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

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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)		Reference
					Less serious (ppm)	Serious (ppm)	
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; retar- dation 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 macro- phages in the lungs, respi- ratory diffi- culty)	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)		

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TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	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)		Reference
					Less serious (ppm)	Serious (ppm)	
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)		Reference
					Less serious (ppm)	Serious (ppm)	
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
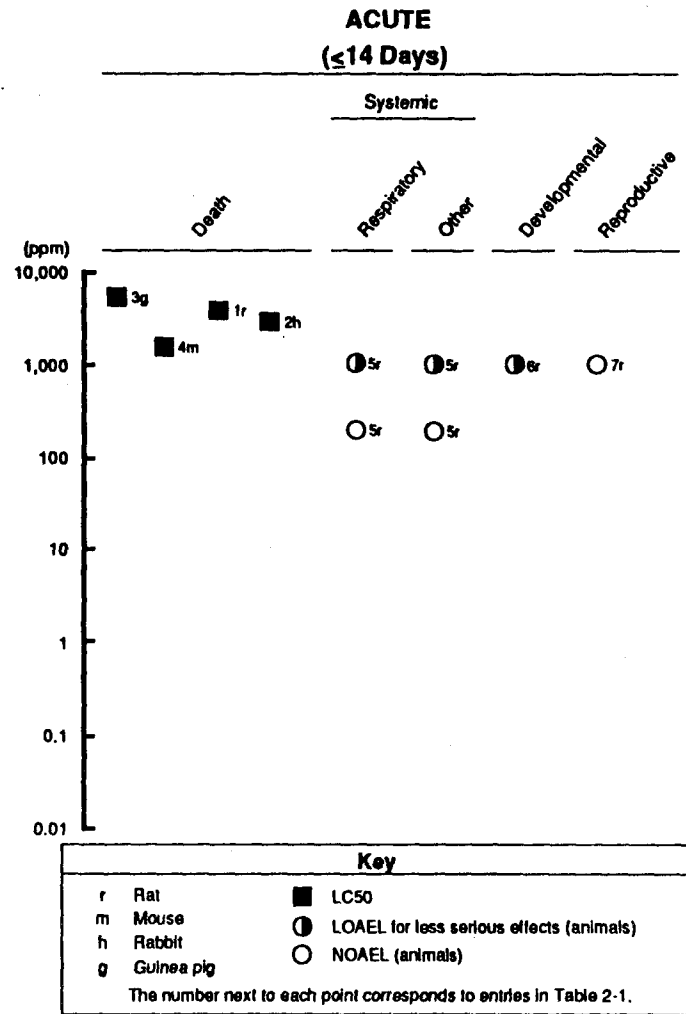
ACUTE

(≤14 Days)

FIGURE 2-1 (Continued)

INTERMEDIATE
(15-364 Days)

Systemic

Death Respiratory Cardiovascular Gastrointestinal Hematological

Key

r	Rat	● LOAEL for serious effects (animals)	Minimal risk level for effects other than cancer
m	Mouse	◐ LOAEL for less serious effects (animals)	
		○ NOAEL (animals)	
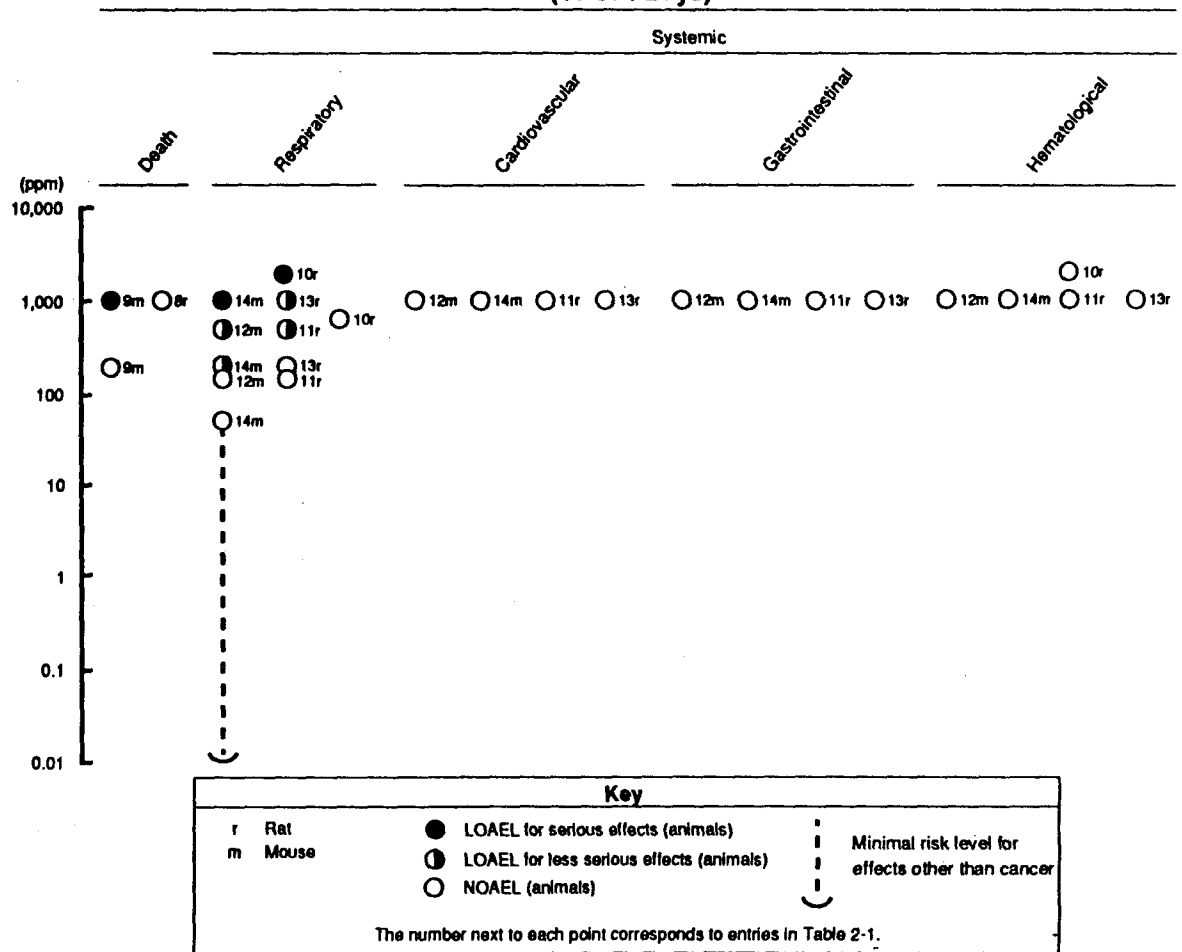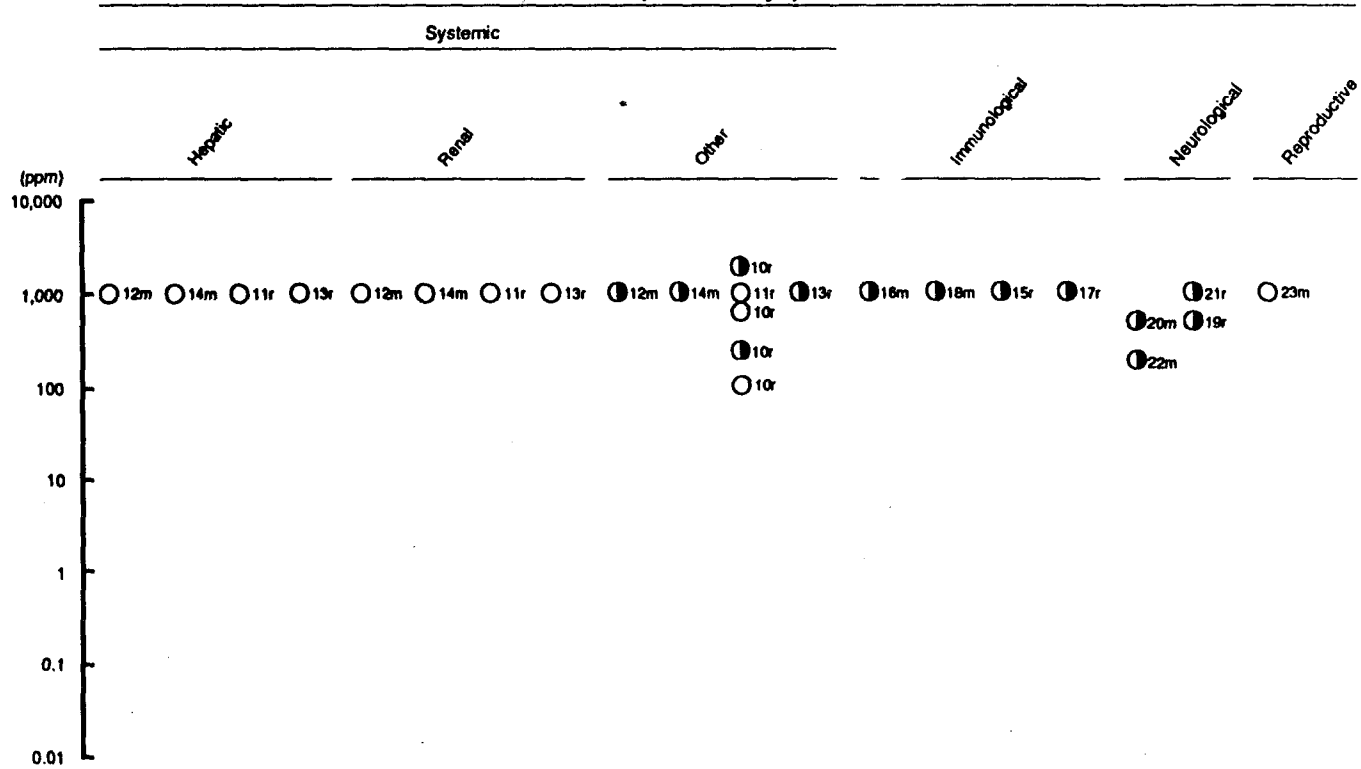
The number next to each point corresponds to entries in Table 2-1.

FIGURE 2-1 (Continued)

INTERMEDIATE
(15-364 Days)

FIGURE 2-1 (Continued)

CHRONIC
(≥ 365 Days)

Systemic

| Death | Respiratory | Cardiovascular | Gastrointestinal | Hematological | Hepatic | Renal | Other | Immunological | Neurological | Cancer* |

(ppm)

| 10,000 | | | | | | | | | | |

1,000 ── ○25m ○24r ●28m ○28m ○27r ○28m ○27r ○28m ○27r ○28m ○27r ○28m ○27r ◐28m ◐27r ◆32r

◐28m ◐27r

100 ── ○28m ○27r ◐29r ◐31m ◐30r

10 ── △28 △28 △28 △28

1

0.1

0.01

Key

	● LOAEL for serious effects (animals)
r Rat	◐ LOAEL for less serious effects (animals)
m Mouse	○ NOAEL (animals)
	△ NOAEL (humans)
	◆ CEL - Cancer Effect Level (animals)

The number next to each point corresponds to entries in Table 2-1.

* Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

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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

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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.

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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.

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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

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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.

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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.

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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

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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

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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)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
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)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
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 Cardio Gastro Hemato Hepatic Renal Derm/oc Other	235 235 235 235 235 235 235 235			Hazleton 1988a

TABLE 2-2 (Continued)

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

ACUTE
(≤14 Days)
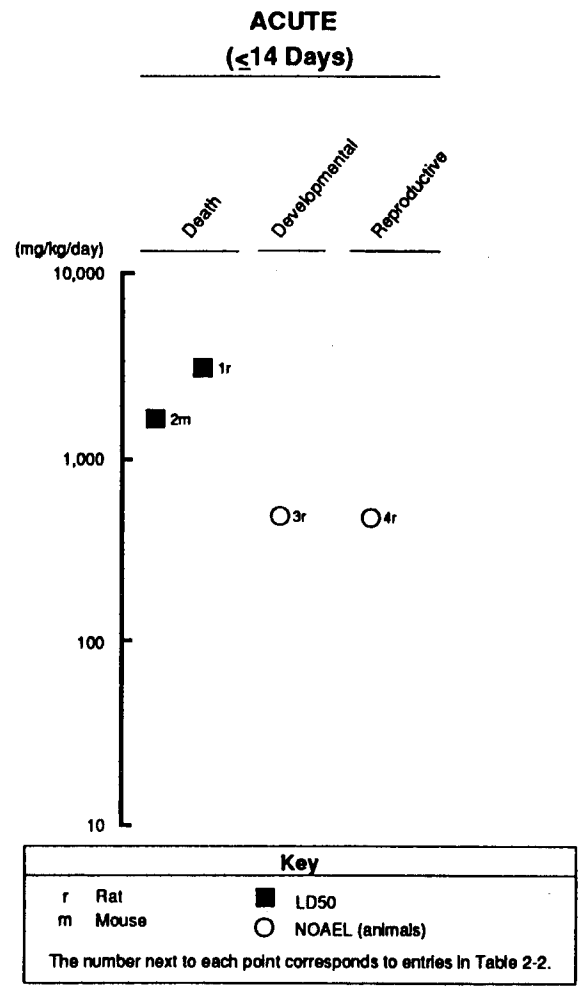
FIGURE 2-2 (Continued)

INTERMEDIATE
(15-364 Days)
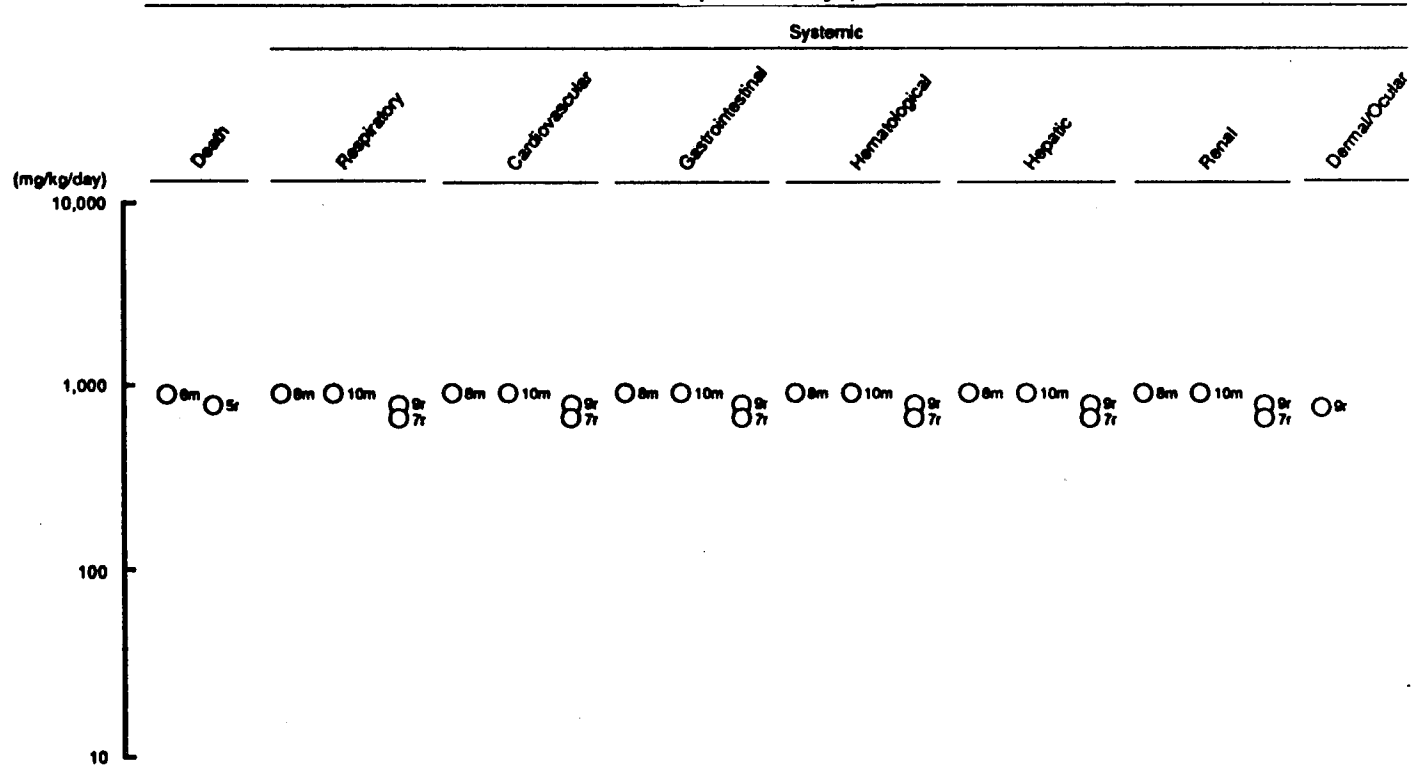
	Key	
r Rat	O NOAEL (animals)	
m Mouse		
The number next to each point corresponds to entries in Table 2-2.		

FIGURE 2-2 (Continued)

INTERMEDIATE
(15-364 Days)
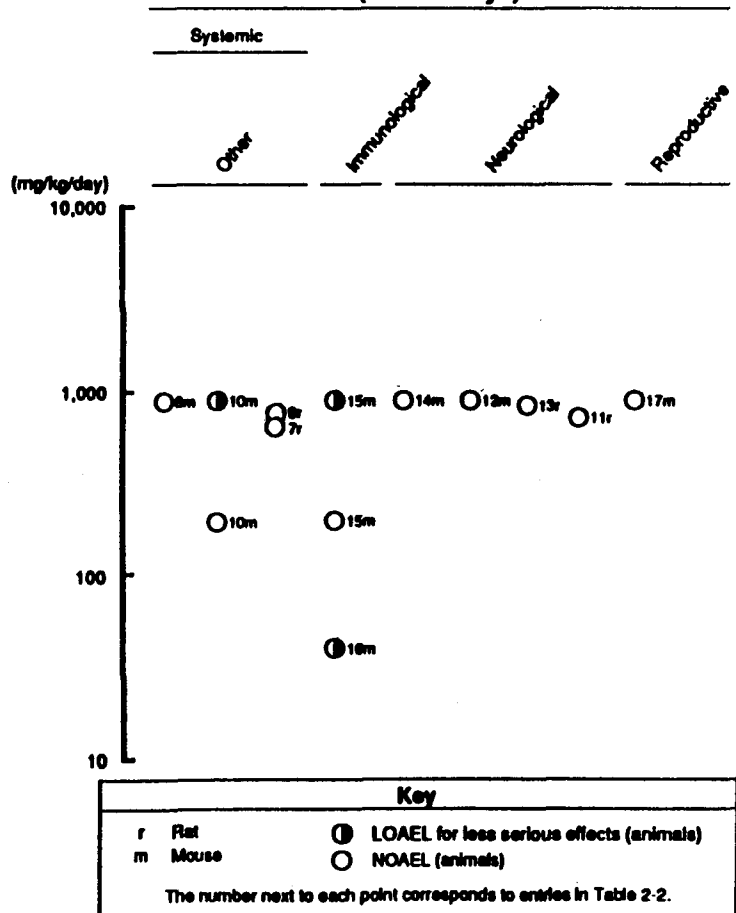
FIGURE 2-2 (Continued)

CHRONIC
(≥ 365 Days)

Systemic

Respiratory Cardiovascular Gastrointestinal Hematological Hepatic Renal Dermal/Ocular Other Neurological Developmental Reproductive

(mg/kg/day)

10,000

1,000

○20r   ○21r

○18r ○18r ○18r ○18r ○18r ○18r ○18r ○18r ○19r

○20r

100

10

Key		
r　Rat	◑　LOAEL for less serious effects (animals)	
	○　NOAEL (animals)	
The number next to each point corresponds to entries in Table 2-2.		
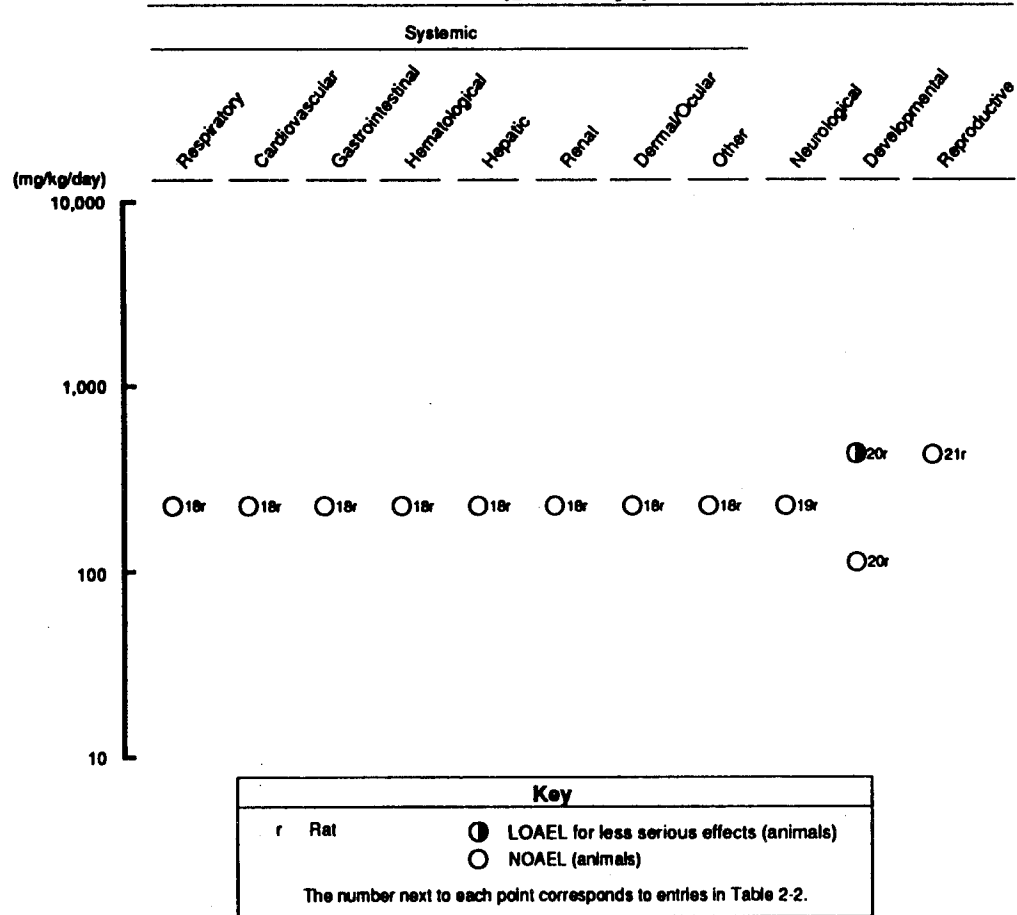
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The majority of the information available on the systemic effects of oral exposure to vinyl acetate was obtained from unpublished 4-week, 3-month, and 104-week studies conducted by Hazleton Laboratories, Europe. In these studies Sprague-Dawley rats 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 in utero 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

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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).

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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.

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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.

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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

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(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

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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 ≤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		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

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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.

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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

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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

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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

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FIGURE 2-3. Proposed Metabolic Pathways for Vinyl Acetate
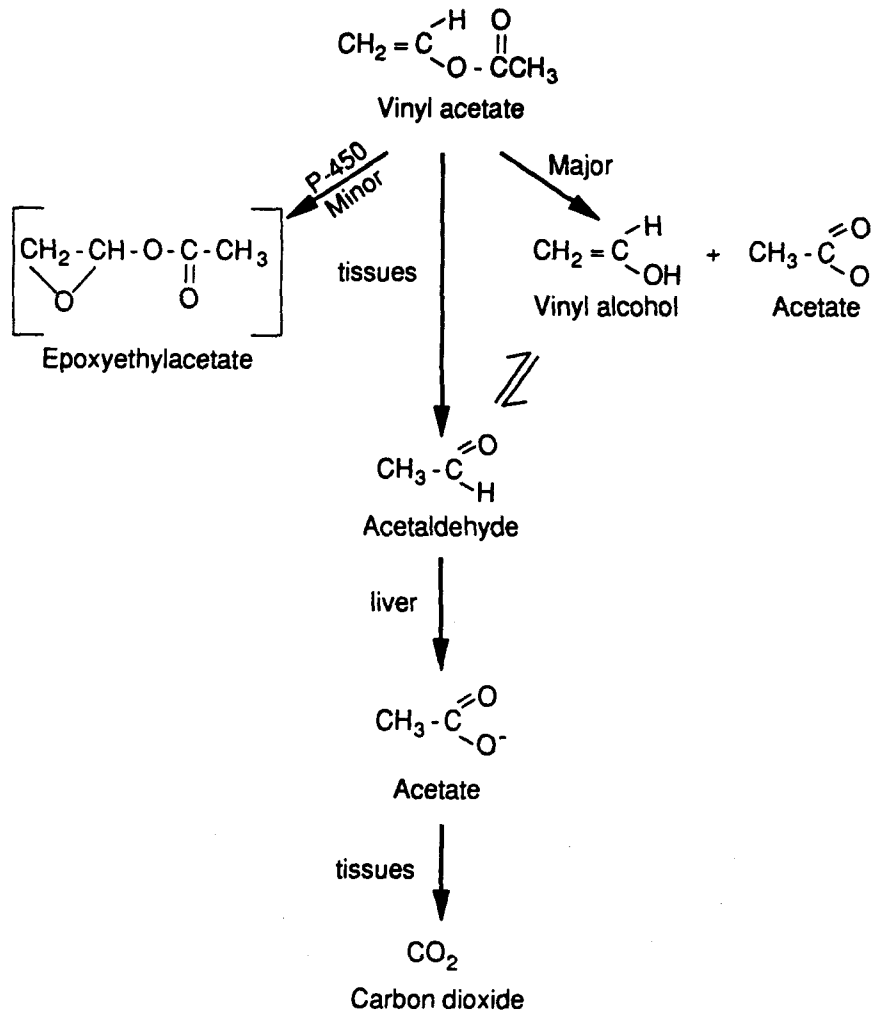
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concentrations (800-1,400 ppm) and first-order kinetics at lower
concentrations. This indicates that the metabolic pathways of vinyl
acetate are saturable at high levels. Following 6 months of exposure to
10-500 mg/m^3 (2.8-142 ppm) of vinyl acetate 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

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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

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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:

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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

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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.

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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

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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	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

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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

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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 in utero 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,

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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.

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

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

HUMAN

ANIMAL

● Existing Studies

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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

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(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, 1980c; 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

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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 <u>in vitro</u> 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 <u>in vitro</u> 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.