and increased esterase levels in the media.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Despite large releases of vinyl acetate to the atmosphere, data on ambient air levels are limited to a single report from Texas City, Texas (Houston/Gulf Coast area), of concentrations of 0.07-0.57 ppm (Gordon and Meeks 1975). Note that these values should not be considered to represent typical ambient air concentrations, since a number of the manufacturers of vinyl acetate are located in Texas City (see Section 4.1). The compound has also been detected in air samples taken at the Kin-Buc waste disposal site located near Edison, New Jersey at a concentration of 0.5 μg/m^3 (0.00014 ppm) (Pellizzari 1982).

5.4.2 Water

No information was found in the available literature regarding concentrations of vinyl acetate in domestic surface waters or groundwaters. Available groundwater monitoring data for NPL sites are reported in Section 5.2.2.

5.4.3 Soil

No information was found in the available literature regarding concentrations of vinyl acetate in domestic soils. Available soil monitoring data for NPL sites are reported in Section 5.2.3.

5.4.4 Other Environmental Media

Available monitoring data for other environmental media are limited to reports of vinyl acetate as a constituent of the vapor phase of cigarette smoke at concentrations of 400 ng/cigarette (Guerin 1980) and 0.5 μg/puff (Battista 1976).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Human exposure to vinyl acetate is most well defined for workplace populations. The National Occupational Exposure Survey (NOES), conducted by NIOSH from 1980-1983, estimated that 50,282 workers employed at 5,046 plant sites were potentially exposed to vinyl acetate in the United States in 1980 (NIOSH 1990b). The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey provides only estimates of workers potentially exposed to chemicals in the workplace.

Workers involved in the production, storage, processing, and transport of vinyl acetate are exposed primarily via inhalation-of vapors and skin and eye contact with the liquid or vapor forms of the compound (NIOSH 1978). Workplace air concentration levels reviewed by NIOSH (1978) were generally within the recommended 15-minute ceiling limit of 4 ppm. In another survey of vinyl acetate production facilities in Texas, the following workplace airborne concentrations were reported: average TWA concentrations--5.2-8.2 ppm; average breathing zone concentrations--8.6 ppm; intermittent exposure concentrations --about 50 ppm; and potential short-term exposures--up to 300 ppm (Deese and Joyner 1969).

Monitoring data are insufficient to establish ambient levels of vinyl acetate in environmental media. However, the compound has fairly limited residence times in environmental media as a result of its reactivity (see Section 5.3.2). Contaminated environmental media may be important sources for populations living in the vicinity of continuous emission point sources, such as industrial manufacturing, processing, storage, or disposal sites (e.g., underground injection sites), or hazardous waste sites.

Although few monitoring data exist, given the high production volume and extensive use of vinyl acetate, most people are probably exposed to very small amounts of vinyl acetate through: (1) inhalation of contaminated ambient *air* and cigarette smoke; (2) inhalation, dermal contact, or ingestion of residual monomers in consumer products containing polyvinyl acetate (e.g., paints, adhesives, chewing gum); and (3) ingestion of food items packaged in plastic films containing vinyl acetate.

Inhalation is expected to be the main route of human exposure to the hydrolysis product of vinyl acetate, acetaldehyde. Acetaldehyde has a high vapor pressure and is miscible with water. It rapidly volatilizes (e.g., half-life in river water = 1.9 hours) from surface waters or soils to the atmosphere, where it is transformed via photolysis and reaction with hydroxyl radicals, with a half-life on the order of hours. The high water solubility of the compound suggests that releases to subsurface soil, or to surface soil that do not volatilize, will partition to soil water and possibly groundwater unless degraded by aerobic and anaerobic microorganisms. Acetaldehyde does not sorb to soils or sediments, or bioconcentrate/biomagnify in terrestrial or aquatic organisms/food chains. Acetaldehyde is a natural constituent of foods (HSDB 1991).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers involved in the production, processing, storage, and transport of vinyl acetate are potentially exposed to high concentrations of the compound. Members of the general population living in the vicinity of industrial point emission sources, and individuals living near waste sites that are contaminated with vinyl acetate may also be exposed to potentially high concentrations of the compound. The sizes of these populations and the

concentrations of vinyl acetate in the contaminated media to which these people may be exposed have not been adequately characterized.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of vinyl acetate is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of vinyl acetate.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Data Needs

Physical and Chemical Properties. The physical/chemical properties of vinyl acetate are sufficiently well defined to enable assessment of the environmental fate of this compound (Tables 3-l and 3-2).

Production, Import/Export, Use, and Disposal. Vinyl acetate is released to the environment as a result of its commercial production, use, storage, transport, and disposal. Human exposure occurs mainly in the workplace through inhalation of vinyl acetate vapors.

Domestic production of vinyl acetate in 1986 and 1987 totaled 1.7 billion pounds and 1.8 billion pounds, respectively (Daniels 1983; USITC 1986, 1987). These levels are slightly lower than the recent high of 2.1 billion pounds reported in 1985 (Daniels 1983; USITC 1985). In 1987, imports and exports of the compound totaled 1 million and 736 million pounds, respectively (Mannsville 1988). Vinyl acetate is used primarily as a chemical intermediate in the production of polymeric materials (Daniels 1983; IARC 1986; Mannsville 1982, 1988). Vinyl acetate is contained in polymeric consumer products only as residual monomer (Cincera 1983; IARC 1986; Mannsville 1988). Releases of the compound from industrial processes are mainly to the atmosphere. Underground injection is also an important source of release for certain facilities. No information was found on current disposal methods or the regulations governing disposal of vinyl acetate.

Additional information on disposal methods and pertinent regulations would be useful in evaluating the potential for release of and exposure to vinyl acetate.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA (EPA 1987c). The Toxics Release Inventory (TRI), which contains this information for 1987, became available in May of 1989 (TR187 1989). This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Little information is available regarding the transport and partitioning or transformation and degradation of vinyl acetate. Based on its physical/chemical properties, vinyl acetate is expected to partition to the atmosphere and surface water and groundwater (Fujisawa and Masuhara 1981; Hansch and Leo 1979). Vinyl acetate is not expected to persist, bioconcentrate, or biomagnify (Fujisawa and Masuhara 1981; Hansch and Leo 1979). The most important transformation processes for vinyl acetate are photooxidation and hydrolysis (Joshi et al. 1982; Mabey and Mill 1978); the relative importance of biodegradation is unknown (Chou et al. 1979; Pahren and Bloodgood 1961; Price et al. 1974; Stuckey et al. 1980). Additional information is needed on the transport/partitioning and transformation/degradation of vinyl acetate in all media in order to confirm the predicted behavior described above and establish the relative importance of the various transformation processes. This information will be helpful in defining the relative importance of various routes of exposure to the compound in environmental media.

Bioavailability from Environmental Media. No information was found regarding human absorption of vinyl acetate following inhalation, oral, or dermal exposures from environmental media. Limited data available for laboratory animals suggest that absorption may occur following exposure by all of these routes (Hazleton 1979a, 1980a; Smyth and Carpenter 1948; Weil and Carpenter 1969). Additional information is needed on the uptake of vinyl acetate following inhalation of workplace and ambient air, dermal contact with or ingestion of contaminated soils, and ingestion of contaminated drinking water. This information would be useful in determining the bioavailability of the compound from environmental media.

Food Chain Bioaccumulation. No information was found regarding the bioconcentration of vinyl acetate by plants, aquatic organisms, or animals, or the biomagnification of the compound in terrestrial or aquatic food chains. On the basis of the reactivity, volatility, and water solubility of the compound, bioconcentration and biomagnification are not expected to be important environmental fate processes (Fujisawa and Masuhara 1981; Hansch and Leo 1979). Additional information is needed to confirm this predicted

behavior. This information will be useful in establishing the importance of food chain bioaccumulation as a source of human exposure to vinyl acetate.

Exposure Levels in Environmental Media. Very limited data are available concerning ambient concentrations of vinyl acetate in the atmosphere (Gordon and Meeks 1975). No data are available for surface waters, groundwater, or soils. Additional information is needed on ambient levels in these media, including media concentration levels at hazardous waste sites, and on human intake through contact with these media and ingestion of contaminated foods. This information would be useful in estimating human exposure to vinyl acetate.

Exposure Levels in Humans. Vinyl acetate is rapidly hydrolyzed by esterases in the blood to acetate and vinyl alcohol. Vinyl alcohol is rapidly converted to acetaldehyde, which in turn is metabolized to acetate (Hazleton 1979a, 1980a; Simon et al. 1985). Vinyl acetate metabolism is rapid; in vivo tests with laboratory animals indicate that most of the compound is eliminated within 24 hours after exposure (Hazleton 1979a, 1980a). Therefore, it would be difficult to measure the presence of vinyl acetate or acetaldehyde after reasonable periods following exposure to vinyl acetate. Acetaldehyde and acetate may also not be useful as indicators of vinyl acetate exposure. Because these compounds are incorporated into normal metabolic pathways, it would be difficult to determine which metabolites were due to vinyl acetate exposure and which were endogenous in biological tissues and fluids. Additional investigation of the utility of biomarkers of exposure in characterizing human exposure to vinyl acetate would be useful.

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

5.7.2 On-going Studies

On-going remedial investigations and feasibility studies conducted at NPL sites will add to the available database on exposure levels in environmental media and exposure registries.

No other long-term on-going research pertaining to environmental fate or human exposure potential of vinyl acetate was identified or located.

6. ANALYTICAL METHODS

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

6.1 BIOLOGICAL MATERIALS

The only method of analysis described in the literature for detecting vinyl acetate and metabolites in biological media is by administration of radioactive vinyl acetate (Hazleton 1979a, 1980a). Vinyl acetate is a volatile organic compound that is very rapidly hydrolyzed to acetaldehyde (via the unstable intermediate, vinyl alcohol) and acetate in the bodies of humans and animals (Simon et al. 1985a; Vinegar 1983). The acetaldehyde is converted to acetate and incorporated into the normal biochemical pathways and primarily excreted as carbon dioxide in expired air (Vinegar 1983). Section 2.3 contains more detailed information on the toxicokinetics of vinyl acetate.

6.2 ENVIRONMENTAL SAMPLES

Most analysis of vinyl acetate has been done on workplace air, especially in factories that make or use vinyl acetate. The primary method of analysis for vinyl acetate in air is gas chromatography with flame ionization detection (GC/FID). Infrared spectroscopy and gas chromatography/mass spectrometry (GC/MS) are also frequently used. Problems encountered when analyzing for vinyl acetate include volatility of the sample, interference from other organic chemicals, degradation of vinyl acetate by hydrolysis and polymerization, and desorption (extraction) of the sample. Most of the variation in methodology occurs with sample collection and desorption. Samples have been collected by grab-sampling, by midget impingers, and on solid sorbent tubes.

Grab-sampling of air in Houston followed by analysis by GC/FID or Fourier transform infrared spectroscopy (FTIR), showed that vinyl acetate could be detected in the samples in the presence of a large number of other organic compounds when analyzed by FTIR (Gordon and Meeks 1977). Disadvantages of this method are possible loss of sample through leakage from or decomposition in the collection bags and contamination of the sample by bag

components. Problems encountered with the FTIR hardware under field conditions led the authors to conclude the technique was better suited for laboratory use.

Midget impingers, as well as large-scale impingers, containing toluene have been used to sample the air in a vinyl acetate production plant (Deese and Joyner 1969). Analysis of samples was conducted by GC/FID. Several evaluations indicated that the method was accurate (mean recovery of 99.2%) and reliable for concentrations in the low ppm range. The main problems with this method are that the liquid used in the impingers is subject to spillage (however, unspillable impingers are now available) and it is difficult to scale the impingers down to a suitable size for personal use.

Solid sorbents are the usual collection media for personal sampling tubes used in occupational exposure situations because they are efficient, simple to use, and can be easily be scaled down to a convenient size. Solid sorbents are also the most frequently used for concentrations of organics from air. One of the most commonly used solid sorbents is activated carbon (Foerst and Teass 1980; Kollar et al. 1988; Krajewski et al. 1980; Sidhu 1981). Recoveries on this sorbent can be low due to hydrolysis or polymerization, depending on humidity conditions. Recoveries have ranged from 40% to 101% depending on desorption technique, humidity level, sample storage time, and how the sample was introduced to the sampler (Foerst and Teass 1980; Kollar et al. 1988; Krajewski et al. 1980; Sidhu 1981). Modifications to the activated carbon sampler were made to alleviate some of the problems associated with them (Kimble et.al. 1982). Recoveries approaching 100% were reported with activated charcoal sorbent treated with a polymerization inhibitor (hydroquinone) and preceded by a drying agent (calcium sulfate). When desorbed with carbon disulfide-acetone and analyzed by GC/FID, good sensitivity and precision were obtained (see Table 6-l). Advantages of this technique are apparent sample stability, high breakthrough volume, and readily available desorption and detection techniques. When this approach was repeated by others (Andersson and Andersson 1988), however, both recovery and precision were poor at humidities below 50%. A more recent GC/FID method using collection on the solid sorbent, Ambersorb® XE-347, followed by desorption with dichloromethane containing 5% methanol, yielded excellent recovery and precision over humidities ranging from 20 to 85% (Andersson and Andersson 1990).

The NIOSH-recommended procedure for determining vinyl acetate in air calls for collection on Chromosorb® 107, followed by thermal desorption and analysis by GC/FID (NIOSH 1990a). The lowest quantifiable level with this method is in the low ppb range with an average precision of 8.1% relative standard deviation (RSD) at humidity levels greater than 80%. The NIOSH method was developed and compared to activated charcoal by Foerst and Teass (1979). Although activated charcoal had a higher affinity for vinyl acetate, as demonstrated by its higher breakthrough volume (about 167 L compared to 4L for Chromosorb® 107), vinyl acetate was considerably less stable on the

TABLE 6-1. Analytical Methods for Determining Vinyl Acetate in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collect in midget impingers; inject toluene collection medium	GC/FID	Low mg/m^3 (ppm)	99.2	Deese and Joyner 1969
	Collect on Chromosorb® 107; desorb thermally directly to GC	GC/FID	7 mg/m^3 (2 ppm)	106-110	NIOSH 1990a (NIOSH Method P&CAM 278)
Air	Collect sample on activated charcoal; desorb with carbon disulfide or acetonitrile; inject desorption solvent into GC	GC/FID	NR	40-100	Foerst and Teass 1979
	Collect on activated charcoal; desorb with carbon disulfide	GC/FID	0.35 mg/m^3 (0.1 ppm)	83.2	Sidhu 1981
	Collect on calcium sulfate-hydroquinone inhibited charcoal; desorb with carbon disulfide-acetone	GC/FID	1.33 mg/m^3 (0.38 ppm)	98.6-99.7	Kimble et al. 1982
Air	Collect sample on Ambersorb® XE-347; desorb with methanol/dichloro-methane	HRGC/FID	No data	82-100	Andersson and Andersson 1990
	Collect on Tenax®-GC; desorb thermally directly to GC	GC/MS	No data	>75	Pellizzari 1982
	Collect on calcium sulfate-hydroquinone inhibited carbon; desorb with carbon disulfide-acetone	GC/FID GC/MS	No data	16-96	Andersson and Andersson 1988

Table 6-1 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
	Collect on trans-platinum chloride (ethylene); (pyridine) coated SAW	SAW sensor	No data	No data	Zellars 1989
Waste water effluent	Purge sample and trap volatiles on Tenax®-GC/ silica gel; thermally desorb to GC	GC/MS	No data	No data	EPA 1979 (EPA Method 624)
Waste water effluent	Purge and trap sample on total organics concentrator (Tenax® GC-silica gel-glass wool); desorb thermally to GC	GC/MS	1 µg/L (1 ppb)	96-110	Spingarn 1982 (EPA Method 624)
Coal combustion leachate	Purge sample and trap volatiles on Tenax®-GC/ silica gel; thermally desorb to GC	GC/MS	10 µg/L (10 ppb)	No data	Sorini and Jackson 1988 (EPA Method 624)

EPA = Environmental Protection Agency; FID = flame ionization detector; GC = gas chromatography; HRGC = high-resolution gas chromatography; MS = mass spectrometry; SAW = surface acoustic wave

activated charcoal. Advantages of the Chromosorb® 107 collection technique are improved sample stability, better recovery, and improved precision through a wider humidity range. Disadvantages are a lower breakthrough volume and limited access of most field sites to the thermal desorption technique.

Vinyl acetate has also been determined in air at industrialized areas and near waste disposal sites using Tenax® GC sorbent with thermal desorption. Separation and detection was on a high resolution GC/MS coupled to a computer containing a mass spectra database. Recoveries for this method were greater than 75%. Advantages of this method are its specificity in the presence of large numbers of potentially interfering chemicals and ability to quantify results (Pellizzari 1982). A disadvantage is the requirement for sophisticated and expensive equipment and the expertise to use the method. In addition, the effect of humidity is not known.

A more recently developed technique for use in industrial hygiene situations depends on detection of vinyl acetate by coated surface acoustic wave sensor. The special trans-$PtCL_2$(ethylene)(pyridine) coating makes the technique selective for vinyl acetate, and the apparatus can easily be scaled down for personal use. In addition, the coating is regenerative, increasing the cost/benefit ratio (Zellers 1989). More information is needed to compare this method to those currently in use.

Very little information was found concerning analysis of vinyl acetate in water and soil and no information was found for other media. The EPA recommended method for water (Method 624) specifies sampling on a total organics concentrator (Tenax® -silica gel) used as a purge-trap device (EPA 1979). The sample is thermally desorbed and analyzed by GC/MS. This method was used to detect vinyl acetate in secondary effluent from a publicly owned treatment works (Spingarn et al. 1982). It proved to be sensitive, accurate, and fairly precise. This method was also used to measure vinyl acetate in coal combustion leachate with a detection limit of 10 μg/L (Sorini and Jackson 1988).

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of vinyl acetate is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of vinyl acetate.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate

the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Data Needs

Methods for Determining Biomarkers of Exposure and Effect. There are no reliable biomarkers of exposure for vinyl acetate (see Sections 2.5.1 and 2.9.2). Vinyl acetate is rapidly absorbed and metabolized in the body (Hazleton 1979a, 1980a; Simon et al. 1985a). The metabolites formed, acetaldehyde and acetate, are commonly found in humans and animals, and thus are not specific for exposure to vinyl acetate. Acetaldehyde and acetate are incorporated into the biochemical cycles and converted primarily to carbon dioxide and water. There are no tests currently available for measuring vinyl acetate or its metabolites in biological tissues.

There are no established biomarkers of effect for vinyl acetate; thus, there are no methods for determining biomarkers of effect for this compound. No changes in enzyme levels or body fluids have been documented following exposure to this compound. Genotoxic effects have been found in in vitro tests, but these are not specific for vinyl acetate and there is no established method for monitoring such effects in vivo.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Given vinyl acetate's high volatility, the media of most concern for human exposure is most likely air, with exposure also occurring by both oral and dermal routes (Deese and Joyner 1969; NIOSH 1978; Smyth and Carpenter 1973). Sensitive, reliable, and accurate methods exist for determining vinyl acetate in air (Deese and Joyner 1969; Foerst and Teass 1979; Gordon and Meeks 1977; Kimble et al. 1982; Kollar et al. 1988; NIOSH 1990a). The detection limits of these methods are probably too high for monitoring ambient air, but are sufficient for measuring levels present in occupational settings. At least one sensitive and accurate method exists for detecting vinyl acetate in water (Springarn et al. 1982). Routine methods of analysis for other environmental media were not located. Further studies on measurement of vinyl acetate in air, water and soil would be useful in determining the potential for exposure to this chemical at hazardous waste sites.

6.3.2 On-going Studies

No on-going studies concerning methods for measuring and determining vinyl acetate in biological and environmental samples were located.

7. REGULATIONS AND ADVISORIES

Vinyl acetate 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). ATSDR has derived an intermediate inhalation MRL of 0.01 ppm based on respiratory effects seen in mice (Hazleton 1980b).

The international, national, and state regulations and guidelines regarding vinyl acetate in air, water, and other media are summarized in Table 7-l.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Vinyl Acetate

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification	Group 3[a]	IARC 1987
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL TWA (8-hr, final rule) STEL	10 ppm (35 mg/m^3) 20 ppm (70 mg/m^3)	OSHA 1989
b. Water:			
EPA OWRS	NPDES permit application testing requirements: Toxic pollutants and hazardous substances required to be identified by existing dischargers if expected to be present (vinyl acetate)	Yes	EPA 1983 (40 CFR 122, Appendix D, Table V)
c. Food:			
FDA	May be safely used as a coating or as a component of a coating which is the food-contact surface of polyolefin films intended for packaging food; vinyl acetate/crotonic acid copolymer	Yes	FDA 1977 (21 CFR 175.350)
	Vinyl acetate is regulated as a modifier of food starch. The acetyl groups in modified sauce-starch not to exceed 2.5%	Yes	FDA 1991 (21 CFR 172.892)
d. Other:			
EPA OERR	CERCLA reportable quantity (final)	5000 pounds (2270 kg)	EPA 1985a (40 CFR 302.4); EPA 1986a (40 CFR 117.3
	Extremely hazardous substance TPQ	1000 pounds (454 kg)	EPA 1987a (40 CFR 355, Appendix B)
EPA OSW	Designation of hazardous substances	Yes	EPA 1978 (40 CFR 116.4)
	List of CERCLA hazardous substances	Yes	EPA 1985b (40 CFR 302.4, Appendix A)
	Listing as hazardous waste constituent	No	EPA 1986b (40 CFR 261, Appendix VIII)
	Groundwater monitoring requirement	Yes	EPA 1987b (40 CFR 264, Appendix IX)

7. REGULATIONS AND ADVISORIES

TABLE 7-1. (Continued)

Agency	Description	Information	References
EPA OTS	Toxic chemical release reporting; community right-to-know (proposed)	Yes	EPA 1987c
OSHA	Meets criteria for proposed medical records rule	Yes	OSHA 1982
Guidelines:			
a. Air:			
ACGIH	TLV TWA	10 ppm (35 mg/m^3)	ACGIH 1986
	STEL	20 ppm (70 mg/m^3)	ACGIH 1986
	STEL (proposed)	15 ppm (53 mg/m^3)	ACGIH 1992
	Carcinogen Classification (proposed)	A3[b]	ACGIH 1992
EPA	Hazardous air pollutant under Section 112 of Clean Air Act Amendment	Yes	U.S. Congress 1990
EPA	RfC (Inhalation)	0.2 mg/m^3 (0.06 ppm)	IRIS 1991
	RfD (Oral)	No data	IRIS 1991
NIOSH	Ceiling (15-min)	4 ppm (14 mg/m^3)	NIOSH 1978a
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations		NATICH 1988
Connecticut	(8-hr)	0.6000 mg/m^3	
Massachusetts	(24-hr)	0.0096 mg/m^3	
Nevada	(8-hr)	0.7140 mg/m^3	
North Dakota	(1-hr)	0.6000 mg/m^3	
North Dakota	(8-hr)	0.3000 mg/m^3	
Virginia	(24-hr)	0.0050 mg/m^3	

[a]The Working Group on the Evaluation of Carcinogenic Risks to Humans concluded that this agent is not classifiable as a human carcinogen.

[b]Group A3 carcinogen = The agent is carcinogenic in experimental animals at a relatively high dose, by routes(s) of administration, at site(s), of histologic types(s), or by mechanism(s) which are not considered relevant to worker exposure. Available epidemiological studies do not confirm an increased risk of cancer in exposed humans. Available evidence suggests that the agent is not likely to cause cancer in humans except under uncommon or unlikely routes or levels of exposure.

ACGIH = American Conference of Governmental Industrial Hygienists; A3 = animal carcinogen; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; Clearinghouse; NIOSH = National Institute for Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; RfC = Reference concentration; RfD = Reference dose; STEL = Short Term Exposure Limit; TLV = Threshold Limit Value; TPQ = Threshold Planning Quantity; TWA = Time-Weighted Average

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9. GLOSSARY

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

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

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

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

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

Carcinogen -- A chemical capable of inducing cancer.

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

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

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

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

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

9. GLOSSARY

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects. Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days as specified in the Toxicological Profiles.

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

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

In Vivo -- Occurring within the living organism.

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

Lethal Concentration $_{(50)}$ (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 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 (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

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

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/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 anadditional 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.

9. GLOSSARY

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 S-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 A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance. The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-l and 2-2) are used to summarize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELS) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text.

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

LEGEND

See LSE Table 2-l

(1). Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist,

three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes.

(2). Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

(3). Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.

(4). Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-l).

(5). Species The test species, whether animal or human, are identified in this column.

(6). Exposure Frequency /Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

(7). System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.

(8). NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote “c”).

(9). LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to

quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

(10). Reference The complete reference citation is given in Chapter 8 of the profile.

(11). CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.

(12). Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "c" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See LSE Figure 2-l

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

(13). Exposure Duration The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14). Health Effect These are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.

(15). Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16). NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17). CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

(18). Estimated UDDer-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19). Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

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

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
3 → Systemic	5 ↓	6 ↓	7 ↓	8 ↓	9 ↓		10 ↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11 ↓		
38	Rat	18 mo 5d/wk 7hr/d			20 (CEL, multiple organs)		Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d			10 (CEL, lung tumors, nasal tumors)		NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d			10 (CEL, lung tumors, hemangiosarcomas)		NTP 1982

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

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

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

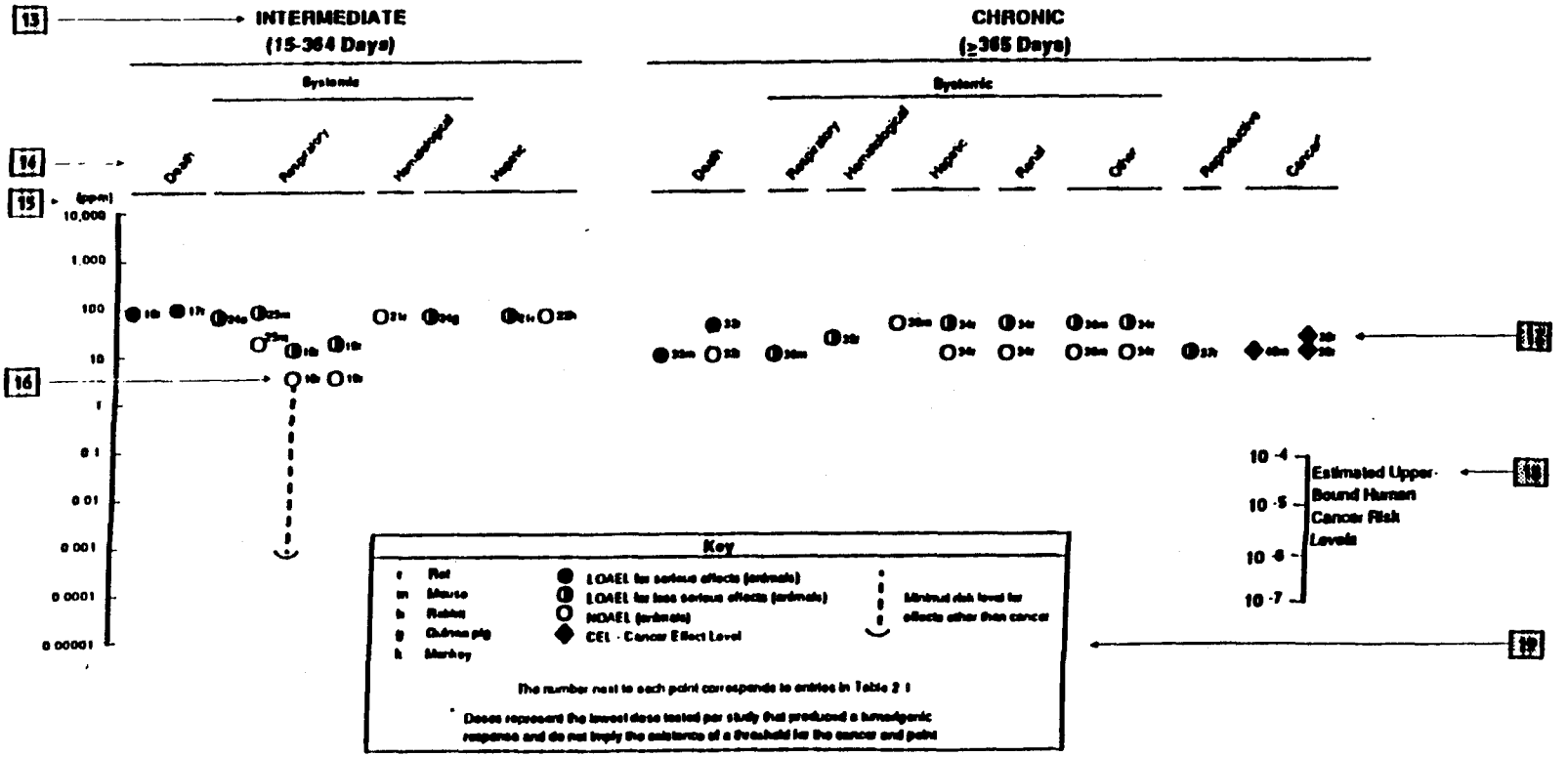

FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

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Chapter 2 (Section 2.4)

Relevance to Public Health

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

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

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

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

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, - intermediate, - chronic). These MRLs are not meant to support regulatory action, but to aquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

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

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive humanhealth effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information frommultiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS USED

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
f_1	first generation
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
HPLC	high performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
Koc	octanol-soil partition coefficient
Kow	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration low
LC_{50}	lethal concentration 50 percent kill
LD_{Lo}	lethal dose low
LD_{50}	lethal dose 50 percent kill

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LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeters
mmol	millimole
μmole	micromole
mppcf	millions of particles per cubic foot
MRL	minimal risk level
MS	mass spectroscopy
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
nm	nanometer
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportional mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short-term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxic Release Inventory
TWA	time-weighted average

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U.S.	United States
UF	uncertainty factor
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

APPENDIX C

PEER REVIEW

A peer review panel was assembled for vinyl acetate. The panel consisted of the following members: Dr. Ghulam Ansari, Associate Professor of Biochemistry and Pathology, University of Texas, Galveston, Texas; Dr. Arthur Gregory, Private Consultant, Sterling, Virginia; and Dr. Shane Que Hee, Associate Professor of Environmental Health, University of California at Los Angeles School of Public Health, Los Angeles, California. These experts collectively have knowledge of vinyl acetate'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 Comprehensive Environmental Response, Compensation, and Liability Act of 1986, Section 104.

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

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

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